30% AcOH and then made alkaline with dil. $NaHCO_3$ and extracted with $CHCl_3$. The solvent was evaporated to give the crude product 26 mg for **6a**, 27 mg for **6b** respectively. The NMR spectra of the crude products were almost identical, although both products exhibited clear two spots on TLC. The column chromatography using 5 g of silica gel and $CHCl_3$–AcOEt as an eluting system gave 14 mg of **6a** and 7 mg of **6b** in the case of the crude product from **6a**. With **6b** 12 mg of **6a** and 4 mg of **6b** were obtained.

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Pharmacological Properties of Galenic Preparations. II.[1] Intestinal Absorption Inhibitor of Alkaloid in the *Scopolia* Extract

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Screening of the inhibitor to the absorption of alkaloid in the *Scopolia* extract was taken up and following results were obtained.

The alkaloid absorption through the intestine in the administration of *Scopolia* extract is affected by scopoletin, tannin-like substance(s) and others, but is not affected by the acidic component(s).

Keywords——*Scopolia* extract; intestinal absorption; alkaloid; isolated mouse intestine; tannin; scopoletin; hyoscyamine

In a previous paper,[1] we have suggested that a part of the pharmacological properties of the *Scopolia* extract should be attributed to the decreased absorption of *l*-hyoscyamine through intestine. This study is concerned with the screening of the inhibitor to the absorption of alkaloid in the *Scopolia* extract.

Experimental

Chart 1 shows the process of fractionation of the extract.

The alkaloid were eventually transferred to Fr. 6 and 7. The absorption rate of alkaloids through the isolated small intestine of mouse was measured according to the method described elsewhere.[1] Each material that contained alkaloids 8.0×10^{-4} g/ml as hyoscyamine by dilution with water was ajusted to become isotonic with sodium chloride. Fraction 3, 5 and 8 were tested after adding the same amount of hyoscyamine. The amount of administration was always fixed at 0.3 ml of material.

Results and Discussion

The quantity of alkaloids which permeated through the isolated intestine is shown for each fraction in Table I and plotted against time in Figs. 1, 2, 3, and 4.

1) Part I: Y. Kano and M. Konoshima, *Yakugaku Zasshi*, **94**, 898 (1974).
2) Location: *a*) *Katuraoka-cho, Otaru*; *b*) *Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto.*

