Synthesis of 6-Fatty Acid Esters of L-Ascorbic Acid[1]

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ABSTRACT AND SUMMARY

High yields (85%) of 6-fatty acid esters of L-ascorbic acid were obtained by reacting L-ascorbic acid (1.2 M) in 98-99% sulfuric acid for 36 hr at 20 C with 36% excess fatty acid. In concentrated sulfuric acid, L-ascorbic acid was rapidly sulfated to produce mainly L-ascorbyl 6-sulfate, which slowly reacted with fatty acid to produce L-ascorbyl 6-acylate.

INTRODUCTION

L-Ascorbyl 6-palmitate (**4**) is used as a food additive to retard development of oxidative rancidity (1,2) in high-fat foods. Other useful functions of **4** have been demonstrated in foods: preventing nitrosamine formation while bacon is fried (3), conditioning yeasted doughs (4), lengthening shelf-life of bread (4), and emulsifying carotinoid pigments (5). Although **4** has not been approved as a source of vitamin C in foods in the United States, it has vitamin C potency equivalent to that of L-ascorbic acid (6).

L-Ascorbyl 6-palmitate is synthesized (7) by reacting L-ascorbic acid with palmitic acid in concentrated sulfuric acid. Since L-ascorbic acid is expensive, it is important that **4** be produced in maximal yield. Re-examining the esterification reaction, we found ways to increase the yield of L-ascorbyl 6-laurate, 6-myristate, 6-palmitate, and 6-stearate from ca. 55% to 85%.

RESULTS AND DISCUCSION

The esterification of L-ascorbic acid (**1**) in concentrated sulfuric acid appears at first to be inconsistent with that compound's rapid dehydration in hot acid (8). But UV and optical rotation properties of a solution of **1** in concentrated sulfuric acid showed the skeletal structure of **1** remained intact at 25 C in that medium. After an initial 5% decline, the absorbance of a solution of L-ascorbic acid in 95-98% sulfuric acid remained constant for 46 days. The absorbance maximum of the solution was at longer wavelength (λ_{max} = 265 nm) than that of unionized (9) L-ascorbic acid (pH 2, λ_{max} = 245 nm), which indicates that a delocalized carbonium ion is formed (Fig. 1). The specific optical rotation of a solution of **1** in 99% sulfuric acid is +76° compared to +23° in water (both measured at 25 C).

The hydroxyallyl cation structure (**2**) was supported by carbon magnetic resonance (CMR) data. Olah et al. (10) found that upon protonating *trans*-3-penten-2-one in SO_2ClF solution with HSO_3F - SbF_5, the C-2 and C-4 resonances shifted markedly to lower field ($\Delta\delta$ = -23.3 and -29.0 ppm, respectively), while the C-3 signal shifted much less and to higher field (+2.9 ppm). Dissolving **1** in 99% sulfuric acid (1.25 M) produced six major ^{13}C signals and six minor ones. The major peaks probably arise from **2** (Fig. 1). The changes in chemical shifts of the major peaks in concentrated sulfuric acid with reference to those observed for L-ascorbic acid in methyl sulfoxide solution were as follows: C-1, -13 ppm; C-2, -3 ppm; C-3, -16 ppm; and C-4, C-5, and C-6, -8 ppm. (The minor peaks gave ca. one-fifth the intensity of the major signals and were 0.3-4.0 ppm to lower field, except for C-2 which was 0.3 ppm to higher field. The spectrum 14 min after dissolving **1** was identical to that after 2 hr).

The stability of L-ascorbic acid in concentrated sulfuric acid is significant in preparing 6-fatty acid esters of L-ascorbic acid. Because esterification is an equilibrium reaction, an excess of fatty acid rather than **1** can be used to shift the reaction towards the ester. At the same time, unreacted fatty acid is more easily recovered than is L-ascorbic acid from a reaction mixture.

