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# TETRONIC ACIDS AND DERIVATIVES—VII[1]

## STRUCTURE OF DEHYDROASCORBIC ACID OSAZONE AND RELATED COMPOUNDS

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**Abstract**—$^{13}$C NMR spectral examination of ascorbic acid and tetronic acid osazones favours a bis(phenylhydrazono) formula and not, as recently reported, a phenylhydrazino-phenylazo structure. Similar conclusions were reached for related 5*H*-furan-2-ones **2–4** bearing at the C-3 and C-4 positions an oximino or an oximino and a phenylhydrazono group. Based on $^{1}$H NMR, IR and UV data, the mutarotation in solution and the chelated structures of compounds **1–4** are discussed.

Much attention has been devoted to the chemistry of osazones derived from tetronic acids **1a**, **1b** (R=H, methyl), and from dehydro-L-ascorbic acid **1c**, R=CHOH−$CH_2OH$.[2-4] Two structural investigations have been reported[5,6] which come to the opposite conclusions. Rao[5] formulated the osazone of ascorbic acid as 3,4-bis(phenylhydrazono)-5H-furan-2-one; he attributed mutarotation to conversion of the *Z,Z*-configuration to the *E,E*-configuration in basic solvents. Recently, Roberts[6] by pointing out the difference in the chemical behavior of ascorbic acid and sugar osazones preferred a 3-phenylhydrazino-4-phenylazo-5*H*-furan-2-one formulation, which he supported by its remarkably high UV absorption.

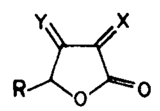
Based upon chemical properties, X-ray analysis, and spectroscopic studies, including $^{15}$N NMR examination, the structure of sugar osazones was unequivocally established as a chelated system in which mutarotation to the O-chelated structure is limited to the extent of a few percent and involves only the C-2 phenylhydrazono residue.[7,8]

We have prepared a series of compounds **1–4** related to the ascorbic acid phenylosazone[1] and report, in this paper, the results of the $^{13}$C NMR investigation of these compounds.

### RESULTS AND DISCUSSION

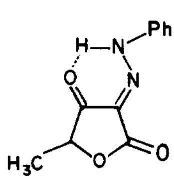
Comparison of the $^{13}$C chemical shifts of the aromatic carbons in azobenzene and phenylhydrazine shows a substantial difference for both types of ortho and para carbon atoms; the substituent effect in azobenzene causes deshielding of 3.3 ppm for the para carbon and shielding of 5.5 ppm for the ortho carbons, whereas in phenylhydrazine, the para and ortho carbons are shielded respectively by 8.6 ppm and 15.7 ppm as compared with those of benzene.[9] As chemical shift reference for the phenyl carbon atoms, we have examined 3-phenylhydrazono-5-methyl tetronic acid **6** for which a ketonic structure is supported by the extensive studies on related aliphatic α-phenylhydrazono-β-diketo compounds.[10,11] This compound and its homologues about the C-5 substitution were found to exist under a 45–55 *syn–anti* mixture chloroform-. No interconversion in basic solvents could be demonstrated; see P. Pollet, Thesis, Lyon, 1979. The ketonic structure was confirmed using $^{13}$C NMR. The C-4 signal appeared at 194.4 ppm for the *anti* configuration as in **6** I,[12] and the chemical shift deviations from benzene, were essentially those of phenylhydrazine (shielding for p-carbon 9 ppm, o-carbons 11.5 ppm) (Table 1), thus excluding structure **6** II.

The $^{13}$C NMR parameters of the compounds **1b** and **1c** show that, although the assignment of the phenylhydrazono carbon atoms may be uncertain, it was easy to identify the o, m and p-carbon atoms by using the off-resonance decoupling technique or from their respective intensities. The deviations from benzene were found to be of the same magnitude as those of compound **6** and were incompatible with an azo-hydrazino structure. The similarity between the

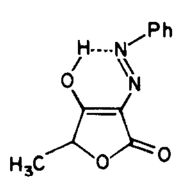


**1:** X = Y = N-NH-Ph
**2:** X = N-OH, Y = N-NH-Ph
**3:** X = N-NH-Ph, Y = N-OH

**4:** X = Y = N-OH
**a:** R = H; **b:** R = Me; **c:** R = CHOH-$CH_2OH$



**6-(I)**



**6-(II)**

Table 1. $^{13}C$ chemical shifts of compounds **1**–**6** (a) in ppm (δ)

