The ultraviolet (UV) and nuclear magnetic resonance (NMR) data supported that VIII as well as IX underwent hydrogenation at 16,17-double bond,[4] and CD data disclosed the configuration at C-21: 21*R* for X and 21*S* for XI.[6,7]

The reduction of X and XI with $NaBH_4$ in the presence of NaOH and the subsequent acidification afforded digitoxigenin 3-acetate (IVb) and 17α-digitoxigenin 3-acetate (III), respectively in good yield. The result offered us a new method for the conversion of gitoxigenin (Ib) to digitoxigenin 3-acetate (IVb) and also allowed the assigment of the full stereochemistry of X and XI.[8] From these results, the structures of 16,17-dehydro-21*R*-ethoxydigitoxigenin 3-acetate and 21*R*-ethoxydigitoxigenin 3-acetate were assigned to VIII and X, and the structures of 16,17-dehydro-21*S*-ethoxydigitoxigenin 3-acetate and 21*S*-ethoxy-17α-digitoxigenin 3-acetate were also assigned to IX and XI, respectively.

The overall yield of IVb starting from Ib could have been raised to 22.6% by improving the yield of VIII by using 0.03% K_2CO_3 in dilute ethanol, where VIII was obtained in 61.6% along with 12.6% VII and trace of IX. In terms of the transformation of Ib to IVb, the present method is apparently superior than the previous method (3.4%), though three more steps are required.

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8) The stereospecific hydrogenation of 16,17-double bonds in VIII and IX could be explained by the participation of 21-ethoxy groups. Since 16,20(22)-dienolactone system is believed to take a transoid form,[9] as shown in structures, attack of hydrogen was strongly favored on the opposite side of the 21-substituent.

9) The transoid form of II was proved by CD Cotton effect of the mixture of II and some transition metal salt, and the results will be published in the near future.

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Ammonia Adducts of Chloramphenicol and Chloramphenicol Palmitate

Chloramphenicol and chloramphenicol palmitate were found to form adducts with ammonia. Both ammonia adducts are so unstable at room temperature that ammonia free antibiotics are easily recovered by rapid elimination of ammonia. Particle size was reduced for chloramphenicol palmitate by repeating sorption and subsequent desorption of ammonia.

Keywords——chloramphenicol; chloramphenicol palmitate; ammonia compound; ammonia adduct; particle size reduction

We have studied the particle size reduction of barbiturates, sulfonamides, antidiabetics, and others by desorption of ammonia from their ammonia compounds, or their ammonia adducts. Recently, chloramphenicol (CP) and chloramphenicol palmitate (CP-palmitate) were found to form adducts with ammonia.

It was recognized from the X-ray powder diffraction pattern that the crystals obtained by dissolving commercial CP in liquid ammonia and subsequent evaporation of excess ammonia are completely different chemical species (structure) from the original CP. The differential scanning calorimetry (DSC) pattern of the crystals obtained shows an endothermic peak at 50—70° which is attributed to decomposition of an ammonia adduct and a melting peak at

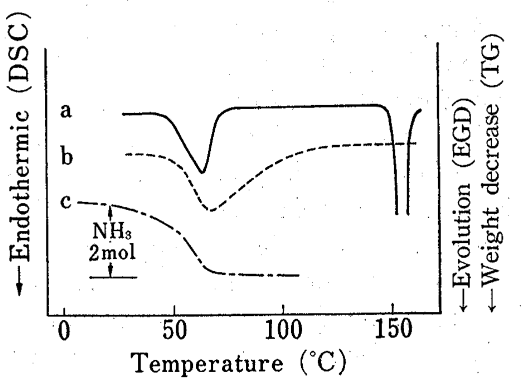

Fig. 1. Thermograms of Chloramphenicol Ammonia Adduct

(a) and (b) Simultaneous DSC and EGD curves under semiclosed conditions: sample weight as chloramphenicol, 17.67 mg; heating rate, 16°/min.

(c) TG curve: sample weight, 4.89 mg; heating rate 8°/min.

