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Isolation of *l*-Ephedrine from "Pinelliae Tuber"

HARUJI OSHIO,[1a] MAKOTO TSUKUI, and TOSHIRO MATSUOKA[1b]

Pharmacognostic Research Laboratory, Takeda Chemical Industries, Ltd.[1]

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The basic fractions of methanol and water extracts of a crude drug, "Pinelliae Tuber," showed a relaxant action and antihistamine like action upon an isolated rectum of Japanese quails. And *l*-ephedrine hydrochloride was isolated in the yield of 0.002% as the active principle.

Keywords——alkaloid; *l*-ephedrine; Pinelliae Tuber; *Pinellia ternata* BREIT; Japanese quail

A crude drug, "Pinelliae Tuber (半夏)", has been used as an antiemetic and sedative in Chinese medicine. The drug is the dried tuber of *Pinellia ternata* BREIT. (Araceae).

This paper deals with the isolation of *l*-ephedrine from "Pinelliae Tuber".

The methanol and water extracts of the pulverized raw material were applied to a column of Amberlite IR 120 B followed by elution with aqueous ammonium hydroxide, and afforded the fractions which showed a relaxant action and antihistamine like action upon an isolated rectum of Japanese quails. The aqueous solution of this fraction was saturated with sodium chloride, alkalized with potassium hydroxide, and extracted with ether. The ethereal extract had a strong activity. This fraction was dissolved in aqueous hydrochloric acid and the insoluble brown substance was filtered off. The active principle was obtained as colorless crystals by evaporation of water.

The active compound, colorless needles (ethanol–tetrahydrofuran), mp 224°, $[\alpha]_D$ −36.2° (H_2O), $C_{10}H_{15}NO \cdot HCl$, shows blue coloration with ninhydrin reagent. The nuclear magnetic resonance spectrum of this compound is as follows; δ 1.32 (3H, d, J=7 Hz, CH_3), δ 3.00 (3H, d, J=2.5 Hz, CH_3), δ 3.65 (1H, m), δ 5.28 (1H, d, J=3 Hz), δ 7.46 (5H, m, aromatic). The doublet signal at δ 3.00 is altered to a singlet on addition of deuterium oxide. Irradiation of the signal at δ 3.65 alters both doublet signals at δ 1.32 and δ 5.28 to singlets, respectively. It was suggested on the basis of the physico-chemical information that the compound agreed to *l*-ephedrine hydrochloride. And it was identified with an authentic sample.

We could not detect other ephedrine analogs from this crude drug.

l-Ephedrine is well known as the main alkaloid of *Ephedra* spp., the stem of which, "Ephedra Herba", is also one of the important Chinese crude drugs. "Ephedra Herba" has never been applied as an antiemetic but as an antitussive. It is interesting that the same biologically active compound is found in the two kinds of crude drugs which are of quite different use in Chinese medicine.

Experimental

Melting points are not corrected. The IR spectra in KBr were measured with a Hitachi 215, the NMR spectra in CF_3COOD with a Varian XL 100 A using TMS as standard and the optical rotations with a Perkin Elmer Type 141.

Bioassay——The rectum of male Japanese quails (*ca.* 100 g body weight) sacrificed by bleeding was cut in a length of 2 cm and suspended in a Magnus tube which was filled with Tyrode solution. The solution was kept at 37°, and oxygen was supplied by airation.

(1) A certain amount of sample was added to the Magnus tube, then the relaxation of the rectum was recorded on a kymograph. The activity of *l*-ephedrin·HCl (10^{-6} g/ml), for example, was recorded as 1.3 cm.

1) Location: *a*) *Jusohonmachi, Yodogawa-ku, Osaka*; *b*) *Ichijoji-Takenouchi-cho, Sakyo-ku, Kyoto.*

(2) The rectum was contracted previously with 10^{-7} g/ml of histamine·2HCl. After *ca.* 5 min, the sample which showed a relaxant action was added, and the recovery from contraction of the rectum was observed. The activity of *l*-ephedrine·HCl (10^{-6} g/ml) was of 41.7%.

Isolation of *l*-Ephedrine·HCl——Three kg of the commercial crude drug was pulverized and extracted twice with MeOH (15 and 10 l) at room temp. for 24 hr. By the concentration of MeOH extract *in vacuo*, 62.3 g of brown oil [activity: 10^{-4} g/ml; inactive] was obtained. The oil was dissolved in a mixture of 500 ml of *n*-BuOH and 500 ml of 0.5 N HCl, and the aqueous layer was washed again with 500 ml of *n*-BuOH. Then the aqueous solution was applied to a column of Amberlite IRA 410 (OH^- form) to remove Cl^- ion and other acidic substances. After washing the column with 3 l of H_2O, the non-adsorbing eluate was adsorbed to a column of Amberlite IR 120 B (H^+ form) (7×50 cm). The column which was washed with 3 l of H_2O was eluted with 3 l of 5% NH_4OH. The eluate was evaporated *in vacuo* to *ca.* 300 ml [activity of the concd. fraction: 10^{-4} g/ml; 1.7 cm, 46.1%], and to the brown solution 120 g of NaCl and 30 g of KOH were added and the mixture was stirred vigorously under cooling. The basic solution was extracted twice with 500 ml each of Et_2O. The yellow ethereal extracts were combined and dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to dryness [activity of the residual brown oil (43 mg): 10^{-5} g/ml; 1 cm, 59.5%]. The oil was dissolved in a small amount of dil. HCl. After removing the brown resinous substance by filtration, the filtrate was concentrated *in vacuo* to obtain 9.5 mg of colorless crystals. Recrystallization from EtOH–THF gave colorless needles, mp 224°. *Anal.* Calcd. for $C_{10}H_{15}NO\cdot HCl$: C, 59.55; H, 8.00; N, 6.95. Found: C, 59.62; H, 8.09; N, 6.74. $[\alpha]_D^{27}$ −36.2° (c=0.5, H_2O). IR cm^{-1}: 3310, 2830, 2740, 2450, 1582. NMR δ: 1.32 (3H, d, J=7 Hz), 3.00 (3H, d, J=2.5 Hz), 3.65 (1H, m), 5.28 (1H, d, J=3 Hz), 7.46 (5H, m). Mix. mp with an authentic l-ephedrine·HCl showed 220—222°. Activity: 10^{-6} g/ml; 1.8 cm, 50.9%.

After drying, the residue of MeOH extraction described above was mixed with 15 l of H_2O and 3 g of diastage, and the suspended mixture was kept at 55° for 4 hr with stirring. After filtration, the residue was extracted again as above. The yellowish brown extracts were combined, and acidified with conc. HCl to pH 0.5, then washed with 10 l of *n*-BuOH. The light yellow aqueous layer was applied to ion exchangers and treated in the same manner as the MeOH extract. *l*-Ephedrine·HCl (50 mg) was obtained.