# NEW FURO[3,2-b]FURANS DERIVED FROM L-ASCORBIC ACID

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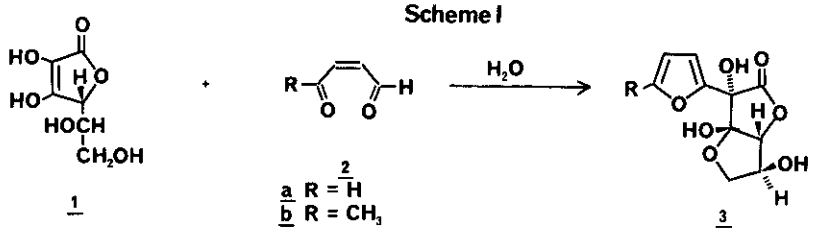
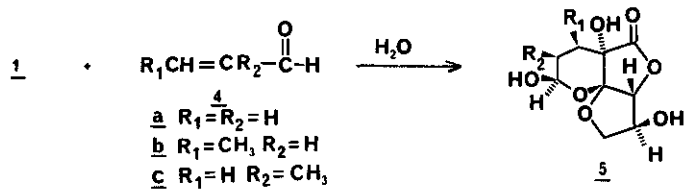
Abstract - The role of ascorbic acid (1) as a Michael carbanion donor has been extended to a cyclic enedione, 2,3-dihydrobenzoquinone (6). Although 6 is a desmotropic form of hydroquinone it reacted with 1 as an α,β-unsaturated monoketone giving rise to 2-(1',4'-diketo-2'-cyclohexyl)-3-keto-L-gulonolactone-3,6-cyclohemiketal which, in turn, was stabilized as the 3,1'-cyclohemiketal (8). The latter structure was proven by X-ray crystallography.

In a previous paper[1] we reported on the reaction of L-ascorbic acid (1) with 1,4-cis-butenedial (2a) and 4-keto-cis-2-pentenal (2b) respectively. The ascorbate-2-carbanion reacted in both cases in the aldol fashion with the aldehyde group, leading ultimately to the formation of 2-furyl derivatives of perhydrofuro[3,2-b]furan (3) (Scheme 1). On the other hand, α,β-unsaturated aldehydes, such as acrolein[2] (4a), crotonaldehyde[3] (4b) and α-methylacrolein[3] (4c) gave the Michael adducts (5) with L-ascorbic acid of the same furo[3,2-b]furan skeleton (Scheme 2). Also, both open chain α,β-unsaturated ketones[2] and cyclic enones[4] lead to Michael adducts (Scheme 3). All new derivatives proved to be furo[3,2-b]furans. Therefore it deemed of interest to explore[5] this newly recognized reactivity of L-ascorbic acid towards an α,β-unsaturated cyclic diketone. As the simplest model cyclohex-2-ene-1,4-dione or 2,3-dihydrobenzoquinone (6) has been selected that was prepared by the (1:1)-Diels-Alder addition of cyclopentadiene to 1,4-benzoquinone followed by hydrogenation of the adduct and a retro-Diels-Alder reaction.[6] (Scheme 4) Surprisingly, this tautomeric form of hydroquinone proved to have spectral data which indicate that it is the stable keto desmotropic modification.[7] Accordingly, it reacted with 1 in the presence of a mineral acid catalyst as a Michael acceptor. As the primary product of addition 2-(1',4'-diketo-2'-cyclohexyl)-3-keto-L-gulonolactone-3,6-cyclohemiketal (7) was expected (Scheme 5). However, the $^{13}C$ nmr spectrum (Figure 1) of the isolated product showed one carbonyl peak at