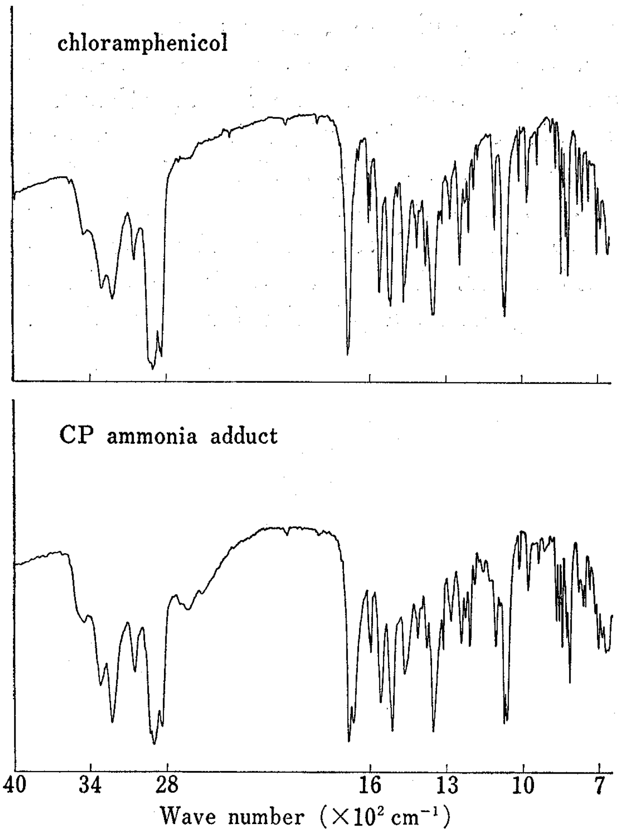

Fig. 2. Infrared Spectra of Chloramphenicol and Its Ammonia Adduct (Nujol Mull)

