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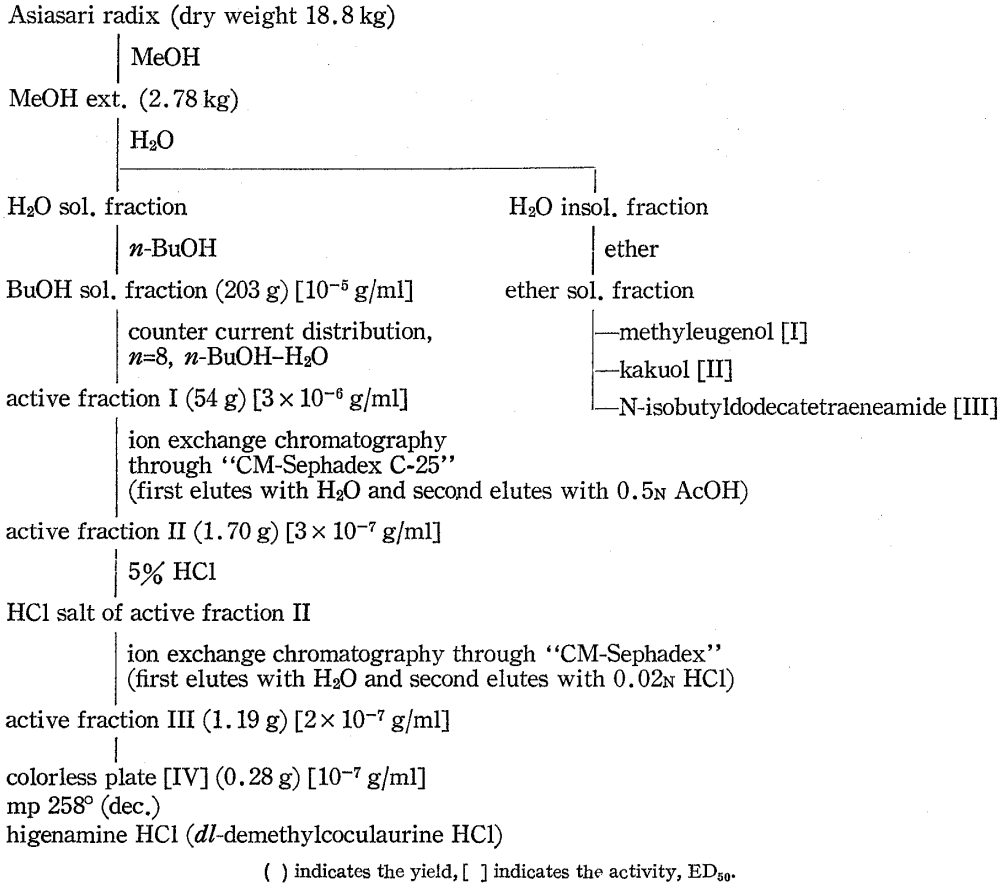
Studies on Antitussive Principles of Asiasari Radix

As one of studies on naturally occurring active principles, antitussive principles in Asiasari radix, namely four active principles [I], [II], [III] and [IV] were isolated by a suitable combination of counter current distribution and column chromatography. [I] oily product, $C_{11}H_{14}O_2$, [II] mp 110°, $C_9H_{10}O_4$, [III] mp 70°, $C_{16}H_{25}NO$, and [IV] mp 258° (dec.), $C_{16}H_{17}NO_3$–HCl were found to be identical with methyleugenol, kakuol, N-isobutyldodecatetraeneamide and higenamine hydrochloride (*dl*-demethylcoculaurine), respectively. This is the first isolation of higenamine from Asaraceae family.

Keywords——Asiasari radix; *Asiasarum heterotropoides* Maek. var. *mandshuricum* Maek.; active principles; antihistaminic potency; isolation; CM-Sephadex; methyleugenol; kakuol; N-isobutyldodecatetraeneamide; higenamine (*dl*-demethylcoculaurine)

Asiasari radix (Saishin in Japanese), *Asiasarum heterotropoides* Maek. var. *mandshuricum* Maek., has long been used as one of the herbs of Chinese medichine as an antitussive (cough remedy), expectorant or anodyne. Any detailed chemical study on the antitussive principle has not yet been reported, since previous studies on Asiasari radix has been mostly focused on essential oil.

This report deals with the isolation and identification of the principles. In the isolation process, the Magnus method using the isolated ileum of guinea pigs was useful for pharmacological measurement of antitussive activity of the material. The activity was shown as the concentration (g/ml) that caused a 50% relaxation of the ileum presented in a state of maximal contraction provoked by histamine HCl (10^{-7} g/ml). The isolation of the material was achieved by following procedures.



( ) indicates the yield, [ ] indicates the activity, ED_{50}.

Chart 1

Asiasarum root (18.8 kg) was ground and extracted with refluxing methanol. Butanol soluble portion (203 g) of the water soluble fraction was separated by counter current distribution using the solvent system of *n*-butanol and water, to give active fraction I (54 g)[ED_{50} 3×10^{-6} g/ml]. Ion exchange chromatography of fraction I through "CM Sephadex C-25" column was accomplished firstly with water and then with 0.5 N acetic acid as elution solvents, to give active fraction II (1.70 g) [ED_{50} 3×10^{-7} g/ml] from the 0.5 N acetic acid elution. Ion exchange chromatography of HCl salt of active fraction II yielded active fraction III (1.19 g) [ED_{50} 2×10^{-7} g/ml] from 0.02 N HCl elution. A crystalline material appeared from active fraction III on standing over night as colorless plates, mp 258° (dec.), $[\alpha]_D^{20}=0°$, (0.28 g) [ED_{50} 10^{-7} g/ml]. It was identified as higenamine hydrochloride (*dl*-demethylcoculaurine HCl), which has already been isolated from aconite root (*Aconitum japonicum* Thunb.) as a cardiac principle by us.[1)]

From the ether soluble fraction of Chart 1, methyleugenol, kakuol and N-isobutyldodecatetraeneamide were also isolated as antihistaminic substances.

It was clarified that higenamine was an adrenergic β-stimulant and that methyleugenol relaxed directly the tracheal muscle.[2)] The results are considered to indicate that higenamine and methyleugenol may mainly play an important role in the antitussive action of Asiasarum radix. It is some of interest that higenamine was isolated from those different families, and also that both the species belong to the same group, "Kyokan yaku"[3)] in Chinese medicine.

Identifications of higenamine in other herbs, especially in the Kyokan yaku herbs, are being carried out by us.

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1) T. Kosuge and M. Yokota, *Chem. Pharm. Bull.* (Tokyo), **24**, 176 (1976); T. Kosuge, M. Yokota and M. Nagasawa, *Yakugaku Zasshi*, in press
2) Pharmacological activity of higenamine and methyleugenol will be published in near future.
3) "Kyokan yaku" is a group in Chinese medical herbs whose main action is said to remove some feeling of coldness in patients.