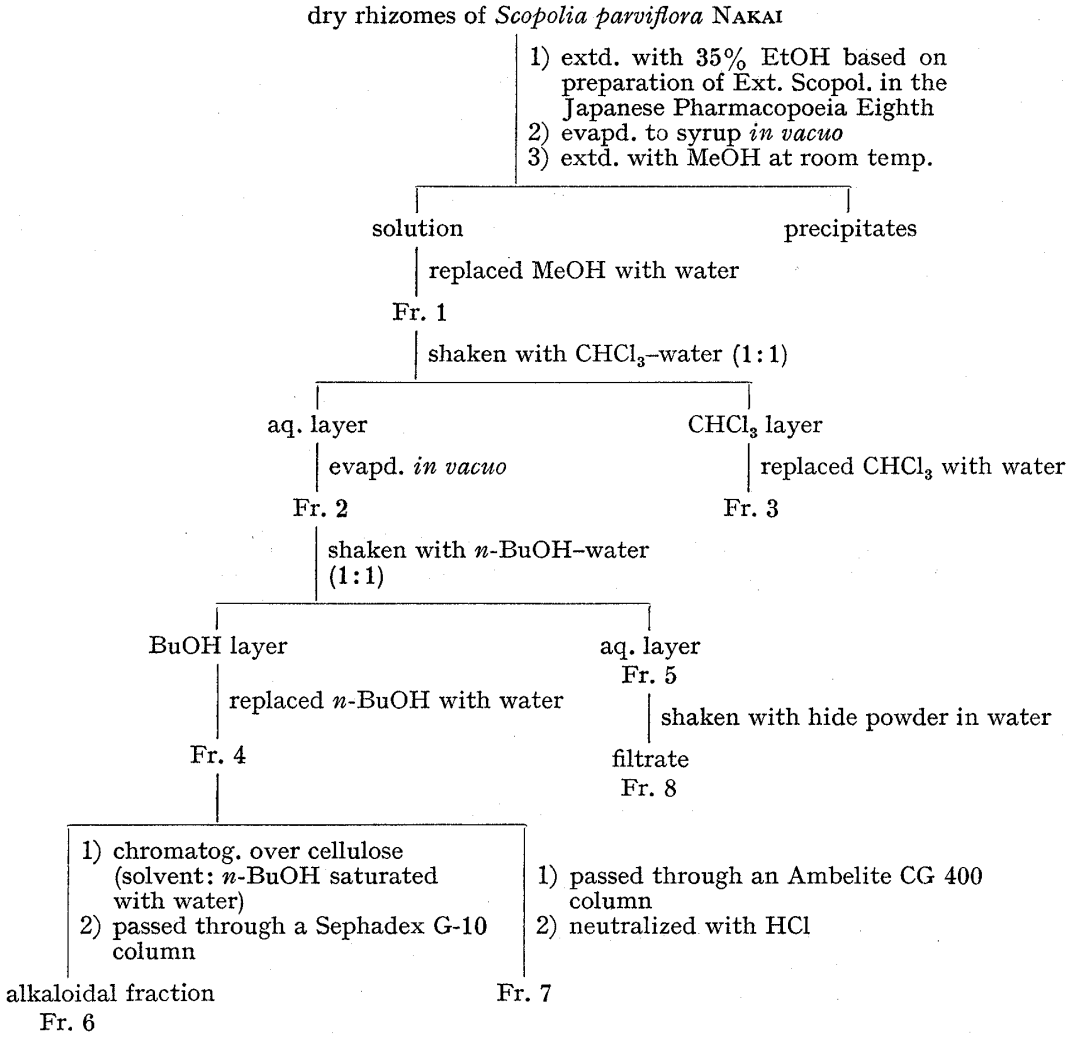

Chart 1. Process of Fractionation

TABLE I. Absorption of Alkaloid in Various Fractions of the *Scopolia* Extract

	Absorption rate (10^{-7} g/min)	Cumulative amt. absorbed (10^{-5} g, 90 min)
Hyoscyamine	15.4	12.61
Fr. 1	2.2	1.91
Fr. 2	3.9	2.33
Fr. 3[a)]	13.2	9.01
Fr. 4	14.0	8.50
Fr. 5	3.5[b)], 9.3	4.00
Fr. 6	18.8	13.20
Fr. 7	15.0	9.10
Fr. 8	13.5	7.55

a) Scopoletin (0.02%) was used as a substitute for Fr. 3 from the reason the latter was practically formed of the former.
b) See Fig. 2.

The absorption rate of pure hyoscyamine dissolved in the Tyrode solution (control) was 15.4×10^{-7} g/min, so that the cumulative amount of transferred alkaloid reached 12.61×10^{-5} g in 90 min after administration. In marked contrast to the control, the absorption rate of

alkaloids of the *Scopolia* extract (Fr. 1) was reduced to 2.2×10^{-7} g/min and the cumulative amount was 1.19×10^{-5} g in 90 min. Thus, the absorption rate of alkaloids was inhibited in Fr. 1 to 15% of the control (Table I).