Most of our esterification reactions were conducted using ⩾ 2M solutions of **1** in 95-99% sulfuric acid and ⩾ 35% excess fatty acid. Thus, the molar excess of sulfuric acid to L-ascorbic acid was at least 790-820%. Polyols undergo several reactions in concentrated sulfuric acid, including protonation, sulfation, racemization, elimination (dehydration), and polymerization (11). Primary alcohols are sulfated (12,13) rapidly in concentrated sulfuric acid, and primary alcohols react three to ten times faster than secondary hydroxyls. We found L-ascorbic acid was indeed sulfated (D.W. Lillard, Jr. and P.A. Seib, in preparation) almost immediately as it dissolved in 99% sulfuric acid at 25 C. The 6-sulfate predominated by a 10:1 margin (ratio of UV absorbances at 245 nm after chromatographic separation) over a minor product, which we have tentatively assigned the 5-sulfate structure, although we cannot rule out the 5,6-disulfate. No 2-sulfation (14) of **1** occurred.

Results with **1** alone in concentrated sulfuric acid help explain the selective 6-acylation of **1** in strong acid. The 1-, 2-, and 3-OHs are not esterified because of their proximity or participation in the hydroxyallyl structure. In fact, dissolution of L-ascorbyl 2-palmitate in 95-98% sulfuric acid gave the thermodynamically more stable L-ascorbyl 6-palmitate (low yield) without a trace of the 2-ester.

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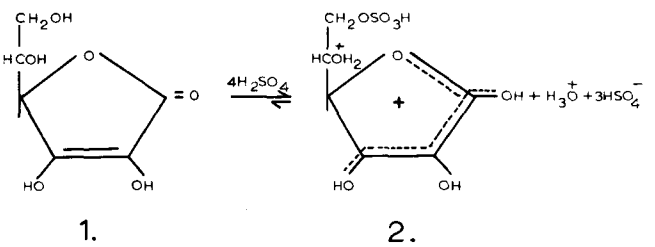
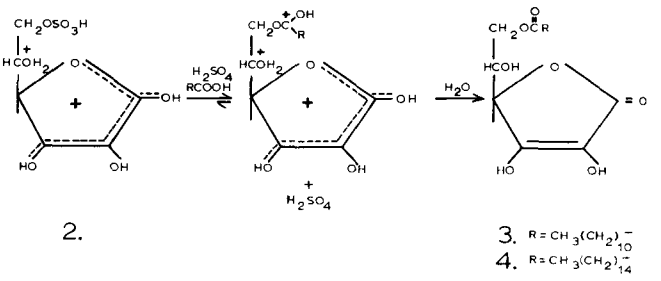


1. 2.

FIG. 1. L-Ascorbic acid in concentrated sulfuric acid.



2. 3. R = $CH_3(CH_2)_{10}^-$ 4. R = $CH_3(CH_2)_{14}^-$

FIG. 2. Formation of L-ascorbyl 6-acylate in concentrated sulfuric acid.

Furthermore, the fact that polysulfates did not form in a large excess of sulfuric acid shows that sulfation of either the 5-OH or 6-OH reduces the reactivity of the neighboring unreacted hydroxyl. The same phenomenon probably retards 5-sulfation of the desired final product, L-ascorbyl 6-acylate.

Isolating high yields of L-ascorbyl 6-acylates indicates that, in the concentrated sulfuric acid medium, formation of a 5-carbonium ion from a protonated 5-OH or from a 5-sulfate apparently is resisted by the positive character of the adjacent 4- and 6-carbons. The 6-carbon is esterified, whereas the 4-carbon is attached to an oxygen involved in resonance stabilization of the carboxonium ion. Racemization at C-5 (and C-4) is minimized since it occurs (13) in concentrated sulfuric acid only after a carbinol is sulfated.

