# THE ALKALOIDS OF GELSEMIUM II. SEMPERVINE AND AN AMORPHOUS ALKALOID

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With notes on their Physiological properties by

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In a previous communication on gelsemium (1), the writer reported the isolation of Gelsemine and Gelsemicine, a new alkaloid from the rhizome and roots of American gelsemium. Gelsemicine which has the molecular formula  $C_{20}H_{25}O_4N_2$ , a specific rotation  $-140^\circ$  and a melting point  $171^\circ$  C, has been found by Hou (2), to be highly potent and toxic and with regard to its toxicity and other physiological properties, can be considered as the representative principle of gelsemium.

The basic residue of fraction 2 as described in the previous communication (1), shows the presence of other alkaloids, one of which has now been isolated only in its amorphous state. The present investigation of fraction 1 has resulted in the isolation of a highly coloured weak base to which the writer gives the name Sempervine, together with some gelsemic acid and gelsemine. Sempervine is very similar to Sayre's sempervirine (3) isolated from American gelsemium in its general chemical behavior but differs from the latter in its melting point. It crystallises out from chloroform in blood-red prismatic needles melting at 223° C and from alcohol in red orthorhombic crystals melting at 254° C, both of them, however give rise to the formation of the same nitrate melting at 282° C with decomposition. It also produces the toxic effects of gelsemium in mammals, but no dilatation of the pupil of the eye was observed.

#### EXPERIMENTAL

The alcohol extract of American gelsemium, when evaporated to syrup at a low temperature as described in a previous communication (1), was taken up with a sufficient quantity of dilute hydrochloric acid nd filtered from the resinous matter. The acid solution when allow ed to stand at ordinary temperature for about 2 weeks, deposited a crystalline mass. This constitutes fraction 1 and the acid solution fraction 2. Fraction 1 was found to consist of the hydrochlorides of gelsemine and sempervine, a new alkaloid together with some gelsemic acid. It was worked up in the following manner:—

#### 1. Gelsemic acid.

The crystalline deposit of fraction 1 was warmed with a sufficient quantity of water over a water bath for some time. Alkaloid salts went into solution, leaving behind gelsemic acid as a crystalline residue on account of its slight solubility in water. It was filtered, washed, dried and recrystallised from chloroform in which it separated out in the form of colourless needles, melting at  $205^{\circ}$  C. It dissolved in dilute nitric acid to a yellow solution which turned blood red on the addition of ammonia and gave a characteristic blue fluorescence in alkaline solutions. As its melting point and properties left no doubt of its being gelsemic acid, it was not further examined. Gelsemic acid has the formula  $C_{10}H_8O_4$  and was first obtained by Wormley (5) from the acidulated fluid extract of the gelsemium root and later on by other workers. Schmidt (4) has shown that it is identical with scopoletin, a substance isolated from *Scopolia japonica*.

#### 2. Sempervine.

After the removal of gelsemic acid as above, the aqueous solution of alkaloid salts was made alkaline with ammonia and the liberated base was extracted with a mixture of ether and chloroform. This removed completely the gelsemine present, and left behind a crystalline insoluble residue, which was found to behave like a weak base dissolving slightly in water to an almost neutral solution, but forming well crystallised salts. The name Sempervine is suggested for this new substance. It was soluble in chloroform and alcohol, slightly soluble in water and insoluble in ether, benzene and petroleum ether. When crystallised pure, it separated out from chloroform in blood-red prismatic needles (fig. 1), melting at 223° C to a dark red liquid, and from alcohol in orthorhombic crystals (fig. 2), melting at 254° C

both of them, however, formed the same nitrate melting at  $282^{\circ}$  C with decomposition. It dissolved in concentrated sulphuric acid to a brown solution, becoming dirty green on the addition of a crystal of  $K_2Cr_2O_7$ . It was unstable towards heat and its crystallisation from chloroform or alcohol had to be carried out as quickly as possible as on prolonged heating over a water bath, it resinified, becoming insoluble in these solvents and in acids. Its salts are however, found to be quite stable. The nitrate and hydrochloride were prepared.