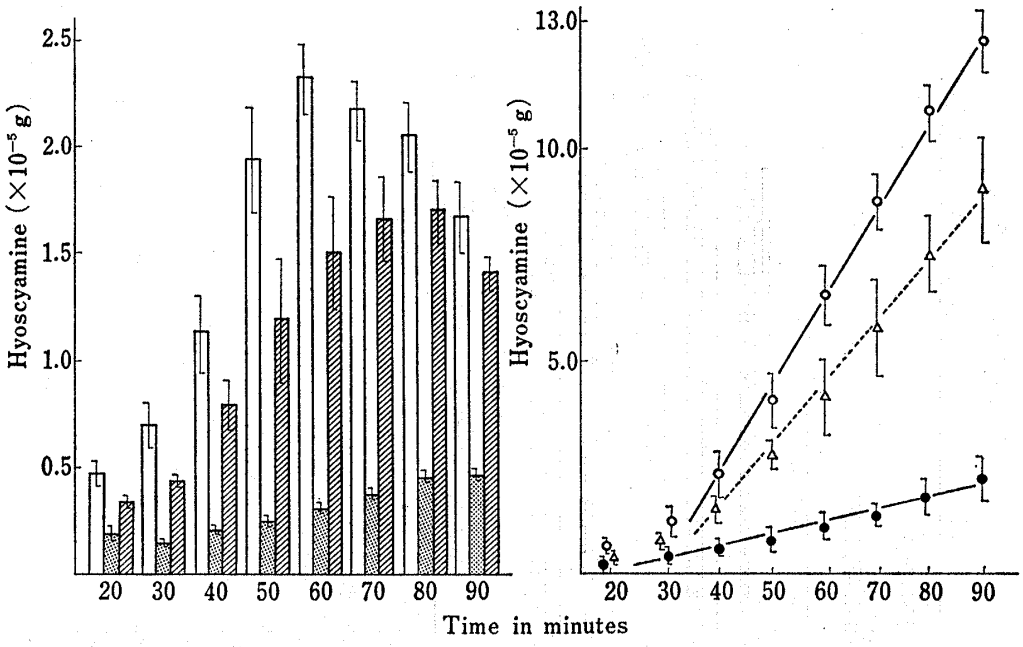

Fig. 1. The Absorption of Alkaloid in Fr. 2 and Fr. 3 through the Isolated Mouse Small Intestine

The left: amount absorbed. ⊓ ⊙ : mean±SD.

The right: cumulative amount absorbed.
□ : hyoscyamine : ○—
▨ : Fr. 2 : ●—
▨ : Fr. 3 : △···