It appears then that 6-acylation of L-ascorbic acid proceeds in two steps, an initial rapid 6-sulfation of **1** followed by slow displacement of bisulfate by an unprotonated carboxylic acid (Figure 2). The proposed reaction mechanism explains why the yield of L-ascorbyl 6-palmitate increased slowly from 23% to 61% in 1 hr to 30 hr, respectively, when **1** was reacted at 25 C with 25% excess palmitic acid in 95-98% sulfuric acid. The driving force for the equilibrium to shift from the 6-sulfate to the 6-acylate (Fig. 2) is the much higher basicity of a carboxylic acid than that of sulfuric acid.

Esterification of L-ascorbic acid (1 M) with 20% excess lauric acid at 26 C for 19 hr in concentrated sulfuric acid produced a maximum yield of L-ascorbyl 6-laurate at an initial sulfuric acid concentration of 98-99% (Fig. 3). Water released by quantitative monoesterification of **1** (1 M) would decrease the weight concentration of sulfuric acid by 1%. When too much water is in the esterification reaction, obviously the equilibrium is displaced away from the ester. As the concentration of sulfuric acid is increased, the yield of the 6-acylate may be lowered through opening (15) the lactone ring or through a higher equilibrium concentration of sulfated species. The side reactions appear less detrimental at lower temperature. Thus, esterification of **1** (1 M) with 36% excess palmitic acid at 20 C for 36 hr gave 82-85% yield in 99% sulfuric acid. Under the same reaction conditions, except for substitution of fuming sulfuric acid (4-5% SO_3) for 99% sulfuric acid, the yield of L-ascorbyl 6-palmitate decreased to 72%. Furthermore, the yield of L-ascorbyl 6-palmitate in any esterification reaction was not substantially improved by increasing the palmitic acid above 35% molar excess.

Response surface methodology (16) (RSM) was used to further refine the conditions to optimize the amount of L-ascorbyl 6-acylate produced in 99% sulfuric acid. The effects of four variables on the yield of L-ascorbyl 6-palmitate were examined: temperature (15-50 C), time (6.3-63.1 hr), excess palmitic acid (0-64%), and concentration of L-ascorbic acid (0.5-1.25 M). From the yields of 31 reactions (RSM experimental design for four variables at five levels), a second order regression equation was derived that explained ~88% of the variability in the yield of the ester. An example of a contour plot showing the yield of ester at various times and temperatures is shown in Figure 4. The curves in Figure 4 and those of other plots showed that good yields of the ester were predicted at the highest possible concentration of L-ascorbic acid (1.25 M), using a minimum of 35% excess palmitic acid and either brief reaction time at a higher temperature (<6 hr at 50 C), or preferably longer reaction times at lower temperature (36-48 hr at 20 C). The solubility of the reactants in sulfuric acid as well as the viscosity of the reaction mixture determined the lowest temperature of a given reaction. For example, 20 C appears to be the lowest temperature for the reaction of palmitic acid (35% excess) with 1.25 M L-ascorbic acid in 99% H_2SO_4. Even without added fatty acid, a 3 M solution of L-ascorbic acid in 99% sulfuric acid at 25 C was extremely viscous.

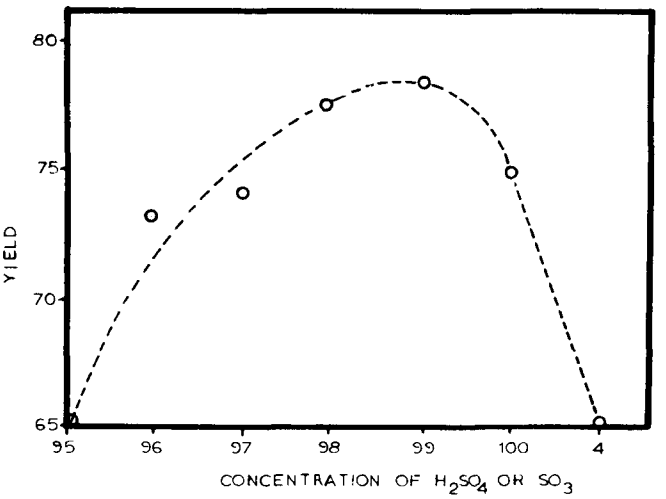


FIG. 3. Esterification of L-ascorbic acid (1 M) in concentrated sulfuric acid or fuming sulfuric acid (4-5% SO_3) with palmitic acid (1.2 M) at 26 C for 19 hr.