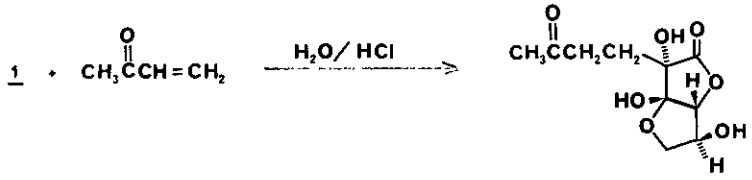
Scheme I

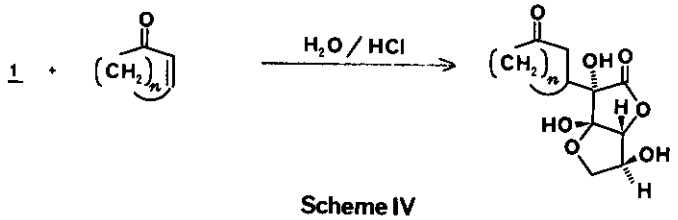


Scheme II

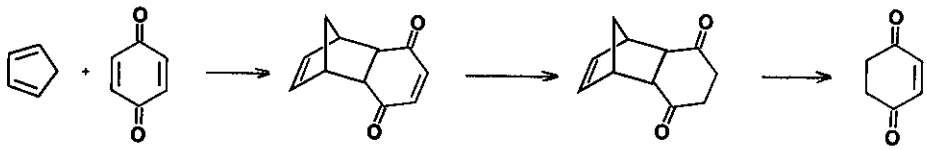


Scheme III

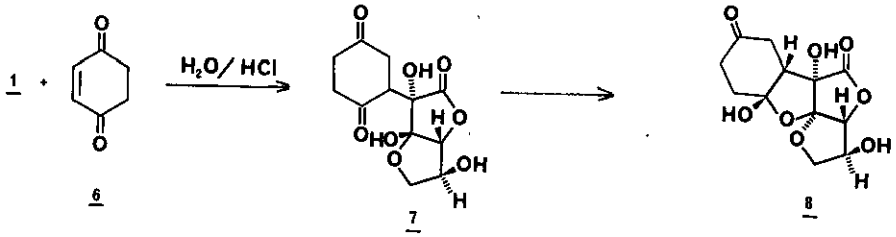




Scheme IV



Scheme V



δ 208.36 ppm and two hemiketal/ketal carbon peaks at δ 114.57 and δ 103.99 ppm, respectively. This evidence indicates the formation of a new hemiketal carbon from the internal cyclization of a hydroxyl with one of the carbonyl groups of the cyclohexanedione substituent. The ir spectrum of the product in solid state also supported this result, showing a single carbonyl absorption at 1700 $cm^{-1}$ besides the γ-lactone absorption at 1780 $cm^{-1}$. A single crystal of the product was subjected to X-ray structure determination. Figure 2 shows the computer drawing that proves the compound having a tetracyclic structure 8 with the following absolute configurations: 2S, 3R, 4R, 5S, 1'R, 2'R.

X-RAY CRYSTALLOGRAPHY DATA

$C_{12}H_{14}O_8$, molecular weight = 286.24, orthohombic, space group $P2_12_12_1$, a = 10.134(3), b = 10.422(3), c = 11.338(3) Å, V = 1194.5 $Å^3$, Z = 4, $d_{calc}$ = 1.587 $g/cm^{-3}$, μ = 0.88 $mm^{-1}$. The 2349 reflections (2119 unique) were measured in the θ/2θ mode to $2\theta_{max}$ = 50° on a computer controlled diffractometer with an incident beam graphite monochromator (Nicolet R3m/v with Mo $K_\alpha$ radiation, λ = 0.71073 Å, T = 295 K). Scan rate was a function of count rate, 6°/min minimum, 30°/min maximum. Corrections were applied for Lorentz and polarization effects, but not for absorption. The structure was solved by direct methods with the aid of the program SHELXTL[8] and refined with a full matrix least-squares.[8] The 193 parameters refined include the coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Carbon hydrogens used a riding model in which the coordinate shifts of the carbons were applied to the attached hydrogens, and C-H = 0.96 Å, and U(H) = 1.1·Ueq(C). The hydroxyl hydrogens were refined isotropically. The final R values for the 1745 observed reflections with $F_o > 3\sigma(|F_o|)$ were R = 0.049 and wR = 0.50. The goodness of fit parameter was 1.512. Tables of coordinates, bond distances and bond angles, have been deposited with the Crystallographic Data Centre, Cambridge, CB2, 1EW, England.

