

## THE ALKALOIDS OF CHINESE CORYDALIS AMBIGUA, CHAM. ET SCH. (YEN-HU-SO) PART I.\*

TSAN-QUO CHOU

**Note on physiological properties of *Corydalis B* and *Corydalis C*.**

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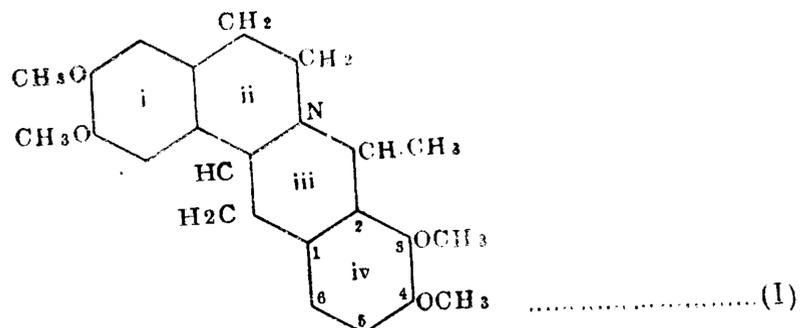
### INTRODUCTION

The knowledge and first description of Corydaline, the principal alkaloid of *Corydalis* roots, go back more than a hundred years. It was discovered in 1826 by Wackenroder (28) in the roots of *Corydalis tuberosa* and was subsequently examined by several investigators. Mention should be made of the work done by Wicke (29), who in 1866 analysed well crystallised salts of the alkaloid and assigned to it the formula  $C_{18}H_{19}O_4N$  which was changed to  $C_{22}H_{23}O_4N$  by Birsmann (3). It was not prepared in pure state until 1892, when Dobbie and Lauder (7) published a more complete and careful account of Corydaline (isolated from the dried root of *C. tuberosa*), than had hitherto appeared, accompanied by numerous analyses of the base and its compounds. From these they deduced the formula  $C_{22}H_{28}O_4N$  and gave its melting point as  $134.5^\circ$  and its specific rotation as  $+311^\circ$ . Freund and Josephy (12) found, however, that the alkaloid was better represented by the formula  $C_{22}H_{27}O_4N$  which is now generally accepted.

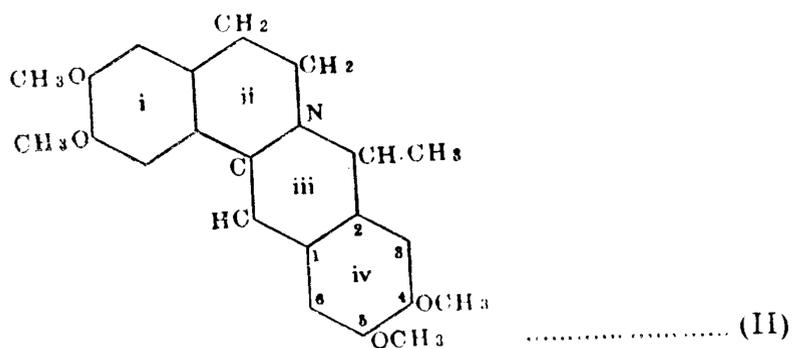
The susceptibility of Corydaline to the action of light and heat is well known, as its solution in alcohol rapidly assumes a yellow colour on standing unless it is kept in a cool dark place. This probably accounts

\*A preliminary report was presented at the meeting of February, 9, 1928, to the Peking Branch of the Society for Exper. Biol. and Med., and an abstract was published in the Proceedings for that meeting.

for the difficulty in producing the pure alkaloid by certain workers. Corydaline forms a large number of salts and derivatives; *ethyl sulphate*, melting at  $152.5^{\circ}$  or  $150-160^{\circ}$  according to Dobbie and Lauder (8), and crystallising from water in beautiful prisms; *hydrochloride* prisms with two molecules of water of crystallization, melting at  $207^{\circ}$  as given by Freund and Josephy (12), some times found to be either crystallisable with difficulty on account of the tendency of its solution to become gummy (7) or non-crystallisable (5). The constitutional formula of Corydaline (formula I) was first suggested by Dobbie and Lauder (10) after a careful study of its various oxidation products.

