hydrochloride as prisms, m.p. 144~145°(from MeOH-ether). *Anal.* Calcd. for $C_{17}H_{25}O_2N \cdot HCl$: C, 65.47; H, 8.40; N, 4.49; Cl, 11.37. Found: C, 65.56; H, 8.44; N, 4.53; Cl, 11.51. IR ν_{max}^{KBr} cm^{-1} : 3375 (OH), 2650 (N^+H).

N-Methylation of the Acetoxy-1-benzazepin-2-one (XXVI)—The acetoxy-1-benzazepin-2-one (XXVI) (90 mg.) was methylated with NaH and CH_3I by the same method as described for the N-methylation of the benzazepin-1-one (XXV). The resulting N-methylbenzazepinone (XXVIII) (86 mg.) was crystallized from petroleum ether as prisms, m.p. 115°. *Anal.* Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.72; H, 7.71; N, 4.35. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1738, 1650 (CO). UV λ_{max}^{EtOH} $m\mu$ (log ϵ): 247 (4.44), 290 (shoulder 3.65).

Reduction of the N-Methyl-1-benzazepin-2-one (XXVIII) with Lithium Aluminum Hydride—The N-methyl-1-benzazepin-2-one (XXVIII) (90 mg.) in THF (50 ml.) was heated under reflux with $LiAlH_4$ (114 mg.) for 4 hr. Working up in the usual manner gave a basic oil which was chromatographed in $CHCl_3$ on Al_2O_3 . The $CHCl_3$ eluate gave the hydroxy-1-benzazepine (III) (64 mg.) as an oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3686 (OH). UV λ_{max}^{EtOH} $m\mu$ (log ϵ): 254 (3.83), 299 (3.38). $\lambda_{max}^{EtOH-HCl}$ $m\mu$ (log ϵ): 225 (4.02), 280 (3.19).

The oily amine (III) gave the crystalline hydrochloride, m.p. 134~136°(from MeOH-ether). *Anal.* Calcd. for $C_{17}H_{25}O_2N \cdot HCl$: C, 65.47; H, 8.40; N, 4.49; Cl, 11.37. Found: C, 65.41; H, 8.38; N, 4.41; Cl, 11.43. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3650 (OH), 2480 (N^+H).

Summary

4-Acetoxy-7'-methoxyspiro[cyclohexane-1,1'(2'H)-naphthalen]-4'(3'H)-one (XXIV) has been synthesized and subjected to the Schmidt reaction to give the isomeric benzazepinones (XXV and XXVI). N-methylation followed by reduction with lithium aluminum hydride of these compounds (XXV and XXVI) afforded the 1- and 2-benzazepine (II and III), respectively. In contrast to the inhibitory effect of galanthamine (I) on acetylcholinesterase, neither of these two synthetics showed appreciable anticholinesterase activity.

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143. Hiroaki Nomura and Keiichi Sugimoto: Synthesis of L-Ascorbic Acid Acyl Derivatives stabilized against Oxidation.*1

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Benzoylations of the enediol system in L-ascorbic acid have been studied with the aim of obtaining L-ascorbic acid derivatives which are antiscorbutically active and stabilized against oxidation.

This paper deals with the relationship between the reaction conditions and the structures of the products which were inter alia identified as 2-O-benzoyl-L-ascorbic acid, 3-O-benzoyl-5,6-isopropylidene-L-ascorbic acid, 2,6-di-O-benzoyl-L-ascorbic acid, 3,6-di-O-benzoyl-L-ascorbic acid, and 3,5,6-tri-O-benzoyl-L-ascorbic acid as shown in Chart 1.

Only a few reports relate to the syntheses of the acyl derivatives of L-ascorbic acid in which the enediol system has been acylated; these include 3-acetyl-5,6-isopropylidene-L-ascorbic acid,¹⁾ tribenzoylated-L-ascorbic acid²⁾ and 3-palmitoyl-L-ascorbic acid.³⁾

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1) C. S. Vesting, M. C. Rebstock: J. Biol. Chem., **152**, 585 (1944).

2) F. Hoffmann-La Roche & Co.: Ger. Pat., 701561 (1940).