| Compound N° | tetronic ring C-2 | C-3 | C-4 | C-5 | C-6 | 3-phenylhydrazono residue C'-1 | C'-2,6 | C'-3,5 | C'-4 | 4-phenylhydrazono residue C'-1 | C'-2,6 | C'-3,5 | C'-4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1b | 164.9 | 122.1 | 142.6 | 71.8 | 16.7 | 141.5 | 114.3 | 129.4 | 120.6 | 143.6 | 112.7 | 129.1 | 123.3 |
| 1c | 165.4 | 123.2 | 140.2 | 76.0 | (b) | 141.9 | 114.2 | 129.5 | 120.6 | 143.6 | 112.6 | 129.2 | 123.4 |
| 2b | 164.4 | 135.0 | 141.9 | 72.6 | 17.1 | | | | | 143.9 | 113.2 | 128.8 | 120.9 |
| 3b | 164.5 | 124.1 | 154.2 | 72.2 | 17.3 | 141.5 | 114.6 | 129.4 | 120.6 | | | | |
| 4b | 163.9 | 136.9 | 148.9 | 73.2 | 17.1 | | | | | | | | |
| 6 | 165.1 | 127.6 | 194.4 | 81.2 | 16.9 | 139.9 | 117 | 129.7 | 119.5 | | | | |
| | | | | | | C-1 or C-2 phenylhydrazono residue C'-1 | C'-2,6 | C'-3,5 | C'-4 | C-2 or C-1 phenylhydrazono residue C'-1 | C'-2,6 | C'-3,5 | C'-4 |
| 5 | (c) | | | | | 143.8 | 112.4 | 129.2 | 119.4 | 144.2 | 111.7 | 129.2 | 119.7 |

(a) Recorded in DMSO-$d_6$ after 20 h of equilibration to ensue a full mutarotation to EE configuration for compounds 1–4, and immediatly after dissolution for 5; in $CDCl_3$ for 6
(b) Chemical shifts of 1,2-dihydroxyethyl side chain: 67.3 (secondary C); 61.9 (primary C). .
(c) C-6 63.2, no attempt was made to assign the resonances at C-3, C-4 or C-5 71.3, 72.0, 74.4.

$^{13}C$ NMR data of compounds **1b,c** and those of glucose osazone **5** (Table 1) supports the 3,4-bis(phenylhydrazo structure or possibly, a "non classical aromatic" system.[8,13] Closely related shifts for the C-2, C-3 and C-4 carbon atoms in compounds **1b** and **1c** provide additional evidence for the 1,4-lactone structure of ascorbic acid osazone. For alternate discussion, see refs 5, 6.

The $^{13}C$ NMR of the isomeric oxime-phenylhydrazones **2** and **3** was also consistent only with their formulation as 3-oximino-4-phenylhydrazono and 4-oximino-3-phenylhydrazono-5*H*-furan-2-ones respectively (Table 1). Additional evidence is provided by the close parallelism between the ring carbon atoms in 3,4-dioximino-5*H*-furan-2-one **4b** for which the α-dioximino structure is well documented,[14] with the related eastern (C-2, C-3) and western (C-4, C-5) zones in respectively monoximes **2** and **3**. Another argument in favour of the s-*cis* arrangement of the azomethine double bond (exocyclic) and the lactone carbonyl double bond was also found in the shift of the C-2 carbon resonance (165 ppm). A compilation of all known data for this carbon atom in the tetronic ring showed a shift upfield of 170 ppm in all cases where there is an exocyclic double bond at the C-3 position and downfield in the case of an s-trans arrangement with an endocyclic (C-3 C-4) double bond.[12,15]

The almost identical shifts of the phenyl carbon atoms in compounds **1b,c** and in isomeric compounds **2** and **3** allow the tentative assignment of the two phenylhydrazono residues at the C-3 and C-4 positions in osazones **1** by a direct comparison with the monophenylhydrazones **2** and **3**. As shown below, spectral examination (UV, IR) clearly indicates that each phenylhydrazono residue, respectively at the C-3 and C-4 positions are, after equilibration in DMSO, in the same geometrical arrangement as in the osazones **1**.

The behavior of osazones **1a** and **1b** in aprotic solvents was found to be similar to that of dehydroascorbic acid osazone,[5] which provides the first reported example of a geometric isomerisation of the hydrazone moieties and replacement of one chelated system by another in non-sugar osazones.[8] However, the structural change of *Z,Z* to *E,E*-configurations in DMSO for **1a** and **1b** is more rapid (1–2 hr) than for **1c** (few days). IR, $^1H$ NMR spectra are given in Tables 2,4.