The geometry of 8 is shown in Figure 2 which was drawn from the experimental coordinates. The absolute configuration of 8 was determined by using the known chirality of atoms C(4) and C(5) in L-ascorbic acid as a reference to the four additional chiral centers present. Bond distances and angles fall within expected values and the angles about the carbons involved in ring fusions indicate that the ring system formed without significant strain. The six-membered ring is in a distorted chair conformation (absolute values of ring torsion angles range from 37.1 to 55.9°), and the five-membered rings are distorted envelopes with C(2), C(5), and C(7) out of the least squares plane through the four remaining atoms of the respective rings. The two five-membered ring junctions are cis as is the junction between the five and six-membered rings. The relevant torsion angles are: O(3)-C(3)-C(4)-H(4) = -12.0°, O(2)-C(2)-C(3)-O(6) = 24.7°, and H(7)-C(7)-C(12)-O(12) = 29.6°.

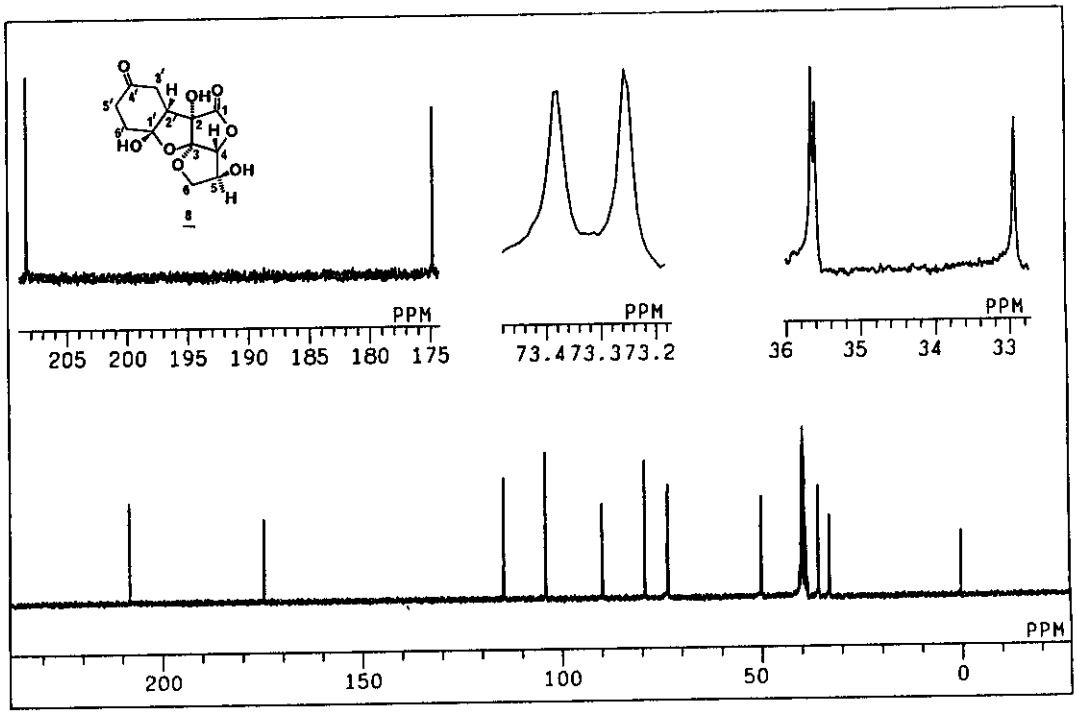



Figure 1. $^{13}C$ Nmr spectrum of 8 in $Me_2SO-d_6$ (TMS).