3) H. A. Staab, A. Mannschreck: Chem. Ber., **95**, 1293 (1962).

Theoretically, partial acylations of the enediol system would give rise to the following two isomers (I) and (II) (Chart 2, R=acyl).

Although the color reaction with ferric chloride can be used to determine whether it is I or II, little attention has been paid³⁾ to the fact that acyl groups of the partially acylated L-ascorbic acids are rather labile and might have been migrated during the color reaction. In fact, most acylated L-ascorbic acids give blue or violet coloration with aqueous or ethanolic ferric chloride under neutral or slightly alkaline medium where the acyl migration may readily arise, and care should therefore be taken in determining the structure of acyl ascorbic acid derivatives. In the present studies physical measurements such as infrared (IR) and nuclear magnetic resonance (NMR) spectra have been found rather informative and successfully used for this purpose.

The benzoylation of one mole of 5,6-isopropylidene-L-ascorbic acid at room temperature with five moles of benzoyl chloride and two and half moles of pyridine, yielded a dibenzoyl-L-ascorbic acid (III), m.p. 103~104°.

Chart 3.

TABLE I. Infrared Absorption Spectra of Benzoylated
L-Ascorbic Acids in Carbon Tetrachloride
($\sim 10^{-4}$ mol./L.)

Compounds	Hydroxyl (cm^{-1})		
2-O-Benzoyl-5,6-cyclohexylidene-, (VI)	—	3530	—
3-O-Benzoyl-5,6-isopropylidene-, (VII)	—	3470	—
2,6-Di-O-benzoyl-, (III)	—	3543	3601
3,6-Di-O-benzoyl-, (IV)	3140	3590	3632
3,5,6-Tri-O-benzoyl-, (V)	3140	—	—

TABLE II. Nuclear Magnetic Resonance Spectra of Benzoylated L-Ascorbic Acid (60 Mc.p.s.)

Compounds	Solvent					
	Trifluoroacetic acid			Deuteriochloroform		
	4-H	5-H	6-H ₂	4-H	5-H	6-H ₂
2-O-Benzoyl-	4.56 d	5.35 m	5.72 m	—	—	—
3-O-Benzoyl-5,6-isopropylidene-	4.88 d	5.25 m	5.53 m	5.24 d	5.58 m	5.83
2,6-Di-O-benzoyl-	4.13 d	5.22 s	5.22 s	4.52 d	5.84 s	5.84 s
3,6-Di-O-benzoyl-	4.60 d	5.10 s	5.10 s	5.02 d	5.43 s	5.43 s
3,5,6-Tri-O-benzoyl-	4.38 d	3.74	4.96	4.74 d	4.03 m	5.25 m
6-O-Benzoyl-	4.77 d	5.18 s	5.18 s			
6-O-Stearoyl-	4.87 d	5.39 s	5.39 s			

Multiplicities of signals are represented as: d (doublet), s (broad singlet), m (multiplet).

While treatment of L-ascorbic acid with benzoyl chloride and pyridine in the mole ratio of 1:2:3, yielded another dibenzoyl-L-ascorbic acid (N), m.p. 149~151°. Compounds (III) and (N) were both acidic, and required one equivalent of sodium hydroxide for

neutralization, gave intense violet colors with ferric chloride and were not attacked by an iodine solution.

In the infrared spectrum measured in a very dilute carbon tetrachloride solution, in which intermolecular interaction can be neglected, compound (III) showed absorption maxima at 3601 cm^{-1} and 3543 cm^{-1} , the latter absorption being attributed to an intramolecular hydrogen bond between C_3 and C_5 hydroxyl groups (Chart 3).

On the other hand, compound (IV) showed a characteristic strong and broad band with absorption maximum at 3140 cm^{-1} , indicating that of very strong hydrogen bond attributable to a chelated hydroxyl adjacent to a carbonyl group was present.