Inspection of the same data for compounds **2a**, **2b**, **4a**, **4b** (identical results are obtained with the 5,5-dimethyl derivatives) revealed marked differences. Unlike the case of compounds **1**, they do not exist in the solid state or in chloroform in the unique *Z,Z*-configuration. According to IR (bonded carbonyl at 1740 cm$^{-1}$) and $^1H$ NMR spectra (C-5 proton signal ratio measured immediately after dissolution), the *Z,Z* percentage can be estimated to be about 50%. In contrast, compounds **3**, in chloroform showed only an *E,E*-configuration, based on single sets of signals in the IR (1770 cm$^{-1}$) and $^1H$ NMR spectra at 60 or 100 MHz. In the solid state, the presence of a broad band at 1730 cm$^{-1}$ could be due to an intermolecular bonding in an *E,E* configuration. After equilibration only one monochelated *E,E* configuration, in DMSO could be demonstrated from the IR data (unbounded carbonyl at 1770 cm$^{-1}$) and $^1H$ NMR shifts of the NH or OH protons.

Further evidence for these phenomena is provided by the UV data of compounds **1a** and **1b**; **2** and **4** which showed (as in the case of ascorbic acid phenylosazone,[5] a hypsochromic shift of the high wavelength absorption on standing, corresponding to the conversion of a dichelated form (*Z,Z*) to a monochelated form (*E,E*). The exception presented by the compound **3** (which displayed a constant UV absorption maximum on standing) is also in agreement with the unique *E,E*-configuration. The notably high values of the visible absorption maxima (Table 3) strongly suggest a chelated rings involving a phenylhydrazono group in *E,E*- and *Z,Z*-osazones **1** (444 and 468 nm) *Z,Z*-oxime-phenylhydrazone **2** (396 nm) and *E,E*-phenylhydrazone-oxime **3** (383 nm), as compared with known data for the glucose osazone (390 nm).[6] The lack of model compounds with an oximino residue in the chelated ring does not allow, at this point, an extension to compounds **2** (*E,E*) and **4**.

Table 2. IR Carbonyl absorption of compounds **1**–**4b** ($R=CH_3$) ($\nu$, $cm^{-1}$)

| Compd/Solvent | Nujol | $CHCl_3$ | DMSO | $CH_3CN$ |
|---|---|---|---|---|
| 1b | 1735 | 1735 | 1770 (a) | 1770 (60 %) (b)<br>1740 (40 %) |
| 2b | 1770 (40 %)<br>1740 (60 %) | 1770 (40 %)(c)<br>1740 (60 %) | 1770 (d) | 1770 (c) |
| 3b | 1730 (broad) | 1770 (c) | 1770 (c) | 1770 (c) |
| 4b | 1785 (50 %)<br>1750 (50 %) | 1785 (50 %)(c)<br>1750 (50 %) | 1785 (a) | 1785 |

(a) After 5 mn of equilibration
(b) Stabilized after 1 h 30 of equilibration ; unmodified on standing and by dilution
(c) Immediatly after dissolution; unmodified on standing and by dilution
(d) The initial two signals (as in solid state) observed immediatly after dissolution disappears after 15-20 mn of equilibration.

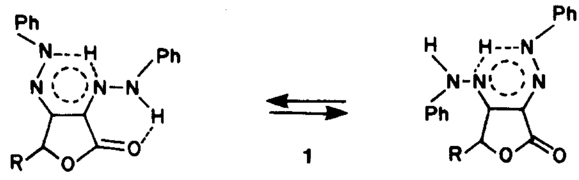
Table 3. Evolution of the UV absorption of compounds **1**–**4b** ($R=CH_3$) on standing in ethanol

| Compd/Time | t=0 | t=18h | t=36h | t=100h |
|---|---|---|---|---|
| 1b | 262 (16040)<br>354 (9020)<br>468 (14400) | 260 (17040)<br>350 (9020)<br>444 (16040) | unmodified | unmodified |
| 2b | 244 (11800)<br>396 (7760) | 244 (13400)<br>304 (8955)<br>396 (4170) | 244 (14200)<br>304 (9250)<br>396 (2014) | 244 (14200)<br>304 (9400)<br>396 (< 1000) |
| 3b | 234 (12440)<br>382 (17900) | unmodified | unmodified | unmodified |
| 4b | 226 (5550)<br>267 (4930)<br>308 (3700) | 222 (6170)<br>267 (4900)<br>308 (sh. 3000) | 230 (8300)<br>267 (sh. 3700)<br>308 (1000) | 230 (8420)<br>267 (sh. 3700) |