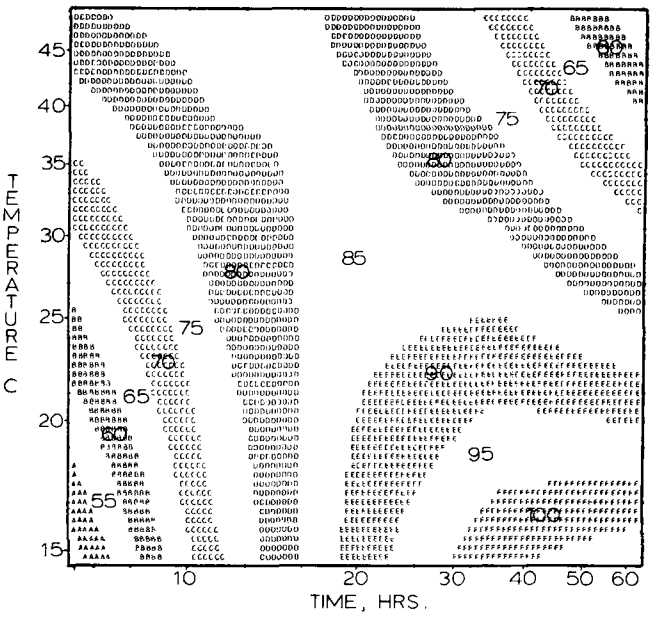


FIG. 4. Contour plot obtained by surface response methodology. Yield of L-ascorbyl 6-palmitate predicted at various times and temperatures for reaction of L-ascorbic acid (1.25 M) in 99% sulfuric acid with 35% excess palmitic acid.

The optimal conditions deduced from the RSM experiment on palmitic acid were also applied to lauric acid. When the reaction conditions originally described by Swern et al. (2) were systematically changed as suggested by the RSM study, the yield of crude L-ascorbyl 6-laurate was increased from 54% to 86% (Table I). The 86% yield of ester was obtained when a 1.25 M solution of L-ascorbic acid was reacted with 35% excess lauric acid for 48 hr at 20 C (reaction 18). Under those reaction conditions, the regression equation predicts an 87% yield. When the esterification was run at 50 C for 4 hr or 8 hr (reactions 13 and 14), a 76% yield of 6-laurate was realized. Increasing the L-ascorbic concentration from 1.25 M to 2.0 M gave no further improvement in yield at 50 C (reactions 15-16).

The ether solubles from an optimized reaction with lauric acid were ~95% pure L-ascorbyl 6-laurate as determined by iodine titration and UV absorbance. No L-ascorbyl 2-

laurate or higher ester fractions were detected by thin layer chromatography (TLC). In addition, the carbonyl region in the ^{13}C spectrum of the crude product in methyl sulfoxide showed only two resonances assigned to C-1 (170.2 ppm) of the L-ascorbyl moiety and to the fatty acid carbonyl (172.5 ppm). Reverse-phase high-performance liquid chromatography failed to resolve contaminants at the 3% level. Thus, the crude product contained little, if any, of either ascorbyl 5-laurate, or 6-esters of stereoisomeric forms of ascorbic acid. Our results indicate that displacement of the sulfate from L-ascorbyl 5-sulfate or its racemate by a fatty acid is very slow in concentrated sulfuric acid. Since C-5 sulfation in sulfuric acid apparently discourages esterification at C-6, high yields of L-ascorbyl 6-acylate appear to depend on minimizing the formation of L-ascorbate 5-sulfate.