The nuclear magnetic resonance spectra are shown in Table II. Except for the aromatic protons in the lower field, compound (III) showed two set of resonance signals, namely a doublet ($\tau=4.13$, $J=2\text{ c.p.s.}$) for the proton attached to carbon-4 and a broad singlet ($\tau=5.2$) for the three protons at carbon-5 and -6. The spectrum of compound (IV) similarly showed a doublet ($\tau=4.60$, $J=2\text{ c.p.s.}$) and a broad singlet ($\tau=5.10$). The intensity ratio 1:3 indicates that the both hydroxyls at carbon-6 of compound (III) and (IV) are benzoylated and that the proton signals due to carbon-6 and carbon-5 are overlapping. That the signal due to the proton at C-4 in compound (IV) is upfield shifted from that for the corresponding proton in III might suggest that the former receives a shielding effect due to the benzoyl group.

During the progress of our investigations, Kobayashi, *et al.*⁴⁾ reported the synthesis of a di-O-benzoyl-L-ascorbic acid, m.p. $152\sim153^\circ$, for which they proposed the structure "2,6"-di-O-benzoyl-L-ascorbic acid, on ambiguous evidence. By our hand it was proved that the compound was identical with compound (IV) by direct comparison of the IR spectra and mixed melting point determination, and therefore the compound should be corrected to 3,6-di-O-benzoyl-L-ascorbic acid.

In order to obtain 2,5,6-tri-O-benzoyl-L-ascorbic acid, a mixture of one mole of L-ascorbic acid, ten moles of benzoyl chloride and five moles of pyridine in acetone was refluxed for 30 min. and after working up by the usual processing was obtained a tribenzoyl derivative, which melted at $188\sim189^\circ$. This compound, however, turned out to be 3,5,6-tri-O-benzoyl-L-ascorbic acid (V) rather than 2,5,6-isomer on the basis of IR absorption spectra. ($\nu_{\text{max}}^{\text{CCl}_4}=3140\text{ cm}^{-1}$ (chelated hydroxyl)). Compound (V) was also prepared by the method previously reported by German Patent²⁾ in which the structure had been left undetermined.

Two isomeric monobenzoyl L-ascorbic acids were prepared as follows:

Treatment of 5,6-isopropylidene-L-ascorbic acid in acetone with one mole of benzoyl chloride and a half mole of pyridine gave a monobenzoyl derivative, m.p. $158\sim160^\circ$ (VI). Similarly, treatment of 5,6-isopropylidene-L-ascorbic acid with one mole of benzoyl chloride and 3 moles of pyridine yielded another monobenzoyl product (VIII), m.p. $148\sim150^\circ$. The IR spectra of 2-O-benzoyl-5,6-cyclohexylidene-L-ascorbic acid (VII) measured in a dilute carbon tetrachloride showed the absorption at 3528 cm^{-1} , while 3-O-benzoyl-5,6-isopropylidene-L-ascorbic acid (VIII) revealed its IR band at 3470 cm^{-1} thus providing evidence for the proposed structures. The NMR spectra indicated that the chemical shift of the proton at C-4 in compound (VIII) appeared upfield from that for the corresponding proton in 2-O-benzoyl-L-ascorbic acid (VI). Although the IR band corresponding to enolic hydroxyl of VIII appeared somewhat in a high frequency, our presumption that compound (VIII) was 3-benzoyl-5,6-isopropylidene-L-ascorbic acid and that the other compound (VI) 2-O-benzoyl-L-ascorbic acid seems most reasonable.

Compound (III) was also obtained by careful treatment of VI with two moles of benzoyl chloride and one mole of pyridine.

4) K. Kobayashi, *et al.*: Japan. Pat. Appl., 9134 (1965).

TABLE III. Ultraviolet Absorption Maxima and PK Values of Benzoylated L-Ascorbic Acid

UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (ϵ)	234 (1.97×10^4)	230 (2.3×10^4)	237 (3.2×10^4)	230 (3.2×10^4)	230 (5.9×10^4)
PK (MeOH)	6.45	4.20	5.90	4.00	4.00

As indicated in Table III the UV spectra and PK values were consistent with the structures proposed, *i.e.*, 3-O-benzoyl derivatives of L-ascorbic acid, IV, V and VIII, showed absorption maximum at 230 m μ in ethanol, while 2-O-benzoyl derivatives, III and VI, showed maxima at longer wave lengths.

The potentiometric titration technique indicated that 3-O-benzoyl derivatives were stronger in acidity than 2-O-isomers.