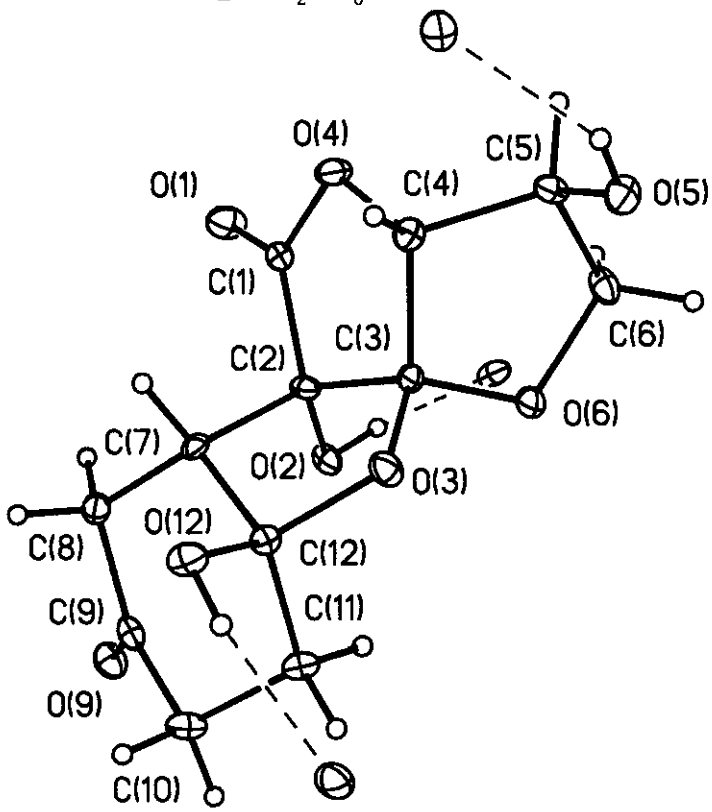



Figure 2. Thermal ellipsoid plot drawn from experimental coordinates of 8. Thermal ellipsoids are drawn at the 20% probability level. The dashed lines represent hydrogen bonds to symmetry related oxygens.

The relatively high density of this compound is due in part to the intermolecular hydrogen bonding present. Three hydrogen bonds are formed with a range of bonding parameters: O--O = 2.80 to 2.86 Å, H--O = 1.99 to 2.22 Å, and angle O-H--O = 152.5 to 172.4°.

Supplementary Material for 2-(1',4'-diketo-2'-cyclohexyl)-3-keto-L-gulonolactone-3,1'-cyclo-hemiketal-3,6-cycloketal.

Table 1. Atomic Coordinates ($x10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$)

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 569(4) | 1683(4) | 5710(4) | 24(1) |
| O(1) | 156(3) | 1532(3) | 4733(3) | 39(1) |
| C(2) | 17(4) | 1204(3) | 6862(3) | 20(1) |
| O(2) | -513(3) | -34(3) | 6761(3) | 26(1) |
| C(3) | 1140(4) | 1398(3) | 7749(3) | 20(1) |
| O(3) | 603(3) | 1880(3) | 8805(2) | 29(1) |
| C(4) | 2081(4) | 2343(4) | 7136(4) | 25(1) |
| O(4) | 1707(3) | 2353(3) | 5899(2) | 32(1) |
| C(5) | 3452(4) | 1757(4) | 7274(4) | 25(1) |
| O(5) | 4084(3) | 2287(3) | 8292(3) | 32(1) |
| C(6) | 3176(4) | 361(4) | 7479(4) | 31(1) |
| O(6) | 1860(3) | 288(3) | 8000(3) | 32(1) |
| C(7) | -1045(4) | 2114(4) | 7362(3) | 20(1) |
| C(8) | -2469(4) | 1827(4) | 6954(4) | 26(1) |
| C(9) | -3123(4) | 770(4) | 7618(4) | 27(1) |
| O(9) | -3838(3) | -10(3) | 7121(3) | 34(1) |
| C(10) | -2934(4) | 763(5) | 8927(4) | 33(1) |
| C(11) | -1468(4) | 842(4) | 9236(4) | 26(1) |
| C(12) | -823(4) | 1996(4) | 8691(3) | 21(1) |
| O(12) | -1198(3) | 3145(3) | 9226(3) | 29(1) |

