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Note

Synthesis of 4-[2-(*p*-bromophenyl)triazol-4-yl]-2-hydroxytetronimide and some derivatives: bromophenyltriazolyl analogs of imino-L-ascorbic acid

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Many analogs of L-ascorbic acid and related tetronic acid derivatives have been found to show effective biological activities as antineoplastic[1], antibacterial[2], hypnotic[3], and analgesic[4] agents. A (bromophenyl)triazolyl analog of dehydro-L-ascorbic acid was synthesized, and its reactions were studied.

In continuation of our previous work on aryl analogs of imino-L-ascorbic acid[5–7], 4-[2-(*p*-bromophenyl)triazol-4-yl]-2-hydroxytetronimide (**7**) was prepared by the reaction of 2-(*p*-bromophenyl)-4-formyl-1,2,3-triazole (**4**) with glyoxal sodium bisulfite monohydrate (1.5 mol) and potassium cyanide (2.6 mol) in alkaline solution under a nitrogen atmosphere, followed by acidification. Such conditions were found to be most favorable for the formation of many of the tetronimide derivatives prepared, but not for ring enlargement[8–10]. A mechanism similar to that reported[11] may be suggested, wherein acyloin condensation occurs between the (bromophenyl)-formyltriazole **4** with glyoxal in the presence of cyanide ion, giving the intermediate **5**, which then reacts with the cyanide, affording the cyanohydrin **6** that undergoes cyclization to the tetronimide derivative **7**.

Compound **7** possesses strong reducing properties, and gives the color reactions characteristic of the tetronimide nucleus[11,12]. 2-Formyl-1-naphthol gave unsuccessful results, and this may be attributed to the high electron-donating ability of the hydroxyl group, which tends to decrease the partial, positive charge on the carbonyl of the aldehydic group. The infrared (i.r.) absorption spectrum of the tetronimide **7** showed a broad, medium band at 3350 cm^{-1} (NH), a broad, strong band at 3090 cm^{-1} characteristic of the OH group, a carbonyl band at 1710 cm^{-1}, a medium band at 1640 cm^{-1} indicative of the -C=C-C=N group, a broad medium band at 1550 cm^{-1} due to the NH deformation mode that coupled with the lower frequency of the C–N stretching mode, *i.e.*, NH, C–N coupling, and a strong –C–O–C– group absorption band in the region of 1190 cm^{-1}. Its p.m.r. spectrum showed the imino proton as a singlet at δ 9.6, and the aromatic protons as a multiplet at δ 7.05–8.25.

Acylation of the new tetronimide **7** afforded the corresponding 2-acyloxy-3-oxobutaniminolactones (**8**). Their i.r. spectra had a strong band in the region of

3480–3300 cm^{-1} (NH), a broad, medium band characteristic of $\overset{+}{N}H_2$ at 3120–2960 cm^{-1}, a small carbonyl-group absorption band in the region of 1720–1700 cm^{-1}, characteristic of the carbonyl of the ketone form of compound **7**, a strong carbonyl band at 1760–1735 cm^{-1} for the *O*-acyl group, a medium band at 1640 cm^{-1} (C=N), a medium band at 1580 cm^{-1} due to coupled NH, C–N, *i.e.*, due to the NH deformation mode that coupled with the lower frequency of the C–N stretching mode, and a strong band at 1235–1220 cm^{-1} indicative of a –C–O–C– group.

Oxidation of the 2-hydroxytetronimide **7** with nitrous acid afforded 4-[2-(*p*-bromophenyl)triazol-4-yl]-2,3-dioxobutano-1,4-lactone (**12**), the corresponding analog of dehydro-L-ascorbic acid. Its i.r. spectrum had a carbonyl (lactone) band at 1715 cm^{-1}, and two other carbonyl bands, one weak (in the region of 1700 cm^{-1}), and the other strong, at 1775 cm^{-1}.