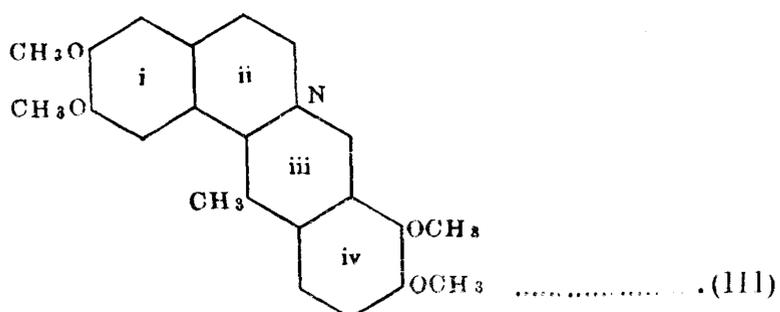


The writer (24) in attempting to synthesize Corydaline according to the above formula, condensed tetrahydropapaverine with methylal in the presence of hydrochloric acid and named the resulting product Nor-coralydine, which on oxidation with iodine in alcohol and subsequent treatment with magnesium methyl iodide, gave rise to the formation of a methyl base (formula II).



On further oxidation of this base with iodine and alcohol, salts of dehydro-coralydine were obtained instead of those of dehydro corydaline. This was attributed to the fact that the 2 methoxyl groups in ring *iv* occupied

two different positions, viz. 4 and 5, instead of the positions 3 and 4 as in Corydaline. More recently Späth and Lang (25) threw some doubt on Dobbie and Lauder's constitutional formula for Corydaline with regard to the position of the methyl group in ring *iii* and Gadamer and Bruchhausen (15) agreed with their conclusions and accepted formula III annexed for Corydaline.



This has been further confirmed by the recent work of Bruchhausen and Stippler (5).

Since the discovery of Corydaline by Wackenroder, a dozen other alkaloids have been successively isolated from *Corydalis cava* and other species of *Corydalis* roots by Dobbie and Lauder (9), Freund and Josephy (11), Merck (22), Gadamer (13), Späth (26), Heyl (17), Makoshi (19), Asahina (2), and others, and to most of these molecular and constitutional formulae have now been assigned. The following is a list of the more important *Corydalis* alkaloids.

Corydaline  $C_{22}H_{27}O_4N$ , m.p.  $135^\circ$ ;  $[\alpha]_{20/D} = +300.1^\circ$  (in chloroform).

Dehydro-corydaline  $C_{22}H_{23}O_4N$ , m.p.  $112 - 113^\circ$

Corybulbine  $C_{21}H_{25}O_4N$ , m.p.  $238^\circ$ ;  $[\alpha]_D = +303.3^\circ$  (in chloroform).

Iso-corybulbine  $C_{21}H_{25}O_4N$ , m.p.  $179^\circ - 180^\circ$   $[\alpha]_D = +299.8^\circ$   
(in chloroform).

d-Tetrahydropalmatine  $C_{21}H_{25}O_4N$ , m.p.  $142^\circ$ ;  $[\alpha]_{17/D} = +292.5^\circ$   
(in alcohol).

Corypalmine  $C_{20}H_{23}O_4N$ , m.p.  $235^\circ - 236^\circ$ ;  $[\alpha]_{16/D} = +280^\circ$   
(in chloroform).

Corycavine  $C_{23}H_{23}O_6N$ , m.p.  $218^\circ - 219^\circ$ ;  $[\alpha] = 0^\circ$ .

Corycavamine  $C_{21}H_{21}O_5N$ , m.p.  $149^\circ$ ;  $[\alpha]_{20/D} = +166.6^\circ$   
(in chloroform).

Corycavidine  $C_{22}H_{23}O_5N$ , m.p.  $212^\circ - 213^\circ$   $[\alpha]_{20/D} = +203.1^\circ$   
(in chloroform).