EXPERIMENTAL PROCEDURES

General

Solutions were evaporated under diminished pressure below 40 C. Melting points, determined on a Fisher-Johns melting-point apparatus, were not corrected. TLC was performed on plates coated with Silica Gel G (Brinkman Instruments, Inc., Westbury, NY). After the plates were developed in chloroform-acetic acid (4:1), components were located by spraying with 50% aqueous sulfuric acid and charring on a hot plate. A Beckman DB-G spectrophotometer was used to record UV spectra. All solvents were purged with nitrogen (prepurified grade, Matheson Co., Inc., East Rutherford, NJ). Proton-noise-decoupled, CMR spectra were obtained at 25.2 MHz on a Varian XL-100-15 spectrometer fitted with a Nicolet 1080 data system. The spectra were recorded at 30 C in methyl sulfoxide solution (~0.5 M) with 12 mm sample tubes using a pulse time of 30 μsec. The ^{13}C signal of methyl sulfoxide was used as internal calibrant, and the *d*-signal in deuterium oxide in a coaxial tube was used as a lock signal. Chemical shifts were converted to δ_{Me_4Si} by the equation $\delta_{Me_4Si} = \delta_{Me_2SO} - 40.5$. The CMR spectrum of L-ascorbic acid in sulfuric acid was measured with the signal of deuterium oxide in a coaxial tube as lock signal. The deuterium oxide contained sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS), which was used as reference signal. L-Ascorbic acid was obtained from ICN Pharmaceuticals, Inc., Cleveland, OH. Lauric acid (Aldrich Chemical Co., Inc., Milwaukee, WI) was 99.5% pure (mp 44-6 C) and palmitic acid (Sigma Chemical Co., St. Louis, MO) was 99% pure. Absolute sulfuric acid was prepared by the "fair and foggy" method described by Kunzler (17). Other concentrations of sulfuric acid were prepared by diluting absolute sulfuric acid or 99% sulfuric acid (37.0 ± 0.15 N, Fisher Scientific, Fairlawn, NJ). Sulfuric acid containing ca. 4-5% sulfur trioxide was prepared by diluting 10.0 ml (18.97 g) of fuming sulfuric acid (20-23% SO_3) with 39.2 ml (71.8 g) of 100% sulfuric acid.

L-Ascorbic Acid in Sulfuric Acid

A solution of L-ascorbic acid (**1**, 2.8 x 10^{-5}M) in 95-98% sulfuric acid was stored at room temperature. Samples were withdrawn at intervals and their absorbances measured at the solutions's λ_{max} of 264 nm. The times and absorbance readings were: 0 hr, 0.245; 19 hr, 0.232; 90 hr, 0.235; 290 hr, 0.233; 430 hr, 0.235; and 1100 hr, 0.235 (ϵ = 8.4 x 10^3). The specific rotation of L-ascorbic acid in concentrated sulfuric acid after 10 min and 48 hr was $[\alpha]_D^{27^\circ}$ + 76° (*c* 8.0, 99% H_2SO_4).

The CMR spectrum of a 1.25 M solution of **1** in 99% sulfuric acid was measured 14 min to 2 hr after dissolution. The strong acid solution gave six major and six minor ^{13}C signals. The chemical shifts for L-ascorbic acid in methyl sulfoxide were assigned from the proton-coupled spectrum and from the spectrum of 4-deuterio-L-ascorbic acid (18).