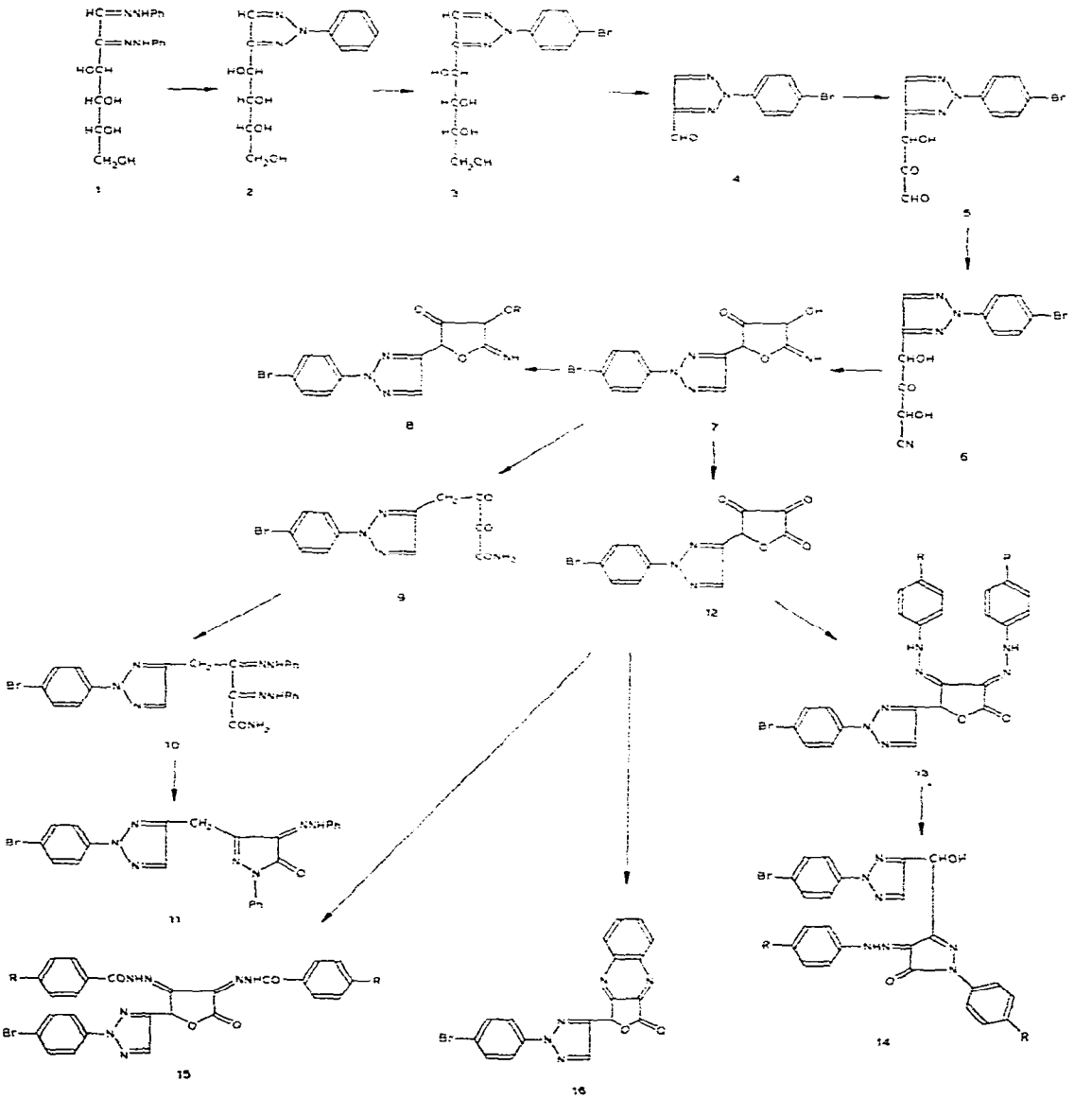
Compound **7** reacted readily with phenylhydrazine in aqueous acetic acid, giving the orange, deoxygenated analog of the pyrazolone **14**, namely, [2-*p*-(bromophenyl)-1,2,3-triazol-4-yl]-[1-phenyl-4-(phenylhydrazono)-2-pyrazolin-5-one-3-yl]-methane (**11**), that differs from the red bis(phenylhydrazone) (**13**, R = H) and from its more stable derivative (**14**, R = H). The i.r. spectrum of compound **11** showed a band in the region of 1660 cm^{-1} (OCN), but neither a carbonyl nor a hydroxyl group band. Furthermore, product **11** failed to give acyl derivatives under conditions similar to those utilized for the preparation of the acyl derivatives **8**. The p.m.r. spectrum of **11** had the methylene protons as a singlet at δ 4.2, the imino proton at δ 10.93, and the aromatic protons as a multiplet at δ 7.1–7.9.