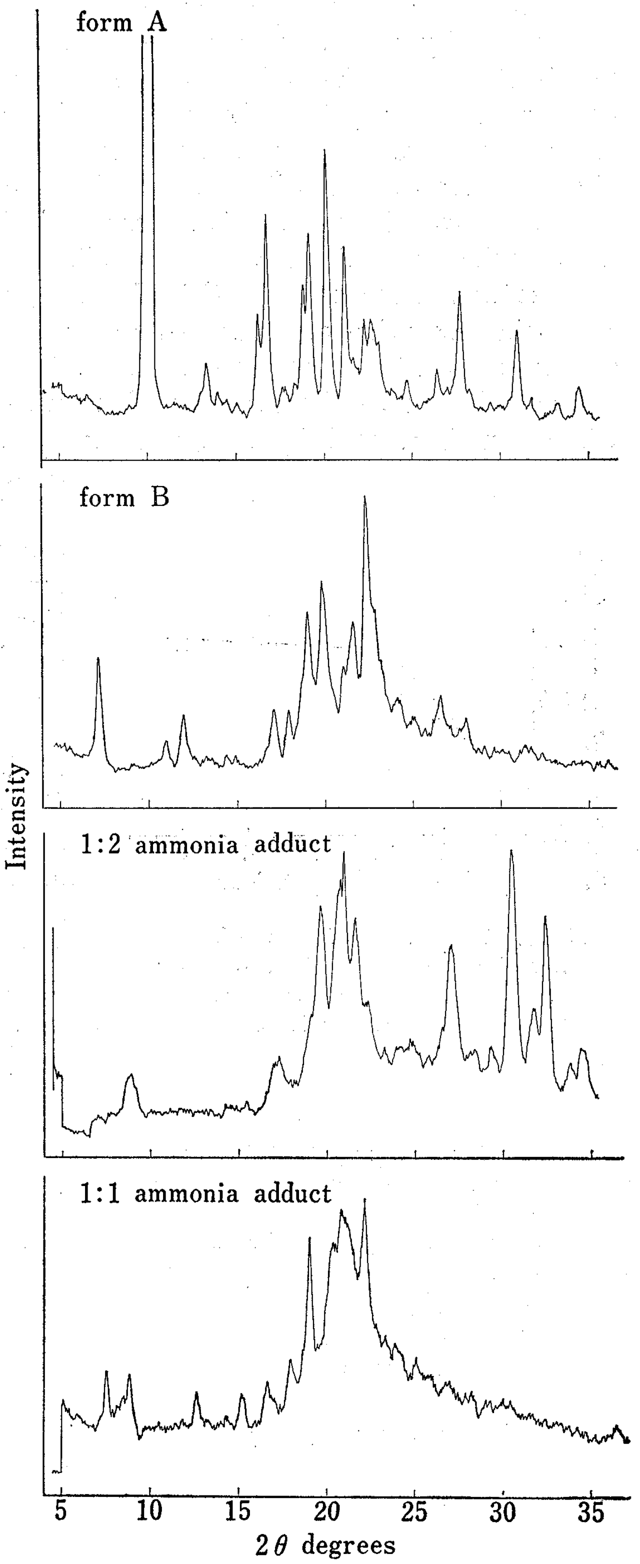

Fig. 3. X-ray Diffraction Patterns for Polymorphs of Chloramphenicol Palmitate and Their Ammonia Adducts

about 150° which coincides with the melting point of the original CP. The combining ratio was calculated to be 1: 2 (CP: ammonia) from the weight decrease measured by thermogravimetry (TG). The characteristic DSC and TG curves are shown in Fig. 1. The infrared (IR) spectra for CP and its ammonia adduct are shown in Fig. 2. New absorption peaks appeared at 1670, 1160, and 860 cm^{-1} in the CP ammonia adduct spectrum.

Ammonia adduct formation was confirmed with CP-palmitate form A,[1] a stable but therapeutically inactive form at room temperature,[2] by suspending it into liquid ammonia for about 2 hours, since CP-palmitate is only slightly soluble in liquid ammonia. Its X-ray powder diffraction pattern differs from CP-palmitate forms A, B, or C,[2] as shown in Fig. 3. When form B was suspended in the same manner, the powders obtained showed the identical X-ray pattern as that of CP-palmitate ammonia adduct formed with form A. Further, both crystals recovered by desorption of ammonia from their ammonia adducts reproducibly, each showing the identical X-ray pattern as its ammonia free form B which is metastable at room temperature. Although the CP-palmitate ammonia adduct is relatively stable at 1—3°, ammonia desorption proceeds easily at room temperature. The molecular combining ratio was determined to be 1: 2 (CP-palmitate: ammonia) from the weight decrease measured on the semimicrobalance. The formation of 1: 1 (CP-palmitate: ammonia) adduct was also confirmed with an another sample by a weight decrease curve and a new X-ray powder diffraction pattern (Fig. 3).

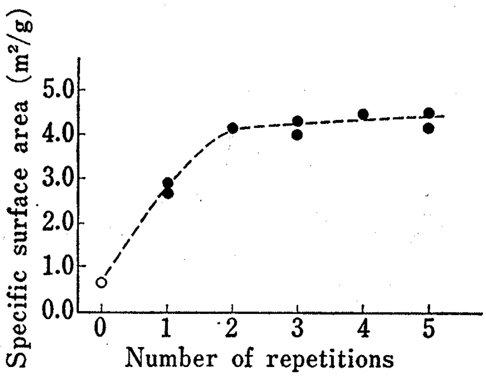

Fig. 4. The Effect of Repetition of Sorption and Desorption of Ammonia upon Specific Surface Area of Chloramphenicol Palmitate

The degree of particle size of the powders recovered by desorption of ammonia from their ammonia adducts was investigated by gas adsorption method (BET). The specific surface area obtained for CP recovered *via* its ammonia adducts was determined to be 2.0 m^2/g.

In the case of CP-palmitate, its solubility in liquid ammonia is quite low, as mentioned before. Therefore, the effect of repeating the process of sorption and desorption of ammonia on particle size of CP-palmitate was investigated. The results obtained are depicted in Fig. 4. The specific surface area of 4.1 m^2/g was obtained by repeating the process two times. Further repetition made no significant increase. The degree of fineness of this sample will suggest the application for practical use.

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