*Equivalent isotropic U defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

Table 2. Bond Lengths (Å)

| | | | |
|---|---|---|---|
| C(1)-O(1) | 1.194(5) | C(1)-C(2) | 1.506(5) |
| C(1)-O(4) | 1.365(5) | C(2)-O(2) | 1.402(4) |
| C(2)-C(3) | 1.532(5) | C(2)-C(7) | 1.543(5) |
| C(3)-O(3) | 1.409(5) | C(3)-C(4) | 1.536(5) |
| C(3)-O(6) | 1.397(4) | O(3)-C(12) | 1.456(5) |
| C(4)-O(4) | 1.453(5) | C(4)-C(5) | 1.526(5) |
| C(5)-O(5) | 1.430(5) | C(5)-C(6) | 1.499(6) |
| C(6)-O(6) | 1.460(5) | C(7)-C(8) | 1.544(5) |
| C(7)-C(12) | 1.529(5) | C(8)-C(9) | 1.490(6) |
| C(9)-O(9) | 1.226(5) | C(9)-C(10) | 1.496(6) |
| C(10)-C(11) | 1.529(6) | C(11)-C(12) | 1.502(5) |
| C(12)-O(12) | 1.395(5) | | |

Table 3. Bond Angles (°)

| | | | |
|---|---|---|---|
| C(2)-C(1)-O(1) | 129.1(4) | O(4)-C(1)-O(1) | 120.6(4) |
| O(4)-C(1)-C(2) | 110.3(4) | O(2)-C(2)-C(1) | 112.1(3) |
| C(3)-C(2)-C(1) | 104.4(3) | C(3)-C(2)-O(2) | 117.4(3) |
| C(7)-C(2)-C(1) | 111.9(3) | C(7)-C(2)-O(2) | 109.2(3) |
| C(7)-C(2)-C(3) | 101.3(3) | O(3)-C(3)-C(2) | 108.5(3) |
| C(4)-C(3)-C(2) | 104.4(3) | C(4)-C(3)-O(3) | 113.3(3) |
| O(6)-C(3)-C(2) | 114.4(3) | O(6)-C(3)-O(3) | 108.9(3) |
| O(6)-C(3)-C(4) | 107.4(3) | C(12)-O(3)-C(3) | 109.7(3) |
| O(4)-C(4)-C(3) | 106.2(3) | C(5)-C(4)-C(3) | 105.2(3) |
| C(5)-C(4)-O(4) | 109.8(3) | C(4)-O(4)-C(1) | 111.6(3) |
| O(5)-C(5)-C(4) | 109.6(3) | C(6)-C(5)-C(4) | 103.6(3) |
| C(6)-C(5)-O(5) | 109.5(4) | O(6)-C(6)-C(5) | 106.5(3) |
| C(6)-O(6)-C(3) | 110.6(3) | C(8)-C(7)-C(2) | 115.0(3) |
| C(12)-C(7)-C(2) | 102.1(3) | C(12)-C(7)-C(8) | 114.6(3) |
| C(9)-C(8)-C(7) | 114.1(3) | O(9)-C(9)-C(8) | 121.4(4) |
| C(10)-C(9)-C(8) | 116.6(4) | C(10)-C(9)-O(9) | 121.9(4) |
| C(11)-C(10)-C(9) | 110.5(3) | C(12)-C(11)-C(10) | 111.8(4) |
| C(7)-C(12)-O(3) | 103.9(3) | C(11)-C(12)-O(3) | 109.2(3) |
| C(11)-C(12)-C(7) | 113.9(3) | O(12)-C(12)-O(3) | 107.6(3) |
| O(12)-C(12)-C(7) | 108.6(3) | O(12)-C(12)-C(11) | 113.0(3) |