Compound	C-1	C-2	C-3	C-4	C-5	C-6
L-Ascorbic acid in methyl sulfoxide	170.9	118.2	153.2	75.0	68.8	62.4
L-Ascorbic acid in sulfuric acid						
major peaks	183.2	121.1	167.9	82.6	76.8	70.8
minor peaks	183.5	120.8	169.5	84.5	80.8	72.6

L-Ascorbyl 6-Palmitate; Yield Related to Reaction Time

The procedure described by Swern et al. (7) was used except L-ascorbic acid was decreased so that palmitic acid was the limiting reagent. Palmitic acid (20 mmole) was added to a solution of L-ascorbic acid (16.0 mmoles) in 50 ml of sulfuric acid (initially 95-98%). After being stirred 1 hr at 30 C, the homogeneous reaction mixture was allowed to stand at 25 C an additional 3-30 hr. The solution was then poured with rapid stirring onto 300 g of crushed ice, and the mixture extracted with ether (1 x 400 ml, 1 x 100 ml). The combined organic layers were gently washed with brine (5 x 75 ml), and the brine extracts were combined and washed with ether (200 ml). The combined ether layers were dried over sodium sulfate, and evaporated. The solid residue was extracted with hexane (3 x 350 ml), and the insoluble material was dried in a vacuum desiccator. Evaporation of the petroleum ether extracts gave 1.5-2.3 g of palmitic acid containing only traces of L-ascorbyl 6-palmitate (TLC). The reaction times in hours and yields of crude ester (%) were: 1(23), 4(40), 8(45), 20(53), 23(52), and 30(61).

Each product had mp 100-112 C and gave a single spot (R_f = 0.4) on TLC. The ether-soluble, hexane-insoluble products had 95-96% of the iodine-reducing capacity of L-ascorbic acid, and 93-96% of the absorbance of L-ascorbic acid (λ_{max} = 264 nm at pH 7.0). The purity assay of the crude material obtained from the 30 hr reaction mixture is given as an illustration. The dry, crude product (50.0 mg) reduced 1.70 ml of ~0.1N iodine solution compared with 4.22 ml reduced by 25.0 mg L-ascorbic acid. All solvents were nitrogen-purged before being used in UV measurements. The crude product (100 mg) was dissolved in ethanol (250 ml), and an aliquot (5.0 ml) was added to water (~90 ml). The solution was adjusted to pH 7 with 1M aqueous sodium hydroxide, the solution made to volume (100 ml), and the absorbance read at 265 nm (A = 0.310). With the same dilutions and the same period of time for each step, L-ascorbic acid (50.0 mg), which was originally dissolved in a mixture of ethanol and water (75:25, v/v) and finally in water, gave A_{265nm} 0.760 (ϵ = 13.4 x 10^3).

Crystallization of crude L-ascorbyl 6-palmitate from chloroform gave better recovery (90%) of purer material than that (60%) by crystallization from a mixture of ethyl ether and petroleum ether. The pure material had mp 115-6 C, $[\alpha]_D^{25^\circ}$ + 21.0° (*c* 2, methanol), lit. (7), mp 116-117 C. CMR data (ppm) obtained in methyl sulfoxide solution were as follows: C-1 (170.2), C-2 (118.2), C-3 (152.1), C-4 (75.1), C-5 (65.6), C-6 (64.5), C = 0 of palmitoyl group (172.5), and eight signals (12-33) for the aliphatic carbons of the palmitoyl group.

Anal. Calc. for $C_{20}H_{34}O_7$: C, 63.70; H, 9.24. Found: C, 63.44; H, 9.21.

Effect of Sulfuric Acid Concentration on Esterification

Six esterification reactions were run in concentrated sulfuric acid (95%, 96%, 97%, 98%, 99%, and 100%) and one in fuming sulfuric acid (4-5% SO_3). To 25 ml of sul-

