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THE CONSTITUENTS OF CHINESE DRUG, HSI-HSIN, *ASARUM SIEBOLDI*, MIQ.

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Hsi-hsin belongs to the Aristolochiaceae family, being generally identified as Asarum Sieboldi, Miq. [1853, 1933] and appears in Chinese drug stores in the form of fibrous roots having a strong aromatic smell and a subacrid taste. It contains much essential oil to which its medicinal value is generally attributed. The Pentsao Kang Mu [1596] assigns to this drug emetic, expectorant, diaphoretic, diuretic, and purgative properties. In the practice of Chinese medicine, it is often used in the place of Ma-huang, Chinese ephedra. The essential oil obtained from various species of asarum, on account of its ecomonical and medicinal value, has been much investigated by many workers with the isolation of a large number of constituents. The following is a summary of the more important work done on asarum species:

As early as 1820, Asarum europaeum, L. was studied by Lassaigne and Feneulle [1820]. The oil was found to consist, among other substances, of asarone, pinene, methyl eugenol, and dimethyl protocatechuic acid.

Miller [1902] found that Asarum arifolium gives an oil which contains *l*-pinene, eugenol, safrol, methyl eugenol, methyl-iso-eugenol, asarone, a sesquiterpene and an unidentified phenol.

The oil of asarum Canadense was found by Power and Lees [1902] to contain a phenol $C_9H_{12}O_2$, pinene, d-linalool, *l*-borneol, *l*-terpineol, geraniol, methyl eugenol, a lactone $C_{14}H_{20}O_2$, palmitic and acetic acids.

The oil of Asarum Candatum was found by Burlage and Lynn [1927] to contain pinene, methyl eugenol, asarone and azulene.

From the oil of Asarum Blumei, Buch., Asahina [1907] obtained eugenol, safrol and a terpene.

The oil of Asarum seiboldi, Miq, was found by Takeyn Takahashi [1930] to contain palmitic acid, methyl eugenol, a phenol $C_{10}H_{10}O_4$ and an asaryl ketone. These constituents, with the addition of pinene and safrol were later also isolated by Kaku and his co-workers [1931] from the oil of asarum sieboldi, Miq. var. seoulensis Nakai; when further examined, the phenol $C_{10}H_{10}O_4$ was found to melt at 110° C, forming an acetate, m.p. 129-130° and a benzoate, m.p. 123° and the ketone, resembling eucarvone, has the molecular formula $C_{10}H_{14}O$ and a boiling point 200°, giving a semicarbazone, m.p. 185°.

The present investigation of the essential oil obtained from Hsi-hsin by steam distillation has resulted in the isolation of pinene, methyl-eugenol, a phenol, a ketone and some organic acids not further examined, the phenol and the ketone being found to be identical with those obtained by Kaku and others as mentioned above. From the non-volatile resinous matter obtained by extracting the Hsi-hsin with benzene, there has been isolated a crystalline neutral principle having a molecular formula $C_{10}H_9O_3$, a melting point 124° C and a specific rotation —130°. The yeild came to about 0.2 per cent of the air-dried plant. It is insoluble in caustic alkalies and does not react with acetic anhydride or phenylhydrazine. It contains no methoxyl groups.

EXPERIMENTAL

The volatile oil.

The finely powdered plant was macerated with water and subjected to steam distillation. The oily layer was separated, a further quantity being obtained by saturating the aqueous distillate with common salt. The collected oil was dried with anhydrous sodium sulphate and weighed. The yield came to about 2.75 per cent of the air-dried plant. It has the following properties:

Specific gravity	= 1.0308 at 12° C.
Specific rotation $(\alpha)_D$	= 0°
Index of Refraction N25/D	= 1.5212.
Acid value	= 1.44
Saponification number	= 21.89
Saponification number after acetylation	= 39.51

After being washed with one per cent sodium carbonate solution to remove organic acids and then with one per cent sodium hydroxide solution to remove phenolic substances. The oil was dried and submitted to vacuum distillation at 28 mm pressure, the following five fractions being collected, (1) up to 130° (2) 130-140° (3) 140-150° (4) 150-160° and (5) 160-170°. There remained much residue in the distilling flask. The following constituents have been isolated from the alkaline washings and different fractions.

1. *Organic acids.* The sodium carbonate solution was acidified with hydrochloric acid and extracted with ether. The ethereal solution when dried with anhydrous sodium sulphate and distilled, left behind an acid residue, which, on account of its small quantity, has not been further examined.

2. *Phenol.* The sodium hydroxide washings of the oil were acidified with sulphuric acid and subjected to steam distillation. The steam distillate was treated with common salt and exhausted with ether. The ethereal solution was dried and concentrated to a small volume when the phenol crystallised out in orthorhombic prisms, melting at 110° C. It forms an acetate, prismatic needles from methyl-alcohol, m.p. 129-130° and a benzoate, m.p. 124°. All these properties correspond to the phenol $C_{10}H_{10}O_1$ obtained by Kaku [1931] and others. Much phenol was also obtained from the residue after vacuum distillation.