Table 4. Anisotropic Displacement Parameters ($Å^2 \times 10^3$)

| | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 21(2) | 26(2) | 26(2) | 3(2) | 1(2) | 2(2) |
| O(1) | 39(2) | 55(2) | 24(2) | 0(1) | -1(2) | -9(2) |
| C(2) | 20(2) | 17(2) | 24(2) | 1(2) | 7(2) | -3(2) |
| O(2) | 23(1) | 16(1) | 38(2) | -5(2) | 6(1) | 2(1) |
| C(3) | 19(2) | 16(2) | 24(2) | 2(2) | 1(2) | 2(2) |
| O(3) | 22(1) | 42(2) | 24(2) | -3(1) | -2(1) | 0(1) |
| C(4) | 27(2) | 24(2) | 23(2) | -1(2) | -3(2) | 0(2) |
| O(4) | 29(2) | 41(2) | 26(2) | 11(1) | -3(1) | -12(1) |
| C(5) | 21(2) | 31(2) | 23(2) | -2(2) | 3(2) | -6(2) |
| O(5) | 32(2) | 28(2) | 36(2) | 1(2) | -11(1) | -7(1) |
| C(6) | 22(2) | 27(2) | 45(3) | -4(2) | 0(2) | 5(2) |
| O(6) | 22(1) | 27(2) | 47(2) | 12(2) | 3(2) | 2(1) |
| C(7) | 24(2) | 14(2) | 22(2) | 6(2) | 0(2) | -1(2) |
| C(8) | 24(2) | 25(2) | 29(3) | 3(2) | -2(2) | 2(2) |
| C(9) | 19(2) | 27(2) | 34(3) | -4(2) | 0(2) | 4(2) |
| O(9) | 27(1) | 32(2) | 42(2) | -5(2) | -1(2) | -3(1) |
| C(10) | 33(3) | 37(3) | 30(3) | 3(2) | 8(2) | -10(2) |
| C(11) | 34(2) | 24(2) | 21(2) | 1(2) | 4(2) | -6(2) |
| C(12) | 23(2) | 21(2) | 19(2) | -1(2) | -2(2) | -2(2) |
| O(12) | 41(2) | 23(2) | 23(2) | -4(2) | 7(2) | 0(1) |

The *anisotropic displacement exponent* takes the form: $-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$

Table 5. H-Atom Coordinates ($\times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$)

| | x | y | z | U |
|---|---|---|---|---|
| H(4) | 2055 | 3198 | 7449 | 27 |
| H(5) | 4012 | 1911 | 6608 | 28 |
| H(6A) | 3818 | 5 | 8009 | 36 |
| H(6B) | 3198 | -99 | 6746 | 36 |
| H(7) | -956 | 2977 | 7076 | 22 |
| H(8A) | -2445 | 1596 | 6135 | 29 |
| H(8B) | -2985 | 2593 | 7051 | 29 |
| H(10A) | -3295 | 1486 | 9264 | 36 |
| H(10B) | -3295 | -16 | 9246 | 36 |
| H(11A) | -1035 | 83 | 8952 | 29 |
| H(11B) | -1377 | 891 | 10077 | 29 |
| H(2) | 32(38) | -511(40) | 6452(36) | 25(12) |
| H(50) | 4274(45) | 2929(45) | 8158(44) | 35(16) |
| H(12) | -1209(44) | 3008(45) | 9924(41) | 36(14) |

## CONCLUSIONS

The scope of nucleophilic reactivity of L-ascorbic acid towards (activated) electrophiles has been extended to unsaturated 1,4-diketones. 2-Cyclohexene-1,4-dione (dihydrobenzoquinone) reacted as a Michael acceptor, unlike the open-chain unsaturated 1,4-dialdehyde and 4-ketoaldehyde which added the ascorbate carbanion in a 1,2-addition, i.e. aldol mode. However, the two aldehydes led ultimately by a cyclization to a furan stabilization that the diketone cannot show. The yield of our reaction was low (17% isolated product) which could be explained if a part of 2-cyclohexene-1,4-dione underwent tautomeric shift to the aromatic species, hydroquinone that would have escaped reaction with the carbanion donor. The quantitative work-up of our reaction mixture of 1 with 6 is in progress. Unfortunately no resonance energy calculations of 2,3-dihydrobenzoquinone are available while ample data for the studied tautomer were recorded. This rationale is, however, fully supported by Garbisch's kinetic studies on the enolization of 2-cyclohexene-1,4-dione that occurs in aqueous medium but is catalyzed by hydroxide ion. Under our slightly acidic reaction conditions the reaction rates of the Michael addition are obviously competitive with the slow first step of enolization of 2,3-dihydrobenzoquinone. Our previous studies[1,4] on the furo[3,2-b] furans that we have named for convenience as the 3,6-cyclohemiketal of 3-keto-L-gulonolactone, have shown a tautomeric shift towards the 3-ketogulonolactones. This was indicated by a systematic study of $^{13}C$ nmr spectra of the 2-(1'-keto-3'-cycloalkyl)- and the 2-(5'-methyl-2'-furyl) derivatives which showed $^{13}C$ satellites of carbons 4, 5 and 6 that were very close to the carbon shifts of L-ascorbic acid itself. In the case of the diketocyclohexyl derivative (8), however, no trace of satellites was detected (Figure 1). Theoretically, two subsequent steps of tautomerization could have occurred, each leading to the appearance of $^{13}C$ satellites, however this was not observed. Thus the hemiketal-ketal structure of 8 seems to be extremely stable even in solution.