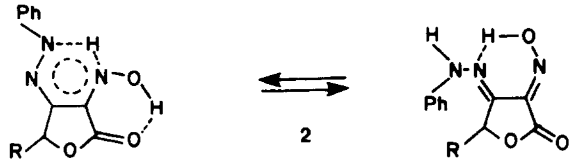
Table 4 Selected $^1H$ NMR data of compounds **1**–**4a** (R=H) (c) in DMSO-$d_6$ ($\delta$, ppm)

| Compd | proton | t=0 | t=10h |
|---|---|---|---|
| 1a | $H_5$<br>NH (a)<br>NH (b) | 5,56<br>10,96<br>12,25 | 5,72<br>12,85<br>10,33 |
| 2a | $H_5$<br>OH (a)<br>NH (b) | 5,1 (0,5H); 5,15 (0,5H)<br>10,33<br>11,26 | 5,15<br>13,58<br>10,26 |
| 3a | $H_5$<br>NH (a)<br>OH (b) | 5,25<br>11,5<br>12,2 | unmodified |
| 4a | $H_5$<br>OH (a)<br>OH (b) | 5,13<br>14,2<br>12,6 | unmodified |

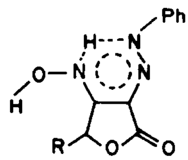
(a) On substituent at C-3
(b) On substituent at C-4; the downfield signals were assigned to the protons intramolecularly bonded with the nitrogen atoms by analogie with sugar osazones [7]
(c) a parallel change was seen for the compounds of series b ($R=CH_3$) but the H-5 multiplet pattern in the ZZ/EE mixtures is not well resolved.



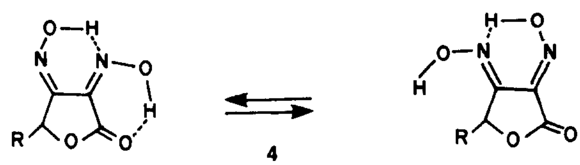
ZZ 1 EE



ZZ 2 EE



EE 3



ZZ 4 EE

Furthermore, it can be pointed out that these high absorption maxima are not, as previously reported,[6] typical of a phenylazo residue in compounds **1**, but are due to the presence of the 5-membered lactone ring adjacent to the chelated system. The bathochromic shift induced by the introduction of a 4-phenylhydrazono group into a tetronic ring could be estimated at about 80 nm by comparing the absorption maxima of 3-oximinotetronic acid ($\lambda_{max} = 316$ nm) and its phenylhydrazone **2a** (396 nm) in the form of the *E,E*-configuration to account for the intramolecular bond involving the phenylhydrazono moiety. The same increment applied to ketone **6** (358 nm) affords a calculated wavelength for osazones **1** (438 nm) in good agreement with the experimental value (444 nm).

## EXPERIMENTAL

$^{13}$C NMR spectra were recorded on a Varian X-100-12FT spectrometer using the natural abundance of $^{13}$C at a concentration of 1M in DMSO-$d_6$ and a probe temperature of 30°. The $^1$H NMR spectra were recorded on a Varian A-60 spectrometer and all the chemical shifts are reported in ppm downfield from tetramethylsilane as internal standard. IR spectra were obtained with a Beckman model Acculab 2 using a RIIC variable cell VC-01 (0.025 mm to 5 mm width) at five successive dilutions ranging from 1% to 0.125% in an appropriate solvent. UV spectra were recorded with a Beckman DB UV-visible spectrophotometer $3.10^{-5}$ M in 95% ethyl alcohol).

Compounds **1**–**4a, b**,[1] **1c**,[5] **6**[16] were prepared as previously described.

Additional $^1$H NMR data (after complete equilibration in DMSO-$d_6$) E,E-form: **1a**: 5.20 (s, 2 H); 6.8–7.7 (m, 10 H); 10.25 (s, 1 H); 12.66 (s, 1 H). **1b**: 1.53 (d, 3 H, J = 7 Hz); 5.71 (q, 1 H, J = 7 Hz); 7.0–7.9 (m, 10 H); 10.25 (s, 1 H); 12.73 (s, 1 H). **2a**: 5.15 (s, 2 H); 6.80–7.70 (m, 5 H); 10.26 (s, 1 H); 13.58 (s, 1 H). **2b**: 1.55 (d, 3 H, J = 7 Hz); 5.58 (q, 1 H, J = 7 Hz); 10.25 (s, 1 H); 13.6 (s, 1 H). **3a**: 5.24 (s, 2 H); 7.1–7.6 (m, 5 H); 11.5 (s, 1 H); 12.2 (s, 1 H). **3b**: 1.63 (d, 3 H, J = 7 Hz); 5.53 (q, 1 H, J = 7 Hz); 7.1–7.6 (m, 5 H); 11.4 (s, 1 H); 12.06 (s, 1 H). **4a**: 5.13 (s, 2 H); 12.66 (s, 1 H); 14.2 (s, 1 H). **4b**: 1.55 (d, 3 H, J = 7 Hz); 5.50 (q, 1 H, J = 7 Hz); 12.66 (s, 1 H); 14.16 (s, 1 H).

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