3. *Pinene.* The first two fractions showed the presence of much pinene which was identified as its dibromide. The oil was dissolved in a mixture of alcohol and ether and a sufficient quantity of bromine was then added drop by drop until the solution coloured dark-blue. On standing, the pinene dibromide crystallised out in needles. When crystallised pure from acetone, it melts at 170°. When analysed, it gave the following results:

0.2227 g sub. gave 0.2800 g AgBr,	Br = 53.51
Calculated for $C_{10}H_{16}Br_2$,	Br = 53.99

4. *Ketone.* The presence of a ketone in the fraction (3) was confirmed by the preparation of a semi-carbazone. The oil was dissolved in alcohol and treated with an aqueous solution of semi-carbazide

hydrochloride and sodium acetate by warming over water bath for some time. The clear solution was allowed to stand over night; the semi-carbazone crystallised out in groups of prisms, melting at 182° C instead of 185° C, the melting point of the semi-carbazone of the ketone $C_{10}H_{14}O$, obtained by Kaku and others [1031] as mentioned above.

5. *Methyl eugenol.* The confirmation of the presence of methyl-eugenol in the fractions (4) and (5) was effected by the preparation of the crystalline bromo eugenol methyl ether dibromide $C_6H_2Br\ (OCH_3)_2.C_3H_5Br_2$ which melts at 78-79° [Wasserman, 1879]. The oil was dissolved in carbon tetrachloride, cooled in an ice mixture and then a requisite quantity of bromine was added drop by drop until a permanent red colour was obtained, the excess of bromine present being afterwards removed by shaking the solution with an aqueous solution of sodium bisulphite. The carbon tetrachloride solution was dried and distilled and the residue taken up with absolute alcohol. Bromo-eugenol methyl ether dibromide crystallised out in colourless rhombic prisms, m.p. 78-79°. The presence of methyl eugenol was further confirmed by its oxidation to veratric acid [Peterson, 1888]. The oil was suspended in one per cent solution of sodium carbonate and treated with a sufficient quantity of powdered potassium permanganate by warming over water bath for some time. The alkaline solution was then cooled, filtered and concentrated to a small volume when veratric acid precipitated out on acidifying with dilute hydrochloric acid. When crystallised pure from alcohol, it formed prisms, m.p. 183°. When analysed, it gave the following results:

0.1668 g sub. gave 0.3629 g CO_2 and 0.0838 g H_2O; C = 59.34 ; H = 5.62

Calculated for veratric acid $C_9H_{10}O_4$, C = 59.31; H = 5.54.

The neutral principle $C_{10}H_9O_3$.

The finely powdered drug was percolated with benzene at room temperature for 2 days. The benzene solution was separated, concentrated and the residue subjected to steam distillation to remove the volatile oil and excess of benzene present. The resinous residue which remained in the distilling flask was taken up with chloroform. The

chloroform solution was dried and concentrated to a small volume when the neutral principle crystallised out on the addition of a sufficient quantity of petrole ether. When crystallised pure from chloroform with the addition of alcohol, it formed colourless prismatic needles, m.p. 124° C. It is easily soluble in benzene or chloroform, less so in alcohol, ether or acetone and insoluble in water, dilute acids and alkalies. Its alcoholic solution is neutral to litmus paper. It does not react with acetic anhydride or phenylhydrazine and contains no methoxyl groups. With conc. H_2SO_4, it gives a reddish brown solution. When warmed over water bath with a 40 per cent KOH solution, it remained unchanged. By prolonged heating with a 10 per cent sulphuric acid, it undergoes some change, but no definite decomposition products could be isolated. A one per cent solution in chloroform in 1 dm. tube gave a specific rotation of -- 1.3°; whence $[\alpha]_D^{30} = -130°$. It has the molecular formula $C_{10}H_9O_3$ according to the following analysis:—

(1) 0.1503 g sub. gave 0.3728 g CO_2 and 0.0707 g H_2O
C = 67.65; H = 5.26

(2) 0.1301 g sub. gave 0.3229 g CO_2 and 0.0607 g H_2O
C = 67.69; H = 5.22

(3) 0.0214 g sub. in 0.2034 g camphor; 23°C Δ; mol. wt. = 183. Calculated for the formula $C_{10}H_9O_3$, C = 67.77; H = 5.12; mol. wt. = 177.

SUMMARY

The essential oil of the Chinese drug, Hsi-hsin was found to contain the following constituents. (1) A small amount of organic acid not identified, (2) pinene, (3) A phenol, m.p. 110°; forming an acetate, m.p. 129-130° and a benzoate, m.p. 124°, (4) a ketone, whose semicarbazone melts at 182°, and (5) methyl eugenol. From the non-volatile resinous matter obtained by extracting the drug with benzene, there has been isolated a well crystallised neutral principle, having a molecular formula $C_{10}H_9O_3$, a melting point 124° and a specific rotation −130°. It contains no methoxyl groups and does not react with acetic anhydride and phenyl-hydrazine.

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中國細辛之研究

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細辛屬馬兜鈴科，爲 *Asarum Sieboldi*, Miq. 之根，中含有揮發油甚多。供於藥用，有發汗，祛痰，止頭痛之效。細辛之種類甚多，歐美人士研究其揮發油之成分者亦甚衆。日本產之細辛，據加來天民氏等之研究，中含有 palmitic acid, safrol, methyleugenol, a phenol $C_{10}H_{10}O_4$ and a ketone $C_{10}H_{14}O$. 作者等今研究中國細辛，發現其揮發油之成分與日本產之細辛相同。惟在揮發油外又發現一中性結晶物。其分子式爲 $C_9H_{10}O_3$，熔點爲124°，，旋轉度爲－130°。化學性甚固定，不易與他種化學物發生變化。其生理性質，俟研究後再行報告。