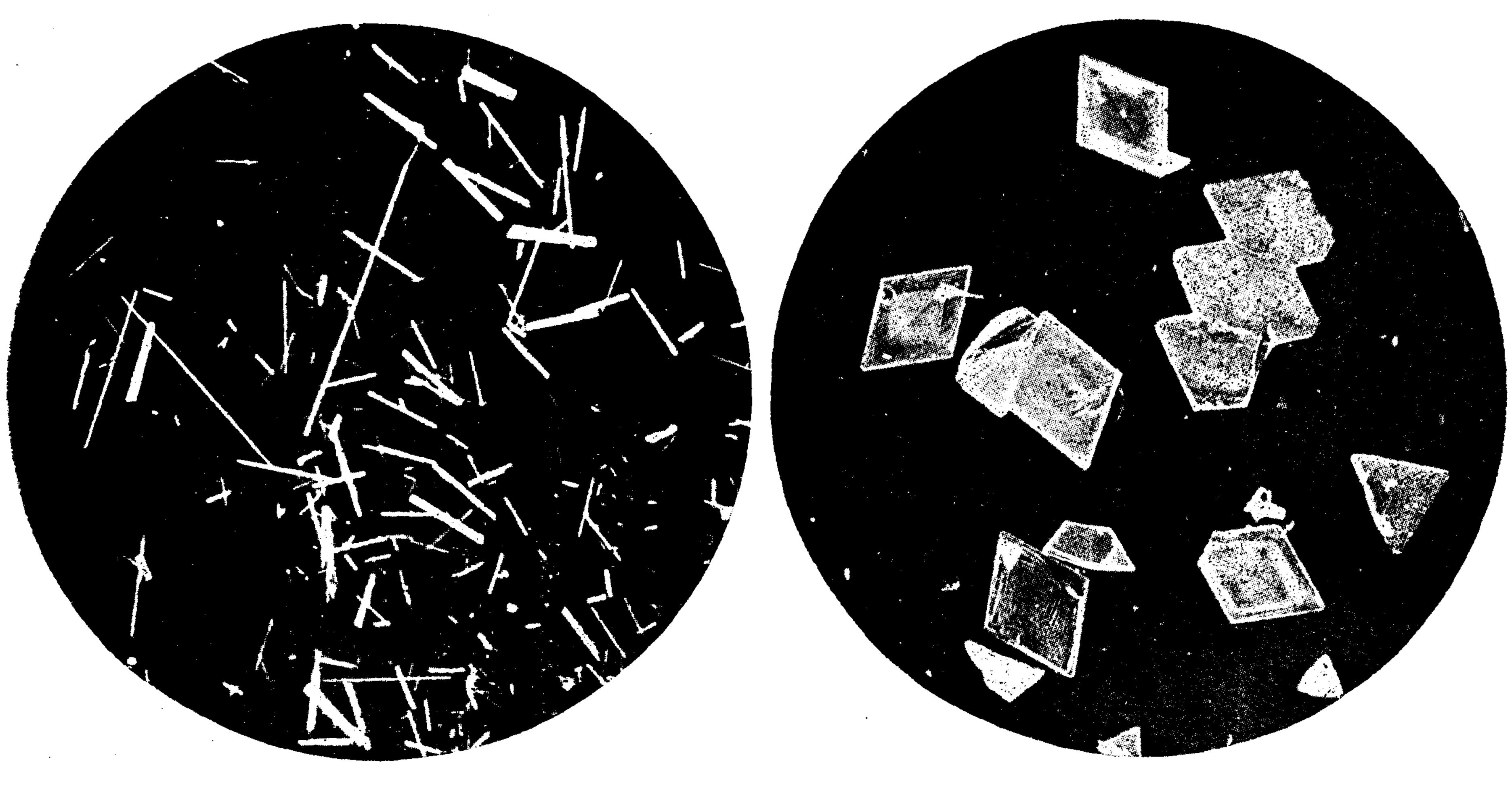


Fig. 1.
Sempervine
Crystallised from CHCl<sub>3</sub>
m.p. 223° C.

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Fig. 2.

Sempervine

Crystallised from alcohol

m.p. 254° C.

- a. Nitrate. Prepared by dissolving sempervine in a sufficient quantity of dilute acetic acid and precipitating with an aqueous solution of NaNO<sub>3</sub>. It was recrystallised from alcohol in which it was easily soluble on warming. On cooling it gave well formed yellow prisms m. p. 282° C with decomposition. It was soluble in water with difficulty.
- b. Hydrochloride. Prepared by dissolving sempervine in dilute hydrochloric acid and evaporating to dryness over water both. The residue was taken up in alcohol from which it crystallised out on the addition of a sufficient quantity of ether in stout yellow prisms melting over 300° C. It is easily soluble in water to a neutral solution and forms precipitates with  $H_2SO_4$  HCl and  $HNO_3$ , but not with acetic acid and with salts such as NaCl, NaNO<sub>3</sub> MgCl<sub>2</sub> PtCl<sub>4</sub> and

 $K_4$ Fe(CN)<sub>6</sub>. Its aqueous solution seems to be optically inactive, although no distinct reading from the polariscope could be made on account of the deep coloration of the liquid.