Bulbocapnine  $C_{19}H_{19}O_4N$ , m.p.  $199^\circ$ ;  $[\alpha]_D = +237.1^\circ$  (in chloroform).

Corydine  $C_{20}H_{23}O_4N$ , m.p.  $124^\circ - 125^\circ$  or  $149^\circ$  (dry)  $[\alpha]_{20/D} = +204.3^\circ$  (in chloroform).

Corytuberine  $C_{19}H_{21}O_4N \cdot 5H_2O$ , m.p.  $240^\circ$ ;  $[\alpha]_{20/D} = +282.65^\circ$  (in alcohol).

Other notable work done on Corydalis alkaloids isolated from various Corydalis roots may be summarized as follows.

In 1893 Birsmann (4) isolated 6 alkaloids from *Corydalis nobilis*, the first one was given the formula  $C_{21}H_{21}O_4N$  and the second  $C_{22}H_{25}O_5N$  named Corydaline nobiline and supposed to be identical with Corydaline. The other four have not been further examined.

In 1905 Haars (16) isolated bulbocapnine from both *Corydalis cava* and *Corydalis solida* with the addition of two new alkaloids (from *Corydalis cava*) (a)  $C_{21}H_{21}O_8N$  melting at  $230^\circ$ ;  $[\alpha]_{20/D} = -112.8^\circ$ ; its platinum chloride melts at  $214^\circ$ , (b)  $C_{21}H_{23}O_7N$  or  $C_{21}H_{25}O_7N$ , m.p.  $137.5^\circ$ ;  $[\alpha]_{20/D} = +96.8^\circ$ . Protopine could not be detected.

In 1910 Heyl (17) obtained a new alkaloid from *Corydalis aurea*, melting at  $148^\circ - 149^\circ$ ; it gives the following colour reactions:— $HNO_3$  (D 1.3) colourless and then faintly yellowish red; Erdmann's reagent, colourless; Froehde's reagent, olive green, slowly becoming bluish grey; Mandelin's reagent, olive to brownish green. Two other bases, melting at  $145^\circ$  and  $132^\circ - 133^\circ$  respectively were also isolated by him from *Corydalis solida* in which protopine was also found to be present.

In 1911 Gadamer (14) reinvestigated the tubers of *Corydalis cava* and isolated protopine, glaucine, Haar's alkaloid  $C_{21}H_{23}O_7N$ , a fourth alkaloid giving a crystalline perchlorate and a fifth amorphous yielding only amorphous salts. These five were non-phenolic. Some phenolic bases were also obtained, including bulbocapnine and two other bases in the form of their l-acid tartrate.

In 1908 Makoshi (20) isolated from Japanese Corydalis root (*Corydalis vernyi*) two alkaloids, one identical with protopine and other like dehydro-corydaline; but Asahina and Fujita (1) stated that the tubers examined by Makoshi were derived from *Corydalis decumbens* and Asahina and Motigase obtained from the same plant, in addition to protopine and bulbocapnine, a non-phenolic base, m. p.  $142^\circ$  and a second phenolic base m.p.  $175^\circ$ . Further work on *Corydalis decumbens* was carried out by Shoji Osada (23) who identified the base melting at  $142^\circ$  to be d-tetrahydropalmatine and isolated two additional new bases melting at  $205^\circ$  and  $228^\circ - 230^\circ$  respectively. The Chinese Corydalis

tubers, Yen-hu-so, identified as *Corydalis ambigua*, Cham. et. Sch. by Matsumura (21) and Stuart (27), are met with as small firm, brownish-yellow flattened pellets, with a depression on one of the surface (see fig. 1). To the drug itself, as appearing in China, is ascribed tonic, diuretic, astringent, alterative and sedative properties (18). Its chemical investigation was first carried out by K. Makoshi (19), who after much labour, isolated from it Corydaline, dehydro-corydaline, corybulbine, protopine and two other alkaloids, (a)  $C_{20}H_{17}O_4N$ , a quaternary base giving a hydrochloride, red needles and an aurichloride, m.p.  $280^\circ$  and yielding on reduction a colourless tetrahydro base  $C_{20}H_{21}O_4N$ , m.p.  $218^\circ$ - $219^\circ$  and (b) a substance, occurring in greyish-white needles, m.p.  $197^\circ$ - $199^\circ$ , resembling, but not identical with bulbocapnine.