It has been observed that acyl groups attached to sugar hydroxyls tend to migrate to a neighboring position in the presence of base and that the acyl migration occurs in a direction away from the carbonyl group of the sugar.^{5,6)} In our case compound (III) was isomerized to IV in a few minutes at room temperature in the presence of base.

Another example of acyl group migration observed was that compound (VI) on treatment with base yielded 6-O-benzoyl-L-ascorbic acid (K) which is prone to attack by an iodine solution and gave a similar NMR spectrum to that of 6-stearoyl-L-ascorbic acid.

These arguments together with the UV, IR, and NMR data as well as PK values of various benzoyl derivatives of L-ascorbic acid prepared are consistent with theoretical considerations based on the proposed structures.

Experimental*3

2,6-Di-O-benzoyl-L-ascorbic Acid (III)—To a solution of 4.3 g. of 5,6-isopropylidene-L-ascorbic acid in 200 ml. of acetone were added 4 ml. of pyridine and 14 g. of benzoyl chloride. The mixture was stirred for one hour at room temperature. Then 20 ml. of methanol was added and after stirring for 10 min. the solvent was evaporated under reduced pressure. The residue was repeatedly washed with water and with benzene, followed by recrystallization from benzene, affording colorless needles (yield 7 g.). m.p. 103~104°. (*Anal.* Calcd. for $\text{C}_{20}\text{H}_{16}\text{O}_8 \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 61.07; H, 4.33. Found: C, 61.04; H, 4.34).

3,6-Di-O-benzoyl-L-ascorbic Acid (IV)—To a solution of 3.5 g. of L-ascorbic acid in 30 ml. of dimethyl formamide were added 4.8 ml. of benzoyl chloride and 4.8 ml. of pyridine. After stirring for 3 hr. at room temperature, the solution was evaporated. The residue was washed repeatedly with water, then with ether and recrystallized from carbon tetrachloride to give colorless needles. 3.9 g. (51%), m.p. 149~151°. (*Anal.* Calcd. for $\text{C}_{20}\text{H}_{16}\text{O}_8$: C, 62.50; H, 4.17. Found: C, 62.34; H, 4.18).

3,5,6-Tri-O-benzoyl-L-ascorbic Acid (V)—a) A mixture of 4.4 g. of L-ascorbic acid, 35 g. of benzoyl chloride and 10 ml. of pyridine in 100 ml. of acetone was refluxed for 30 min. To the reaction mixture methanol was added, and after stirring for 30 min. at room temperature the solvent was evaporated, followed by washing with water and then with benzene. Recrystallization from methanol gave prisms (yield 10.8 g., 90%), m.p. 188~189°. (*Anal.* Calcd. for $\text{C}_{27}\text{H}_{20}\text{O}_9$: C, 66.39; H, 4.10. Found: C, 66.25; H, 4.12).

*3 All melting points are uncorrected.

5) "The carbohydrates," Academic Press Inc., New York, 147 (1957).

6) C.B. Reese, D.R. Trentham: Tetrahedron Letters, No. 29, 2459, 2467 (1965).

b) The colorless prisms, prepared by the same procedures as G.P.-701561, showed no depression in melting point on admixture with a sample obtained in a) IR, UV and NMR spectra of the two samples were practically identical with each other.

2-O-Benzoyl-L-ascorbic Acid (VI)—a) To a solution of 4.5 g. of 5,6-isopropylidene-L-ascorbic acid in 200 ml. of acetone were added 2.8 g. of benzoyl chloride and 0.8 ml. of pyridine. The mixture was stirred for 3 hr. at room temperature, and then methanol was added. After stirring for 10 min., the mixture was evaporated under reduced pressure, the residue was extracted with ether, followed by washing with water and with benzene. Colorless crystals m.p. 158~160° were obtained from benzene-methanol (10:3). *Anal.* Calcd. for $C_{13}H_{12}O_7$: C, 55.71; H, 4.28. Found: C, 55.77; H, 4.42.

b) The same product was obtained in DMF (dimethylformamide) solution under the same reaction condition as a).