The formation of **11** may be explained by a mechanism similar to that reported for the aryl analogs[13], where hydrolysis followed by deoxygenation takes place first for the tetronimide **7**, giving a diketo intermediate (**9**) that combines with phenylhydrazine, yielding the corresponding bis(phenylhydrazone) derivative **10**, that undergoes nucleophilic attack (by the nitrogen atom of the C-3 phenylhydrazone residue) on the carbonyl group, and cyclization, giving **11**.

These results are in agreement with those for the aryl analogs that indicated that deoxygenation cannot take place during the conversion of the red bis(arylhydrazone)s **13** into the more stable pyrazolone derivatives (**14**). [4-(*p*-Bromophenyl)triazol-4-yl]-2,3-dioxobutano-1,4-lactone (**12**), the aryl analog of dehydro-L-ascorbic acid, reacted readily with arylhydrazines, as well as with (2,4-dinitrophenyl)hydrazine, giving the corresponding, red bisarylhydrazones (**13**), similar to the bis(arylhydrazone)s of dehydro-L-ascorbic acid. The i.r. spectrum of these bis(hydrazone)s (**13**) showed a carbonyl lactone band in the region of 1740–1710 cm^{-1}, at a lower frequency than that of the 1,4-lactones. This low frequency had been observed[14,15] for other analogs, and was attributed to the hydrogen bonding of the lactone carbonyl with the imino proton of the hydrazone residue on C-2. Furthermore, the NH group was observed as a weak absorption band in the region of 3415–3215 cm^{-1}, whereas the band for the –C–O–C– group appeared at 1250 cm^{-1}. In addition to these bands, the bis(sulfamylhydrazone)s showed bands in the region of 1305 and 1120 cm^{-1}, indicative of the $SO_2N<$ group, whereas, the nitro derivatives gave bands at 1350 and

850 cm^{-1}, characteristic of the NO_2 group. The p.m.r. spectrum of the bis(phenylhydrazone) contained signals for two chelated, imino protons, at δ 10.98 and 11.97, whereas the corresponding dehydro-L-ascorbic acid derivative showed[14] the imino protons at δ 10.87 and 11.93. The slight difference is probably due to deshielding by the (bromophenyl)triazole ring in the bis(phenylhydrazone) derivative.

On treatment with sodium hydroxide, the bis(arylhydrazone)s **13** underwent lactone-ring opening, 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 **14**, which are analogs of the corresponding dehydro-L-ascorbic acid derivatives. The i.r. spectrum of compounds **14** showed an absorption band at 1662 cm^{-1}, indicative of the OCN group, and a broad band in the region of 3410–3300 cm^{-1} for hydroxyl group.

When 4-(*p*-bromophenyl)triazolyl-2,3-dioxobutano-1,4-lactone (**12**) was treated with acylhydrazines, it gave the corresponding bis(acylhydrazone)s (**15**), whereas equimolar proportions of *o*-phenylenediamine and lactone **12** afforded the quinoxaline derivative **16**. The i.r. spectra of the bis(acylhydrazone)s contained a broad, strong band at 3260 cm^{-1} (NH), a broad, strong carbonyl absorption band in the region of 1750–1700 cm^{-1}, and a medium band at 1260 cm^{-1} indicative of the –C–O–C– group. The quinoxaline derivative **16** showed a carbonyl band at 1685 cm^{-1}. All of the compounds prepared exhibited characteristic, aromatic absorption bands in the region of 1600–1460 cm^{-1}.