The present work consists of a chemical study of the Chinese drug Yen-hu-so, bought from Chichow, China. The writer found that it contains more alkaloids than had hitherto been isolated. The basic products obtained from the drug, were divided into four fractions. Fraction 2 consisting of the largest part and weighing about 20 gm from 16 kg of raw material used, is non-phenolic and was first studied. Up to now five alkaloids have been isolated from fraction 2 and named provisionally Corydalis A, Corydalis B, Corydalis C, Corydalis D and Corydalis E respectively until further confirmation. Corydalis A is identical with Corydaline in all respects; the melting points of its ethyl sulphate, methiodide and hydrochloride, differ, however, somewhat from those obtained by other workers. Its hydrochloride is further found to be easily crystallizable from water. Corydalis B, although having the same melting point as that obtained by Heyl from *Corydalis aurea* (17), shows different colour reactions towards nitric acid and Erdmann's reagent. Corydalis C is identical with protopine in its molecular formula and certain colour reactions, but melts constantly at  $201^\circ$  after repeated recrystallisation instead of  $207^\circ$ , the m.p. of protopine (29). Corydalis E is rather highly leavo-rotatory; in fact it is the first alkaloid isolated from Corydalis plants having a specific rotation  $-295^\circ$ . Corydalis D on account of its small amount in hand, has not been investigated in detail.

Further study of these alkaloids as well as the isolation of other bases from the fractions 1, 3 and 4 are in active progress.

The physiological properties of Corydalis B and Corydalis C are being investigated by Drs. H.P. Chu and C. Pak to whom I am indebted for the notes appended to this paper.

## EXPERIMENTAL

Sixteen kilograms of Chinese Corydalis (Yen-hu-so) were finely powdered and percolated with cold benzene at room temperature for five days. It was surprising to find that the benzene solution already contained some alkaloids including Corydaline. This constitutes fraction 1. The marc was again percolated with benzene in the presence of a sufficient quantity of dilute sodium carbonate in the cold for about a week. The resulting basic products were treated with dilute NaOH in order to separate non-phenolic and phenolic bases. The former is called fraction 2 and the latter fraction 3.

After being twice extracted with benzene as above, the marc was finally treated with 95 per cent alcohol at ordinary temperature to extract quaternary bases and other bases still present. This forms fraction 4.

Fraction 2 consisting of the largest part and weighing about 20 gm after being freed from non-basic impurities, was first investigated. The purification of the bases in this fraction proved a tedious matter. Suffice to say that after spending much time five alkaloids have been isolated in pure state from fraction 2. They are all non-phenolic and are named Corydalis A, Corydalis B, Corydalis C, Corydalis D and Corydalis E. The purity of each base has been ascertained by its constant melting point and further confirmed by comparing with that derived from its various purified salts.

(1) *Corydalis A. (Corydaline)*  $C_{22}H_{27}O_4N$ .

Corydalis A crystallises out from alcohol in six-sided prisms (see fig. 2). m.p.  $135^\circ$ . On exposing to the action of light and heat, it turns rapidly yellow; colourless crystals can only be obtained by keeping its solution in a cool dark place. It is only sparingly soluble in cold alcohol, but dissolves easily on warming. It is easily soluble in ether or chloroform, insoluble in water or alkalis. A 2 per cent solution in alcohol in a 2-dm tube gives a specific rotation  $+11.8^\circ$ ,  $[\alpha]_{25/D} = +29.5^\circ$  instead of  $311^\circ$  or  $300.1^\circ$  as given by certain authors (15). The same rotation was obtained with its chloroform solution. Its molecular formula is found to be  $C_{22}H_{27}O_4N$ , identical with Corydaline according to the following analysis:—

- (i) 0.1222 gm substance gave 0.3212 gm  $CO_2$  and 0.0810 gm  $H_2O$   
                                   C=71.68;                  H=7.36.
- (ii) 0.1310 gm substance gave 0.3438 gm  $CO_2$  and 0.0844 gm  $H_2O$   
                                   C=71.57;                  H=7.15.