TABLE I

Preparation of L-Ascorbyl 6-Laurate

Reaction	Sulfuric acid	Initial L-ascorbic acid, M	Lauric acid % excess	Reaction period, hr	Temp., C	Yield[a], %
1[b]	95%	0.5	−20	16	25	54[c]
2	99%	0.5	−20	16	25	50
3	95%	1.0	−20	16	25	49
4	95%	0.5	+35	16	25	62
5	95%	0.5	−20	48	25	50
6	99%	0.5	−20	48	25	63
7	99%	1.0	−20	16	25	64
8	99%	0.5	+35	16	25	70
9	95%	1.0	+35	16	25	64
10	95%	1.25	+35	19	25	65
11	95%	0.5	+35	48	25	50
12	95%	1.0	−20	48	25	57
13	99%	1.25	+35	4	50	76
14	99%	1.25	+35	8	50	76
15	99%	2.0	+35	2	50	75
16	99%	2.0	+35	6	50	74
17	99%	1.25	+35	19	25	79[d]
18	99%	1.25	+35	48	20	86[d]
19	99%	1.25	+35	42	25	77

[a]Calculated from weight of chromatographcally pure product and based on L-ascorbic acid. Yield precentages reproducible to ± 3%.

[b]Reaction conditions identical to those used in Reference (1).

[c]Determined to be 93% pure by comparison of the sample's UV absorption (265 nm and pH 7.0) with that of an analytically pure sample of L-ascorbyl 6-laurate.

[d]Determined to be 96% pure, see footnote c.

furic acid (95-100%) or fuming sulfuric acid (4-5% SO_3) was added lauric acid (30 mmole) and L-ascorbic acid (25 mmole). After 19 hr at 26 C crude L-ascorbyl 6-laurate (mp 97-105 C, ∿95% pure) was isolated as previously described. Results are shown in Figure 3.

Pure L-ascorbyl 6-laurate was obtained by crystallization from chloroform-petroleum ether(3:2; v/v): mp 109-110 C, $[\alpha]_D^{25}$ + 21.9° (*c* 4.0, methanol); lit. (7) 105.5-6.5 C.

Anal. Calc. for $C_{18}H_{30}O_7$: C, 60.31; H, 8.44. Found: C, 60.61; H, 8.49.

A second series of esterifications were run at various sulfuric acid concentrations (1 M in L-ascorbic acid) with palmitic acid under somewhat different reaction conditions (reaction period 36 hr at 20 C and 36% excess palmitic acid). The results are given below:

Sulfuric acid concentration, (%)	98.5	98.8	99.0	99.3	99.5	4-5% SO_3
Yield of L-Ascorbyl 6-palmitate, (%)	79	82	82	85	85	68

Response Surface Analysis

Effects of four variables on the yield of L-ascorbyl 6-palmitate were examined with response surface methodology (16). The factorial experimental design for four independent variables at five levels called for 31 reactions. Independent variables were time (t), temperature (T), concentration of L-ascorbic acid or volume of sulfuric acid (V), and excess palmitic acid (X); all reactions were run on 25 mmoles of L-ascorbic acid in 99% sulfuric acid (initial concentration). Reaction time varied from 6.3 to 63.1 hr (increment was log t = 0.25), temperature from 14.8 C to 49.0 C (increment was log T = 0.13), volume of sulfuric acid from 20 ml to 50.0 ml (increment was log V = 0.1), and excess palmitic acid (X) from 0 to 64% (increment was X½). Reaction mixtures were stirred until the solids dissolved, then let stand at the appropriate reaction temperature (± 1.5 C). At the end of the reaction period, all reactions were homogeneous except those run at 14.8 C. The ester was isolated in ∿95% purity as previously described.

The regression equation, (R^2 value of 0.78) was derived by a least-squares computer program. Y (% yield) = 70.4 + 3.946t + 3.321T - 4.146V + 4.379X - 5.569tT + 2.681TV - 3.531T^2 .

In a separate series of esterifications with lauric acid, the reaction conditions described by Swern et al. (7) were systematically changed as suggested by the regression equation. L-Ascorbyl 6-laurate was isolated as previously described. The results are given in Table I.

