powder precipitated was filtered, washed with H_2O (1 ml × 2), and dried. DL–XIII which was obtained as a colorless powder (0.50 g, 75%) showed a mp of 191.5—193.5°. Recrystallization of DL–XII from aq. EtOH gave pure DL–XII as colorless prisms, mp 194—196°, which showed no depression (mp 194.5—196.5°) of the mixed melting point with the authentic DL–XII (mp 195—196.5°). The infrared spectrum of this sample was superimposable on that of the authentic sample7) in a solid state.

(+)-N-Acetyl-*R*-α-methylphenylalanine(*R*(+)-XII)——*R*(+)–IX (mp 65—69°, $[\alpha]_D^{25}$ +3.8° (c=1.530, EtOH)) (0.29 g, 0.0018 mole) was treated in a similar way to DL–IX to afford *R*(+)–XII as a colorless powder (0.28 g, 72%), mp 185—192.5°, $[\alpha]_D^{27}$+64.8° (c=1.040, MeOH). The optical purity of this sample was calculated as 82% based on the assumption that *R*(+)–XII showing $[\alpha]_D^{20}$ +79.3° (c=1.082, MeOH) was 100% optically pure. IR ν_{max}^{KBr} cm^{-1}: 3340, 1720, 1633, 1558, 753, 706. This infrared spectrum was identical with that of the authentic *R*(+)–XII in the same state. ORD: $[M]^{28.5}$ (c=0.494, MeOH) (mμ): +103° (700), +143° (589), +215° (500), +279° (450), +380° (400), +586° (350), +1050° (300), +1750° (270). Two recrystallizations of *R*(+)–XII thus prepared from aq. EtOH, afforded pure *R*(−)–XII showing a mp of 199—200.5°, $[\alpha]_D^{24}$ +74.9° (c=0.614, MeOH). The mixed melting point, with the authentic *R*(+)–XII (mp 200—202°), showed no depression (mp 200.5—202°). The infrared spectrum of this sample was identical with that of the authentic *R*(+)–XII in a solid state.

Optical Rotatory Dispersion Curve Measurement of Authentic *R* (+)-XII——$[M]^{17}$ (c=0.512, MeOH) (mμ): +129° (700), +186° (589), +276° (500), +367° (450), +508° (400), +790° (350), +1425° (300), +2330° (270).

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Stability of Ascorbic Acid in Fused System Containing Ascorbic Acid and Mannitol1)

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In manufacturing processes of ointments, suppositories and in spray chilling processes, or other processes including fusing step, one of the most important problem is the stability of the drug in the fused system.

The present paper is concerned with ascorbic acid and mannitol as an example. The stability of ascorbic acid dissolved in fused mannitol was studied in order to determine the condition of above processes, that is, the temperature and time range of fusion required to keep the drug decomposition within a certain limit.

The stability of ascorbic acid in its aqueous solution has been well studied.3–6) Awata, *et al.*7,8) and Ohtani9,10) reported the mechanism of the color formation of ascorbic acid in

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1) Presented at the 85th Annual Meeting of the Pharmaceutical Society of Japan, Fukuoka, 1965. The study was made in relation to the investigation on air oxidation of ascorbic acid in mannitol conglomerate. (Part I: *Chem. Pharm. Bull.* (Tokyo), **16**, 1972 (1968); Part II: *Chem. Pharm. Bull.* (Tokyo), **16**, 1982 (1968).)
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its aqueous solution. Recently, the anaerobic degradation of ascorbic acid in its aqueous solution was discussed,[11–13] and Uprety, *et al.*[14] described its stability in a fruit juice. Although the decomposition of ascorbic acid was thus well investigated on its aqueous solution, very little is known about its decomposition in nonaqueous solution, especially in fused system in the neighbourhood of its melting point. Kanig[15] reported the characteristics of the liquid state of mannitol which has been shown capable of dissolving or dispersing a number of pharmaceutical adjuvant or physiologically active drugs, but did not describe about ascorbic acid and mannitol system.

A preliminary investigation with the fused ascorbic acid and mannitol system indicated that ascorbic acid was clearly soluble into fused mannitol (mp 168°) and made a eutectic mixture at the proportion of mannitol 60% and ascorbic acid 40%, the eutectic temperature being 123°. In practice, however, a mixture of about 10% ascorbic acid and 90% mannitol is more convenient with its rapid congealing property than the slow congealing eutectic mixture.

Experiments were carried out to find the order of the reaction, specific reaction rate, and to examine the applicability of Arrhenius equation to the fused system, and such were indispensable to determine the temperature and the heating time limit in the fusing processes.

Experimental

Materials——Ascorbic acid and mannitol used were of analytical grade.