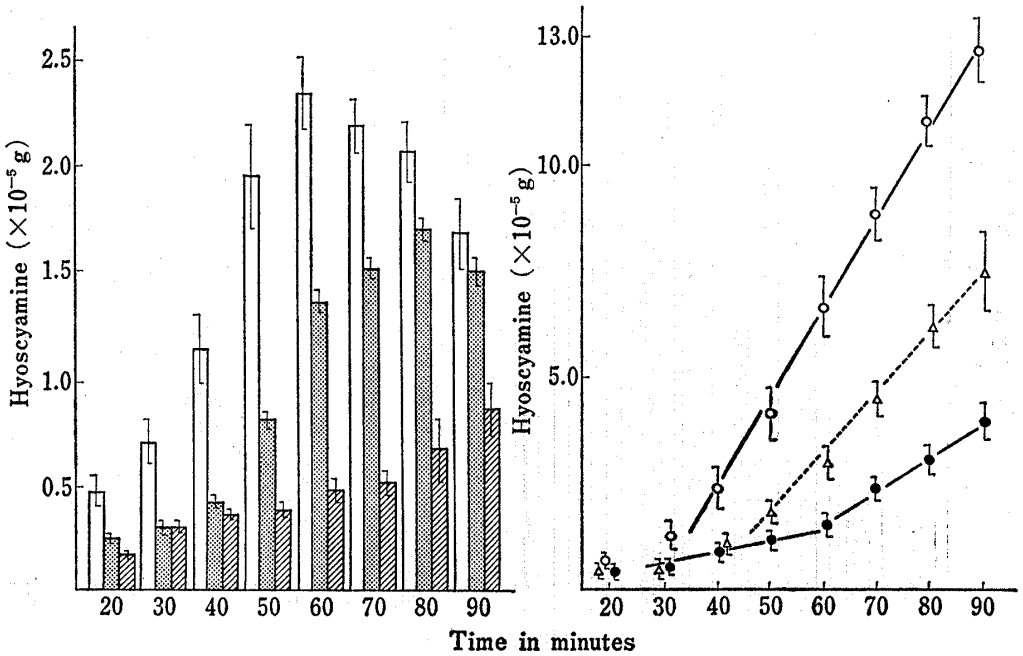

Fig. 2. The Absorption of Alkaloid in Fr. 5 and Fr. 8 through the Isolated Mouse Small Intestine

The left: amount absorbed. ⊓ ⊙ : mean±SD.

The right: cumulative amount absorbed.
□ : hyoscyamine : ○—
▨ : Fr. 5 : ●—
▨ : Fr. 8 : △···

The results obtained from the individual tests of various fractions indicated that the inhibitory activity for alkaloid absorption found in Fr. 1 was transferred mainly to Fr. 2 and Fr. 5. The inhibitory activity of Fr. 3 was much weaker than that of Fr. 2, and scopoletin

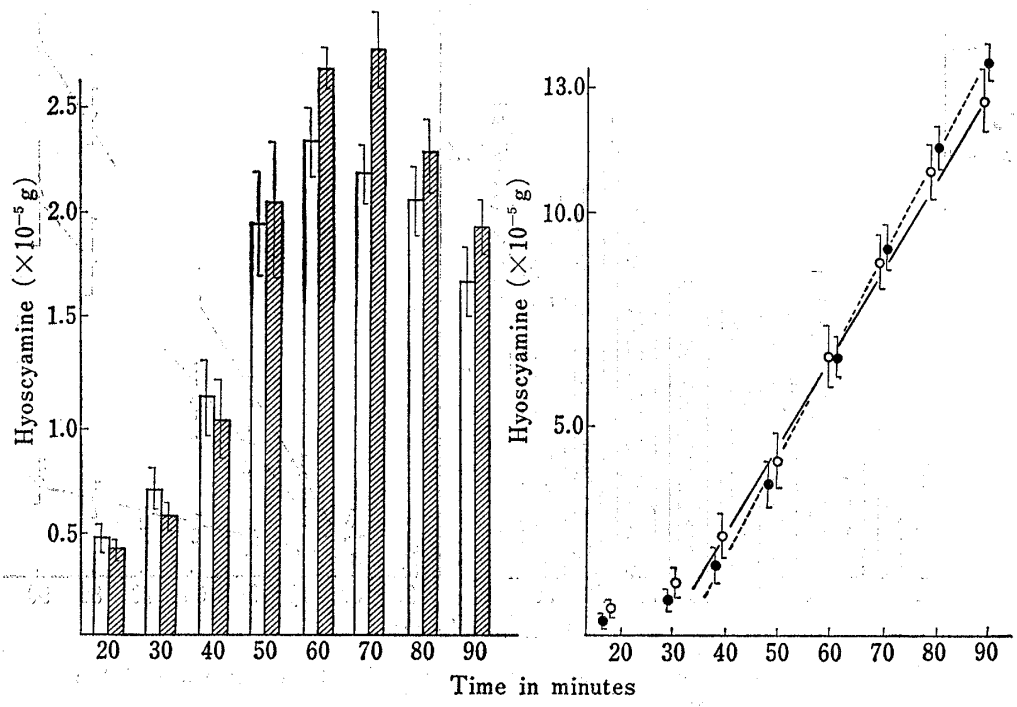

Fig. 3. The Absorption of Alkaloid in Fr. 6 through the Mouse Small Intestine

The left: amount absorbed. ⊓ ⊖ : mean±SD.