EXPERIMENTAL

General. — All melting points were determined in open, glass capillary tubes, and are uncorrected. Microanalyses were performed at the Microanalytical Laboratory, Faculty of Science, Cairo University. Infrared absorption spectra were recorded with a Pye Unicam SP 2000 infrared spectrophotometer, using potassium bromide pellets, and p.m.r. spectra were recorded with a Varian HA 100 instrument.

D-arabino-*Hexose* (p-*Bromophenyl*)*osotriazole* (**3**). — A suspension of D-*arabino*-hexose phenylosotriazole (**2**; 4 g), prepared from **1** in cold water (400 mL), was treated with bromine (3 mL), and the mixture was kept overnight at room temperature, with occasional shaking. The (bromophenyl)osotriazole that separated out was filtered off, washed several times with water, and recrystallized from ethanol; m.p. 196° (lit.[16] m.p. 204°).

2-(p-*Bromophenyl*)-*4-formyl-1,2,3-triazole* (**4**). — A suspension of D-*arabino*-hexose (*p*-bromophenyl)osotriazole (**3**; 1 mmol) in water (60 mL) was shaken at room temperature with aqueous sodium metaperiodate (3 mmol) for 24 h. The crystalline shape of the solid quickly changed, and the product obtained after filtration was recrystallized from dilute ethanol; yield 65%; m.p. 106° (lit.[17] m.p. 114°). It was soluble in ethanol or methanol, and insoluble in water. The same triazolaldehyde **4** was obtained by bromination of 4-formyl-2-phenyl-1,2,3-triazole in aqueous medium; m.p. and mixed m.p. 106°.

4-[*2*-(p-*Bromophenyl*)*triazol-4-yl*]-*2-hydroxytetronimide* (**7**). — Glyoxal sodium hydrogensulfite (15 mmol) was added in one portion to a cold, well stirred solution of potassium cyanide (26 mmol) in 2M sodium carbonate solution (40 mL) under a nitrogen atmosphere. The resulting solution was treated in one portion with a solution of the formyl derivative **4** (0.01 mol) in 1,4-dioxane (25 mL). A precipitate appeared after 20 min, and stirring was continued for an extra 45 min. The flow of nitrogen was discontinued, and the mixture was acidified with glacial acetic acid. Stirring was continued for another 3 h, after which, the tetronimide **7** that had

separated out was washed with water, and recrystallized from ethanol, giving colorless needles; yield 65%; m.p. 181°.

Anal. Calc. for $C_{12}H_9BrN_4O_3$: C, 42.7; H, 2.7; Br, 23.7; N, 16.6. Found: C, 43.0; H, 3.1; Br, 24.0; N, 16.3.

2-Acetoxy-[4-(2-p-bromophenyl)triazol-4-yl]-3-oxobutaniminolactone (**8**, *R* = *Ac.*). — This derivative was prepared by heating a mixture of the tetronimide **7** (2 mmol) with acetic anhydride (2 mL) on a steam bath for 10 min, and keeping for 2 h at room temperature. The mixture was then poured onto ice-cold, saturated sodium hydrogencarbonate solution, and the solid that separated out was filtered off, washed with water, dried, and recrystallized from benzene; colorless needles, yield 70%; m.p. 247°.

Anal. Calc. for $C_{14}H_{11}BrN_4O_4$: C, 44.3; H, 2.9; Br, 21.2; N, 14.8. Found: C, 44.5; H, 3.0; Br, 20.9; N, 14.6.

2-Benzoyloxy-[4-(2-p-bromophenyl)triazol-4-yl]-2-oxo-butaniminolactone (**8**, *R* = *Ph*). — A solution of compound **7** (2 mmol) in pyridine (6 mL) was gently warmed with benzoyl chloride (2 mmol) for 10 min, and then kept for 5 h at room temperature. The mixture was poured into ice-cold, 2M sulfuric acid (25 mL), and the crude product was treated with saturated sodium hydrogencarbonate solution (25 mL), filtered off, washed with water, and recrystallized from benzene; colorless needles, yield 70%; m.p. 238°.