Sempervine shows a striking similarity to Sayre's sempervirine (3) in its chemical behavior and the general properties of its salts, but differs from it in its melting point and in other respects. The following table will serve for comparison.

#### Sempervirine

Reddish brown needles from chloroform and short thick needles from alcohol; fused together at 220° C, but not melted when heated to 280° C.

Dissolved in conc.  $H_2SO_4$  to a reddish brown solution, giving no change on adding a crystal of  $K_3Cr_2O_7$ .

#### Sempervirine nitrate

Yellow needle-shaped crystals from alcohol; darken at 210° C and partially fused at 280° C.

#### Sempervine

Blood-red needles from chloroform, melting at 223° C and red orthorhombic prisms from alcohol melting at 254° C.

Dissolved in conc. H<sub>2</sub>SO<sub>4</sub> to a reddish brown solution, becoming dirty green on adding a crystal of K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>.

#### Sempervine nitrate

Yellow prisms from alcohol; melted at 282° C with decomposition.

#### Physiological properties of Sempervine. (By Dr. H. C. Hou)

Six mg of its hydrochloride per kilo killed a male rabbit weighing 1.53 kg in five minutes. The accompanying symptoms were slowed respirations, strychnine-like convulsions, muscular spasm and crying. Three to five mg per kilo produced in some rabbits no symptoms except a slightly drowsy appearance.

Administration of the drug to the eye produced no mydriasis but lachrymation and some congestion of the conjunctiva. In frogs, 0.15 mg per gram bodyweight produced a gradual depression, stoppage of breathing, paralysis of the extremities and death in 4 hours.

#### 3. The amorphous alkaloid.

The basic residue of fraction 2 from which gelsemine and gelsemicine had been removed as described in the previous communication (1), was taken up with dilute hydrochloric acid and the acid solution filtered, washed repeatedly with chloroform and then treated cautiously with a small amount of NaCl in order to precipitate out some resinous matter. The material, obtained on rendering the acid solution alkaline, was extracted several times with ether to remove gelsemine and gelsemicine still present and then with benzene in which nearly all dissolved. The benzene extract, when dried and distilled, left behind a light yellow coloured amorphous residue which

responded to the usual alkaloid reagents and formed salts easily soluble in water. Neither the free base nor any of its salts could be obtained in a crystalline condition. Differing from gelsemicine and sempervine, its solution in conc. H<sub>2</sub>SO<sub>4</sub> undergoes no change on standing, but turns violet and green on adding a crystal of K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> and the aqueous solution of its hydrochloride gives no precipitate with NaNO<sub>3</sub> or NaCl. A 1 per cent aqueous solution of its hydrochloride in 1 dcm tube gave a specific rotation of  $-0.35^{\circ}$ , whence [ $\alpha$ ]  $D/25=35^{\circ}$  whether this amorphous alkaloid is a single substance or a mixture of several alkaloids needs further investigation.

#### Physiological properties of amorphous alkaloid. (By Dr. H. C. Hou)

Half mg of its hydrochloride produced in rabbits quietness, tremors, incoordination of movement, weakness of legs, slow and spasmodic respiration, but eventually there was recovery. A dose of 0.7 mg per kilo produced much more severe symptoms. There were convulsions, dyspnoea and marked prostration preceding death, which occurred in 50 minutes after the injection. The pupils were dilated.

#### SUMMARY

From the rhizome and roots of American gelsemium, a third crystalline alkaloid sempervine has been isolated. It melts at 223° C when crystallised from chloroform and at 254° C when crystallised from alcohol. A fourth alkaloid has only been obtained in its amorphous state. Gelsemic acid has also been isolated in colourless needles, melting at 205° C.

A preliminary investigation of the physiological properties of both sempervine and amorphous alkaloid has been made.

#### LITERATURE

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WORMLEY, T G.

# 美國鈎吻之有機鱗質

### 其一。鈎吻素丙及鈎吻素丁

## 趙承嘏

附及關於鈎吻素丙及丁之生理性質之略記

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關於鈎吻素甲及鈎吻素乙之提取,已於本雜誌第五卷第二期中詳細報告。今作者又從美國鈎吻中提出二有效質素,命名爲鈎吻素丙(sempervine)及鈎吻素丁(amorphous alkaloid). 鈎吻素丙之熔點有二,如在哥羅芳中結晶時熔點爲 223°C,如在酒精中結晶時熔點則爲 254°C. 鈎吻素丁則爲一不結晶之有機鹻質。

鈎吻酸 (gelsemic acid) 亦同時提出,如針形之結晶物,熔點為 205°C.