Procedure——10 g of ascorbic acid and 90 g of mannitol were thoroughly mixed in a mortar and the mixed powder was fused in a beaker which was put in a constant temperature oil bath (170°, 178° and 185°). At appropriate intervals samples were taken out, cooled into room temperature, weighed, dissolved in water and the solutions were analysed.

Assay——The residual ascorbic acid was determined by the dichlorophenol–indophenol method given by U.S.P. XVII for ascorbic acid injection.

Results and Discussion

In all cases there were nearly linear relationships between time and logarithm of residual ascorbic acid amount as shown in Fig. 1.

The rate of disappearance of ascorbic acid from the fused system, therefore, was found to be apparently first order with respect to ascorbic acid. Table I shows each mean rate constant at each temperature.

Arrhenius plot was made in Fig. 2.

Fig. 2 was expressed in the following equation,

$$\log k = 11.95 - 6250/T \qquad (1)$$

and the activation energy was figured out to be about 28 kcal/mole, which seemed rather high as an ordinary reaction[6] in aqueous solution. The result shows that the reaction is highly temperature dependent. The temperature of the fused materials in the reservoir, therefore, must be as low as possible, as far as undesirable premature congealing does'nt take place. For example, k for 160° is calculated from (1) to be 3.32×10^{-3} min^{-1}, and after 10 minutes heating at 160°, the residual amount of ascorbic acid is calculated to be 92.5% of the

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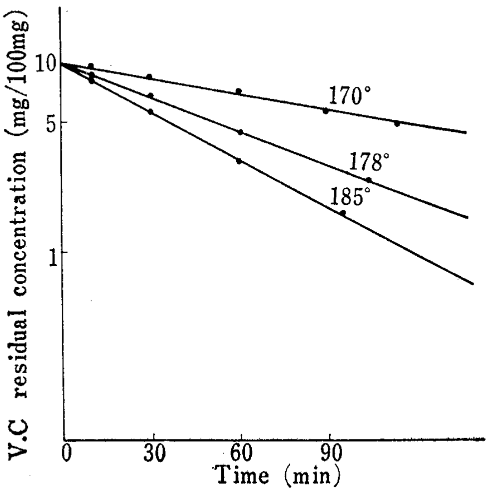

Fig. 1. Plots showing the Overall First-Order Character of the Degradation of Ascorbic Acid at Different Temperature

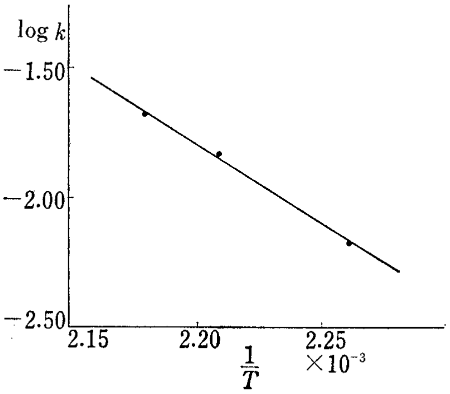

Fig. 2. Plot of Logarithm of Rate Constant *v.s.* the Reciprocal of Absolute Temperature from which the Activation Energy was calculated

Table I. Apparent First Order Rate Constant of Ascorbic Acid Degradation Reaction

Temp.	k
170°	5.99×10^{-3} min^{-1}
178°	1.54×10^{-2}
185°	1.99×10^{-2}

initial value, whereas k for 170° is calculated to be 6.91×10^{-3} min^{-1}, and the residual amount after 10 minutes is calculated to be 85.2% of the initial value. That is, the reaction rate at 170° is more than twice faster than that at 160°.

As shown in Table II, the data at 170° are better expressed as 1/2 order reaction, which suggests a change of reaction mechanism near the melting point. Further studies are indicated in this area.

Table II. Comparison of Rate Constant as First Order and as ½ Order at 170°

Time	Residual ascorbic	k as first order	k' as ½ order[a]
0 min	10.30 mg/100 mg	— min^{-1}	— mg$^{1/2}$ min^{-1}
10	9.83	4.67×10^{-3}	1.60×10^{-2}
30	8.67	5.74×10^{-3}	1.80×10^{-2}
60	7.19	5.99×10^{-3}	1.76×10^{-2}
90	5.68	6.66×10^{-3}	1.82×10^{-2}
115	4.66	6.90×10^{-3}	1.84×10^{-2}

a) k' is rate constant as apparent ½ order reaction, which was calculated from the following equation,

$$k'=\frac{2}{t}\{a^{1/2}-(a-x)^{1/2}\}$$

a=initial concentration of ascorbic acid, $(a-x)$=residual ascorbic acid concentration.