Anal. Calc. for $C_{19}H_{13}BrN_4O_4$: C, 51.7; H, 3.0; Br, 18.1; N, 12.7. Found: C, 51.7; H, 3.1; Br, 18.3; N, 12.6.

[2-(p-Bromophenyl)triazol-4-yl]-[1-phenyl-4-(phenylhydrazono)-2-pyrazolin-5-one-3-yl]methane (**11**). — A mixture of compound **7** (1 g) with 1:1 water–acetic acid (100 mL) was boiled under reflux for 80 min. To the resulting solution was added phenylhydrazine (5 mL), and boiling was continued for 90 min. On cooling, the orange product that separated out was filtered off, washed with alcohol, and recrystallized from ethanol; orange needles, yield 60%; m.p. 206°.

Anal. Calc. for $C_{24}H_{18}BrN_7O$: C, 57.6; H, 3.6; Br, 16.0; N, 19.6. Found: C, 57.5; H, 3.5; Br, 15.8; N, 20.1.

4-[2-(p-Bromophenyl)triazol-4-yl]-2,3-dioxobutano-1,4-lactone (**12**). — A suspension of tetronimide **7** (3 mmol) in acetone (5 mL) and 2M sulfuric acid (8 mL) was cooled to 10°, and treated dropwise with 10% sodium nitrite solution (5 mL). The mixture was warmed to expel the nitrogen gas, and then allowed to cool. The product that separated was filtered off, washed with water, and recrystallized from methanol; colorless needles, yield 40%; m.p. 146°.

Anal. Calc. for $C_{12}H_6BrN_3O_4$: C, 42.9; H, 1.8; Br, 23.8; N, 12.5. Found: C, 43.1; H, 2.1; Br, 24.0; N, 12.2.

4-[2-(p-Bromophenyl)triazol-4-yl]-2,3-dioxobutanolactone bis(arylhydrazone)s (**13**). — A solution of compound **12** (1 mmol) in 1:1 water–ethanol (25 mL) containing a few drops of glacial acetic acid was heated with the chosen arylhydrazine (2 mmol) on a steam bath for 2 h. The red bis(arylhydrazone) that separated out was filtered

TABLE I

MICROANALYTICAL AND SPECTRAL DATA FOR 4-[2-(*p*-BROMOPHENYL)TRIAZOL-4-YL]-2,3-DIOXOBUTANO-1,4-LACTONE BIS(ARYLHYDRAZONE)S (13)

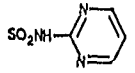
R	*Yield (%)*	*M.p. (degrees)*	*Molecular formula*	*Calculated (%)*					*Found (%)*					ν_{max}^{KBr} *(cm⁻¹)*
				C	*H*	*Br*	*N*	*S*	*C*	*H*	*Br*	*N*	*S*	
H	35	188	$C_{24}H_{18}BrN_7O_2$	55.8	3.5	15.5	19.0		55.8	3.3	15.9	18.7		1740
CO_2H	40	241	$C_{26}H_{18}BrN_7O_6$	51.7	3.0	13.3	16.1		51.5	3.0	13.6	15.8		1725
SO_2NH_2	60	252	$C_{24}H_{20}BrN_9O_6S_2$	42.7	3.0	11.9	18.7	9.5	43.0	3.2	12.4	19.1	9.2	1730
	50	218	$C_{32}H_{24}BrN_{13}O_6S_2$	46.3	2.9	9.6	21.1	7.7	46.5	3.1	9.2	21.5	7.6	1730
NO_2	45	233	$C_{24}H_{16}BrN_9O_6$	47.5	2.6	13.2	20.8		47.7	3.0	13.5	21.1		1735
Bis(2,4-dinitrophenyl)hydrazone	55	151	$C_{24}H_{14}BrN_{11}O_{10}$	32.8	2.0	11.5	22.1		33.1	2.4	11.1	22.5		1730

TABLE II

MICROANALYTICAL AND SPECTRAL DATA FOR 1-ARYL-3-[2-(*p*-BROMOPHENYL)TRIAZOL-4-YL)-HYDROXYMETHYL]PYRAZOLE-4,5-DIONE 4-(ARYLHYDRAZONE)S (**14**)