The right: cumulative amount absorbed. □ : hyoscyamine : ○— ▨ : Fr. 6 : ●···

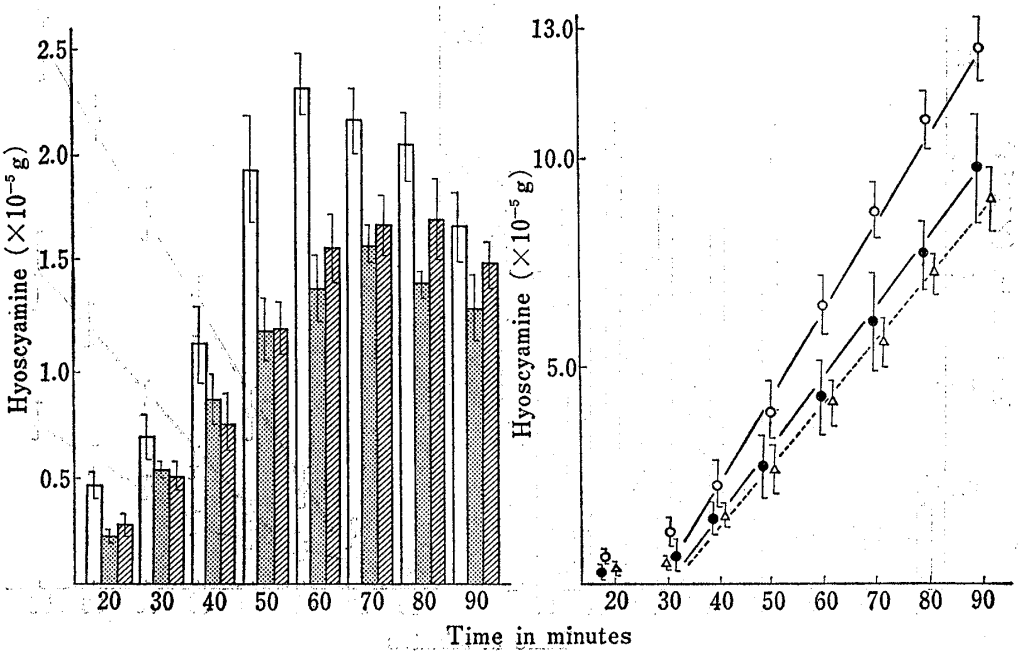

Fig. 4. The Absorption of Alkaloid in Fr. 4 and Fr. 7 through the Isolated Mouse Small Intestine

The left: amount absorbed. ⊓ ⊖ : mean±SD.

The right: cumulative amount absorbed. □ : hyoscyamine : ○— ⣿ : Fr. 4 : △··· ▨ : Fr. 7 : ●—

was isolated as a weak inhibitor from the former. Scopoletin dissolved in the Tyrode solution (0.02 w/v %) caused a 28% reduction in the cumulative amount of permeated alkaloids as compared with the control (Table I, Fig. 1).

The treatment of Fr. 5 with hide powder resulted in a considerable recovery of alkaloid absorption in Fr. 8 derived from Fr. 5 (Table I, Fig. 2). The substance(s) which was adsorbed by the hide powder is presumably a tannin, so that one of the alkaloid absorption inhibitor may be a tannin-like substance.[3)]

In the extract, the alkaloids probably exists as a salt with an acidic component. However, the rate of alkaloid absorption was not affected by the salt (Fr. 6) which was isolated in natural form from Fr. 4 (Table I, Fig. 3).

Fr. 4 was subjected to an Amberlite CG 400[4)] column and the eluate was neutralized with hydrochloride to give Fr. 7. However, no significant difference was found between the two fractions in their effects on alkaloid absorption (Table I, Fig. 4). It is suggested that the acidic components in Fr. 4 are not effective on alkaloid absorption.

These results suggest that the alkaloid absorption through the intestine in the administration of *Scopolia* extract is affected by scopoletin, tannin-like substance(s) and others, but is not affected by the acidic component(s).

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3) P.H. List, W. Schmid, and E. Weil, *Arzneim.-Forsch.*, **19**, 181 (1969).
4) Anion exchanger.