Conversion of L-Ascorbyl 2-Palmitate to L-Ascorbyl 6-Palmitate

The method of preparing L-ascorbate 2-palmitate was a modification of that described by Nomura and Sugimota (19). To a mixture of 5,6-*O*-isopropylidene-L-ascorbic acid (20; B.M. Tolbert, personal communication) (28 g) in dry pyridine (39 ml) and dry acetone (1200 ml, 0.04% water) was added palmitoyl chloride (43.5 g). The mixture was stirred at 25 C for 0.5 hr and concentrated to 3000 ml. After hexane (500 ml) was added, pyridine hydrochloride (15 g) was removed by filtration, and the filtrate was concentrated to dryness. The residue (75 g) was crystallized from 2000 ml of a mixture (7:1, v/v) of hexane and carbon tetrachloride. A solution of the crystalline mass (54 g) in ether (1700 ml) was washed with aqueous copper (II) sulfate (5 x 150 ml), dried over anhydrous sodium sulfate, and evaporated to dryness. The solid residue (46 g), which had mp 96-107 C, appeared homogeneous on TLC (R_f 0.8). The solid material (46 g) was deacetonated by dissolving in dry methanol (500 ml) to which had been previously added 4.0 ml of acetyl chloride. After being stirred 30 min, the solution was concentrated to 200 ml and ether (1200 ml) was added. The ether solution was washed with water (1 x 600 ml), dried, and evaporated to dryness. The solid residue (36 g) was slurried twice with hexane (2 x 600 ml), and the undissolved solids crystallized from petroleum ether-chloroform (3:2, v/v). Yield was 14.0 g (38%) of chromatographically pure (TLC, R_f 0.3) L-ascorbyl 2-palmitate, mp 95-104C; lit. (19), mp 105 C.

Anal. Calc. for $C_{22}H_{38}O_7$: C, 63.74; H, 9.24. Found: C, 63.98; H, 9.38.

The compound was assigned the 2-palmitate structure

based on (a) the reported ionization constants of esters of L-ascorbic acid, and (b) on CMR. The 2,6- di- and 2,5,6-triacylates of L-ascorbic acid, which had been previously prepared (21) by the action of acid chlorides on L-ascorbic acid in pyridine-acetone, were found (21) to have pKa_1 values of 1.9-2.2. It is highly unlikely that the ionization constant of the 2-OH of L-ascorbic acid (pK_1 of 3-OH = 4.25, pK_2 of 2-OH = 11.79) (22) would change by nine orders upon esterification of the 3-OH. The 3-OH of L-ascorbate 2-sulfate, whose structure is known (23) from x-ray crystallography, gave (24) an ionization constant with pK_1 2.77. CMR of L-ascorbic acid (1) and L-ascorbyl 2-palmitate (D.W. Lillard, Jr. and P.A. Seib, in preparation) in methyl sulfoxide readily confirmed the latter compound was unsubstituted at the 5- and 6-OHs. Assignments of the chemical shifts (ppm) of the ^{13}C-resonances of L-ascorbyl 2-palmitate were as follows: C-1 (170.0); C-2 (112.3); C-3 (163.6); C-4 (75.4); C-5 (68.7); C-6 (61.8), carbonyl of palmitoyl group (167.8), and eight resonances (14-33) of the aliphatic carbons of the palmitoyl group.

L-Ascorbyl 2-palmitate (16 mmoles) was stireed at 25 C in 50 ml of sulfuric acid (95-98%). After 30 min the mixture was homogeneous, and was poured onto 300 g of crushed ice. The reaction product, which was isolated in the normal manner, was found by TLC to be pure L-ascorbyl 6-palmitate (R_f 0.5) with no trace of L-ascorbyl 2-palmitate (R_f 0.3). The crude product (1.4 g, 20%) was crystallized from chloroform to give pure material with mp 115-6 C.

ACKNOWLEDGMENTS

J. Paukstelis and D.D. Mueller obtained and interpreted the CMR spectra.

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[Received February 14, 1977]