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(21) Evans and co-workers have observed a similar selectivity for the thioketallization of progesterone (**12**) with ethylenethiobis(trimethylsilane) in the presence of zinc iodide.[7]

## Ascorbic Acid Derivatives. Structure Determinations by Carbon-13 Nuclear Magnetic Resonance

Terence Radford*, James G. Sweeny, and Guillermo A. Iacobucci

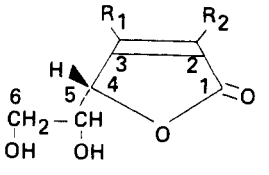
*Corporate Research and Development Department The Coca-Cola Company, Atlanta, Georgia 30301,*

David J. Goldsmith*

*Chemistry Department, Emory University, Atlanta, Georgia 30322*

*Received August 14, 1978*

The well-known susceptibility of L-ascorbic acid toward thermal and oxidative degradation has promoted an interest in derivatives which show increased stability in vitro, while being able to generate antiscorbutic activity in vivo through enzymatic cleavage to free L-ascorbate. In this context the differing chemical reactivities of the two enol groups of L-ascorbic acid were utilized to prepare several monosubstituted, nonreducing derivatives.[1,2] A number of these, including a monosulfate,[3] a monophosphate,[4] and a monomethyl ether,[5,6] were demonstrated to exert vitamin C activity in sensitive species.[7-9] The sulfate is also important as a naturally occurring metabolite of L-ascorbic acid, first found in brine shrimp cysts[10] and since then in the urine of man, monkeys, rats, and guinea pigs.[2]



**1** $R_1 = O^-$ $R_2 = SO_4^-$

**2** $R_1 = OCH_3$ $R_2 = OH$

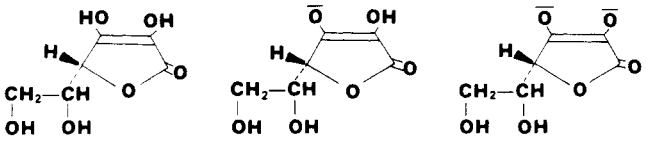
**3** $R_1 = HPO_4^-$ $R_2 = O^-$

**4** $R_1 = O^-$ $R_2 = HPO_4^-$

For a number of years these and several other monosubstituted analogues were regarded as 3-O-substituted L-ascorbic acid derivatives. Recently the dianion of L-ascorbic acid monosulfate was shown to have structure **1** by X-ray diffraction.[11] On the basis of this result prior assignments of substituents to C-3 in other L-ascorbic acid derivatives have been questioned.[2]

We report here $^{13}C$ NMR data and other evidence which supports the structures previously assigned to **1** and **2** but indicate that structure **3** proposed for the dianion of L-ascorbic acid monophosphate[4] should be revised to **4**.

$^{13}C$ NMR chemical shifts have previously been reported for L-ascorbic acid[12] and also a study of their pH dependence was published.[13] The data suggest that species **5**, **6**, and **7** exist in solution under conditions of low, neutral, and high pH, respectively.



**5** **6** **7**

These conclusions are in accord with accepted views regarding the relative acidity of the ene diol protons of L-ascorbic acid,[1] and they are also consistent with the results of X-ray analyses of L-ascorbic acid[14] and its monosodium salt.[15]

Chemical shifts derived from $^{13}C$ NMR spectra of compounds **1**, **2**, and **4**–**6**, determined in aqueous solution at the indicated pH, are given in Table I. It is evident that the C-3 chemical shifts noted for **1** and **4** are close to that observed for the ascorbate monoanion (**6**). Thus the presence of an anion at C-3 is indicated for both **1** and **4**. These results support their formulation as 2-O-substituted derivatives. On the other hand the C-3 chemical shift listed for **2** is clearly consistent with the absence of an anion at C-3 in accord with the previously assigned structure.[5,6]

Confirmatory evidence for the structure of **2** was obtained by chemical modification and mass spectrometry. Hydrogenation of **2** in the presence of Pd–C gave a saturated γ-lactone to which the L-manno configuration was assigned on steric grounds. Reduction of the lactone with sodium borohydride under standard conditions,[16] followed by acetylation, yielded a product **9** whose mass spectrum (Table II) was essentially identical with the spectrum of authentic 1,2,4,5,6-penta-*O*-acetyl-3-*O*-methyl-D-glucitol (**8**), thus confirming the structure of the ascorbic acid methyl ether as **2**. The close similarity between the two sets of data in Table II is to be expected on the basis of previous MS studies of stereoisomeric alditol derivatives.[17]

Further support for structure **2** is available from a $pK_a$ determination.[18] The value obtained, 7.8, is significantly higher than the first acid dissociation constant of **5** (4.25)[19] or the $pK_a$'s of **1** (2.0 and 3.1)[2] and it is only consistent with

**Table I. $^{13}C$ NMR Chemical Shifts of 1, 2, and 4–6 in Water at pH 7.0 with Dioxane as Internal Reference**

| | registry no. | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 |
|---|---|---|---|---|---|---|---|
| 1 | 68582-35-4 | 181.0 | 111.3 | 176.6 | 79.7 | 70.6 | 63.4 |
| 2 | 13443-57-7 | 174.3 | 119.5 | 155.7 | 76.9 | 70.0 | 63.0 |
| 4 | 68582-36-5 | 178.0 | 113.4[a] | 176.5 | 79.4 | 70.5 | 63.4 |
| | | | 113.2 | | | | |
| 6 | 63983-49-3 | 178.2 | 114.1 | 176.3 | 79.3 | 70.5 | 63.6 |
| 5 (pH 2.7) | 50-81-7 | 174.0 | 118.8 | 156.4 | 77.1 | 69.9 | 63.1 |

[a] The origin of this multiplicity was not determined but it probably results from $^{13}C$–$^{31}P$ coupling.