3-O-Benzoyl-5,6-isopropylidene-L-ascorbic Acid (VIII)—To an acetone solution containing 4.3 g. of 5,6-isopropylidene-L-ascorbic acid were added 4.8 ml. of pyridine, and 2.4 ml. of benzoyl chloride and the solution was left for 18 hr. at room temperature. After addition of methanol, the mixture was kept at room temperature for 30 min., and the solvent was removed *in vacuo*. The residue was washed repeatedly with water and then with ether and *n*-hexane. Recrystallization from carbon tetrachloride gave 2.3 g. of crystalline substance VIII. m.p. 148~150°. *Anal.* Calcd. for $C_{16}H_{16}O_7$: C, 60.00; H, 5.00. Found: C, 59.95; H, 4.95.

2,6-Di-O-benzoyl-L-ascorbic Acid (III) from VI—To a solution of VI (0.65 g.) in acetone (25 ml.) were added 0.77 g. of benzoyl chloride and then 0.22 g. of pyridine in this order. The mixture was kept at room temperature for 4 hr. After 10 ml. of methanol was added, the solvent was removed. The residue was washed with water and then with benzene. The product was crystallized from benzene to give 0.35 g. (39.5%) of the colorless needles. m.p. 103~104°. The NMR and IR spectra of the product were in good accord with a specimen prepared by the route described before.

2-O-Benzoyl-5,6-cyclohexylidene-L-ascorbic Acid (VII)—To a solution of 1.5 g. of 2-O-benzoyl-L-ascorbic acid in cyclohexanone (30 ml.) was added 0.5 g. of zinc chloride and the mixture was kept for one day at room temperature. The solvent was removed, followed by extraction with *n*-hexane. The extract was washed with water and the solvent evaporated. Recrystallization from chloroform and hexane gave plate crystals. m.p. 134~136°. *Anal.* Calcd. for $C_{19}H_{20}O_7$: C, 63.33; H, 5.55. Found: C, 63.50; H, 5.68. UV λ_{max}^{EtOH} m μ (ϵ): 233 (1.65×10^4).

6-O-Benzoyl-L-ascorbic Acid (IX)—One gramme of 2-O-benzoyl-L-ascorbic acid was treated with 30 ml. of aqueous 5% sodium bicarbonate solution for 10 min., and the solution was acidified with dilute hydrochloric acid. The solid product precipitated was collected, washed with water and recrystallized from chloroform to give colorless needles. m.p. 176~178°. *Anal.* Calcd. for $C_{13}H_{12}O_7$: C, 55.71; H, 4.28. Found: C, 55.5; H, 4.24. The substance gave an intense violet color with ferric chloride and consumed an equivalent of iodine solution. UV λ_{max}^{EtOH} m μ : 229 (253, sh) (1.45×10^4).

3,6-Di-O-benzoyl-L-ascorbic Acid (IV) from 2,6-Di-O-benzoyl-L-ascorbic Acid (III)—To a solution of III (1 g.) in dioxane (10 ml.), 1 g. of pyridine was added. After being kept standing for 1 hr. at room temperature, the solvent was removed. The residue was washed with dilute hydrochloric acid and extracted with ethyl acetate. After washing with water, the ethyl acetate solution was evaporated under reduced pressure. Crystallization of the residue from carbon tetrachloride gave IV colorless needles (yield 1.05 g.). m.p. 149~151°. The NMR spectrum of this substance was identical with that of a specimen prepared by another route described previously.

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Summary

Benzoylation of the enediol system of L-ascorbic acid and 5,6-isopropylidene-L-ascorbic acid have been investigated with the aim of obtaining O-benzoyl derivatives of L-ascorbic acid stabilized against oxidation. 2-O-benzoyl-L-ascorbic acid, 3-O-benzoyl-5,6-isopropylidene-L-ascorbic acid, 2,6-di-O-benzoyl-L-ascorbic acid, 3,6-di-O-benzoyl-L-ascorbic acid and 3,5,6-tri-O-benzoyl-L-ascorbic acid have been prepared by making choice of suitable reaction conditions, especially of the mole ratios of the three reagents *i.e.* L-ascorbic acid or its isopropylidene homologues, benzoyl chloride and base. The structure of the products were determined on the basis of elementary analyses, IR and NMR data supplemented by UV spectra and PK values.

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