R	*Yield (%)*	*M.p. (degrees)*	*Molecular formula*	*Calculated (%)*					*Found (%)*					ν_{max}^{KBr} *(cm⁻¹)*
				C	*H*	*Br*	*N*	*S*	*C*	*H*	*Br*	*N*	*S*	
H	30	122	$C_{24}H_{18}BrN_7O_2$	55.8	3.5	15.5	19.0		55.8	3.3	15.3	18.8		1665
SO_2NH_2	40	233	$C_{24}H_{20}BrN_9O_6S_2$	42.7	3.0	11.9	18.7	9.5	42.9	3.3	11.6	19.1	9.8	1660
NO_2	40	163	$C_{24}H_{16}BrN_9O_6$	47.5	2.6	13.2	20.8		47.3	2.9	12.9	21.0		1670
2,4-$(NO_2)_2$	30	211	$C_{24}H_{14}BrN_{11}O_{10}$	32.8	2.0	11.5	22.1		33.1	2.2	11.8	21.9		1665

TABLE III

MICROANALYTICAL AND SPECTRAL DATA FOR 4-[2-(*p*-BROMOPHENYL)TRIAZOL-4-YL]-2,3-DIOXOBUTANO-1,4-LACTONE BIS(ACYLHYDRAZONE)S (**15**)

R	*Yield (%)*	*M.p. (degrees)*	*Molecular formula*	*Calculated (%)*				*Found (%)*				ν_{max}^{KBr} *(cm⁻¹)*
				C	*H*	*Br*	*N*	*C*	*H*	*Br*	*N*	
H	30	115	$C_{26}H_{18}BrN_7O_4$	54.6	3.2	14.0	17.1	55.0	3.1	13.8	16.9	1695
Cl	30	186	$C_{26}H_{16}BrCl_2N_7O_4$	48.8	5.1		15.1	49.1	5.5		14.8	1700
NH_2	40	194	$C_{26}H_{20}BrN_9O_4$	51.8	6.4	13.3	20.9	52.1	6.5	13.5	21.1	1690

off, washed with water, and recrystallized from ethanol or chloroform; red needles, yield 35–50% (see Table I).

1-Aryl-[2-(p-bromophenyl)triazol-4-yl]-3-hydroxymethylpyrazole-4,5-dione 4-arylhydrazones (**14**). — These derivatives were obtained by heating the red bis(hydrazone)s **13** (1 g) with 20% aqueous sodium hydroxide solution (40 mL) on a boiling-water bath for 15 min. On cooling, and acidifying with glacial acetic acid, the desired products separated out, and were purified by recrystallization from dilute ethanol; orange needles, yield 30–45% (see Table II).

4-[2-(p-Bromophenyl)triazol-4-yl]-2,3-dioxobutanolactone 2,3-bis(acylhydrazone)s (**15**). — These compounds were prepared by heating a solution of lactone **12** (1 mmol) in 1:1 water–ethanol (20 mL) containing a few drops of glacial acetic acid with an ethanolic solution of the chosen acylhydrazine (2 mmol) on a steam bath for 2 h. On concentration, cooling, and dilution with water, the title compounds separated out; they were recrystallized from methanol or chloroform–methanol; reddish-brown needles, yield 30–40% (see Table III).

Quinoxaline derivative (**16**). — An alcoholic solution of 4-[2-(*p*-bromophenyl)-triazol-4-yl]-2,3-dioxobutano-1,4-lactone (**12**; 1 mmol) and *o*-phenylenediamine (1 mmol) in ethanol (10 mL) was boiled under reflux for 1 h; a precipitate appeared after heating for 5 min. The mixture was allowed to cool, and the solid was filtered off, and recrystallized from ethanol; red needles, yield 40%; m.p. 244°.

Anal. Calc. for $C_{18}H_{10}BrN_5O_2$: C, 52.9; H, 2.5; Br, 19.6; N, 17.2. Found: C, 52.9; H, 2.4; Br, 19.8; N, 16.9.

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