## EXPERIMENTAL

Melting points were determined on a Melt-Temp apparatus and on an Electrothermal melting point apparatus and were uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1310 Infrared Spectrophotometer. $^{1}H$ and $^{13}C$ nmr spectra were recorded on a JEOL JNM-GX270 FTNMR spectrophotometer. Mass spectra were obtained on a Finnigan 4021 mass spectrometer with an INCOS data system by Robert R. Smith (Biochemistry Department, West Virginia University). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Optical rotation measurements were taken on a Perkin-Elmer Model 141 Polarimeter. L-Ascorbic acid (Mallinckrodt) was used without further purification. Cyclohex-2-ene-1,4-dione was prepared as described by Chapman, Musliner and Gates.[6]

2-(1',4'-Diketo-2'-cyclohexyl)-3-keto-L-gulonolactone-3,1'-cyclohemiketal-3,6-cycloketal (8).

L-Ascorbic acid (20.94 g, 0.12 mol) was added to distilled water (82.5 ml) that had been degassed for 1 h with nitrogen. To the resulting solution, cyclohex-2-ene-1,4-dione (13.09 g, 0.12 mol) was added portion-wise with stirring, followed by concentrated hydrochloric acid (0.3 ml). The solution was allowed to stand undisturbed at room temperature for 24 h when the formation of a crystalline solid was observed. The reaction mixture was cooled in an ice-water bath and filtered by suction to give 5.65 g (17%) as colorless solid, mp 198-200°C, $[\alpha]_D^{27}$ = +2.7° (c = 2, methanol). Single crystals were obtained by recrystallization from 2:1 ethyl acetate:methanol.
Ir (KBr) ν, 3450, 3360, 3310 $cm^{-1}$ (s, OH); 2970, 2900 (m, CH); 1780 (s, lactone CO); 1700 (s, CO) $cm^{-1}$. $^1H$ Nmr ($Me_2SO-d_6$) δ 6.75 (1H, OH), 6.44 (1H, OH), 5.65 (1H, OH), 4.64 (1H, s, 4-H), 4.23 (1H, t, J = 6 Hz, 5-H), 3.98 (1H, dd, J = 11 and 6 Hz, 6-H) and 3.86 (1H, dd, J = 11 and 6 Hz, 6-H), 2.62-1.95 (7H, m, cyclohexyl-H). $^{13}C$ Nmr ($Me_2SO-d_6$) 208.36 (C-4'), 174.74 (C-1), 114.57 (C-3), 103.99 (C-1'), 89.79 (C-2), 79.04 (C-4), 73.38 (C-5), 73.25 (C-6), 49.97 (C-3'), 35.65 (C-5'), 35.59 (C-2'), 32.91 (C-6') ppm. Mass m/e 287 $(M+1)^+$, 268, 250, 240, 226, 206, 180, 138, 110 (base peak), 85, 55. Anal. Calc. for $C_{12}H_{14}O_8$: C, 50.35; H, 4.93. Found: C, 50.43; H, 4.92.

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