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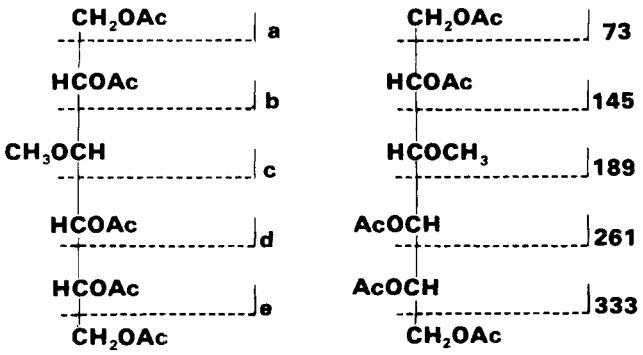
**Table II. Selected Ion Abundances from the EI Spectra of 8 and 9**

| 8[a] | 9[b] | assignment |
|---|---|---|
| 73 (5.2) | 73 (4.2) | a |
| 129 (100.0) | 129 (100.0) | c-$CH_3COOH$) |
| 145 (5.0) | 145 (5.0) | b |
| 189 (77.0) | 189 (71.8) | c |
| 261 (80.5) | 261 (31.5) | d |
| 333 (0.2) | 333 (0.2) | e |
| 347 (1.8) | 347 (2.7) | (M − $CH_3COO\cdot$) |

[a] Registry no., 20250-53-7. [b] Registry no., 68679-97-0.

a structure containing a substituted C-3 hydroxyl.

The variation in reactivities of the C-2 and C-3 hydroxyl groups of L-ascorbic acid may be rationalized in terms of the equilibra (5 ⇄ 6 ⇄ 7). Diazomethane methylation of 5 involves




the more acidic 3-hydroxyl. Conversely, under the basic conditions used to prepare 1 and 4, the dianion 7 predominates and substitution occurs preferentially at the C-2 hydroxyl in accord with its greater basicity.

## Experimental Section

The $^{13}C$ NMR spectra were recorded in $D_2O$ with a Varian CFT-20 spectrometer. Dioxan was used as the internal reference. The mass spectra were obtained at 70 eV using a Dupont 490 spectrometer.

**Reduction of 3-*O*-Methylascorbic Acid (2).** 2 (0.1 g) in ethanol (50 mL) was hydrogenated in the presence of Pd–C. Uptake of the theoretical volume of hydrogen (13.5 mL) and disappearance of the characteristic UV band of 2 (245 nm) were consistent with complete saturation of the olefinic bond. Workup gave a syrup which was reduced with sodium borohydride[16] and acetylated to give 9.

**1,2,4,5,6-Penta-*O*-acetyl-3-*O*-methyl-D-glucitol (8).** 8 was prepared from 3-*O*-methyl-D-glucose (Aldrich) by reduction with sodium borohydride and acetylation.

**Registry No.**—3, 68582-37-6; 7, 63983-50-6; 3-*O*-methyl-D-glucose, 146-72-5.

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# Peracid Oxidation of Aliphatic Amines: General Synthesis of Nitroalkanes

K. E. Gilbert* and W. T. Borden

*Department of Chemistry, University of Washington, Seattle, Washington 98195*

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Nitroalkanes are versatile synthetic intermediates[1] which have recently proved useful in the preparation of alkenes[2] and diazetines.[3] In connection with our work on the synthesis of pyramidalized[4] and torsionally strained[5] alkenes, we required a method for preparing nitroalkanes from amines. Several literature procedures[6] were tried without success before we found that *m*-chloroperbenzoic acid oxidation of amino groups can be made to yield primary and secondary nitroalkanes.[7] Our results are consistent with the intermediacy of nitrosoalkanes in this reaction.

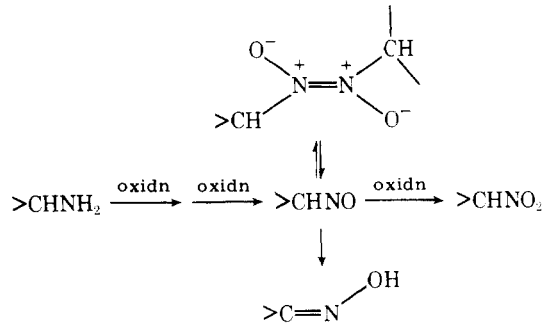
In the early 1950's, Emmons reported that aliphatic amines (cyclohexyl, 2-butyl, and *n*-hexyl) can be oxidized to the corresponding nitroalkanes in good to poor yields (70, 65, and 32%, respectively) with anhydrous peracetic acid.[8] This reagent is not commercially available and was prepared from 90% hydrogen peroxide, which is a hazardous material with which to work. Moreover, as Emmons pointed out, his reaction conditions may facilitate prototropic rearrangement of nitrosoalkane intermediates into oximes, thus leading to reduced yields of nitroalkanes.[8]

Emmons has also reported that oxidation of amines at 0 °C provides a general synthesis of azo dioxides (nitrosoalkane dimers).[9] Since azo dioxides are in equilibrium with nitrosoalkanes, which can be trapped at elevated temperatures with *m*-chloroperbenzoic acid (*m*-CPBA),[3,10] we felt that it should be possible to develop a general, high yield synthesis of nitroalkanes from amines, using *m*-CPBA as the oxidant. In fact, Robinson and co-workers discovered that *m*-CPBA was capable of oxidizing steroidal amines to nitrosteroids,[11] but we have found that their reaction conditions are not generally useful (vide infra).

## Results and Discussion

Attempts to effect direct oxidation of aliphatic amines with 4 equiv of *m*-CPBA in halocarbon solvents gave mixtures of

Scheme I

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