(iii) 0.1058 gm substance gave 3.6 cc moist nitrogen at 20°C and 778 mm pressure N=3.96.

Calculated for Corydaline  $C_{22}H_{27}O_4N$ ,

C=71.54; H=7.31; N=3.79.

The following salts were prepared.

(a) *Ethyl sulphate*. Prepared according to the process of Dobbie and Lauder (8) in principle. Pure base (0.10 gm) was dissolved in 15 cc of 95 per cent alcohol with the addition of one drop of conc.  $H_2SO_4$ . The whole was allowed to concentrate slowly on a water bath to a syrupy consistency when the residue was taken up with 8 cc of warm water. The salt crystallises out in colourless long prisms on standing (see fig. 3). After being twice recrystallised from hot water, it melts constantly at 162° instead of 152.5° of 150°-160° as given by Dobbie and Lauder.

(b) *Hydrochloride*. This was best prepared in aqueous solution: 0.7 gm of pure Corydalis A was dissolved in 5 cc of water with the aid of an amount of hydrochloric acid just sufficient to make the aqueous solution slightly acid to litmus. On being kept in a cool dark place for two days, the hydrochloride crystallised out slowly in large colourless prisms, m. p. 214° when air dried. The hydrochloride prepared in ether-alcohol solution, is usually yellowish in colour. It is soluble in chloroform.

(c) *Nitrate*. Prepared by neutralizing an aqueous solution of Corydalis A with  $HNO_3$  previously diluted with alcohol. Recrystallised from alcohol in yellowish six-sided prisms, m. p. 197° C with decomposition.

(d) *Platinichloride*. Prepared by treating an aqueous solution of Corydalis A with a 5 per cent solution of platinum chloride in the presence of a drop of dilute hydrochloric acid; yellowish precipitate, m. p. 227°.

(e) *Methiodide*. A small quantity of Corydalis A was treated with an excess of methyl iodide in methyl alcohol solution by warming with reflux over water bath for about ten minutes and then allowing to stand in a cool dark place for a week. Grouping of prisms crystallised out, m. p. 228°. On concentrating its mother liquid, a further quantity of well formed prisms was obtained with the same melting point. No amorphous methiodide as mentioned by Bruchhausen and Stippler (5) could be isolated. It is easily soluble in alcohol and insoluble in ether. The properties of Corydalis A and its salts as shown above proved its complete identity with Corydaline.

(2) *Corydalis B.*  $C_{20}H_{23}O_4N$ .

The solubility of this alkaloid in alcohol and its other properties are very similar to those of Corydaline. It dissolves easily in warm alcohol and crystallises out in six-sided plates (see fig. 4) on cooling, m. p.  $148^{\circ}$ - $149^{\circ}$ . Like Corydaline, it turns rapidly yellow on exposure to the action of light and heat. It is readily soluble in chloroform or ether, sparingly so in petroleum ether and insoluble in water or alkalis. Its solution in alcohol or chloroform is optically inactive  $[\alpha]_D = 0^{\circ}$ . Analysis: —

- (i) 0.1302 gm substance gave 0.3367 gm  $CO_2$  and 0.0802 gm  $H_2O$ .  
C=70.52; H=6.84.
- (ii) 0.1280 gm substance gave 0.3301 gm  $CO_2$  and 0.0804 gm  $H_2O$ .  
C=70.33; H=6.97
- (iii) 0.1148 gm substance gave 4.2 cc moist nitrogen at  $18^{\circ}C$  and 778 mm pressure. N=4.30.

Calculated for the formula  $C_{20}H_{23}O_4N$ : —  
C=70.38; H=6.74; N=4.1.

It has the same melting point as that of Heyl's alkaloid (17) from *Corydalis aurea*, but differs from the latter in other properties as shown in table 1. Heyl did not mention its specific rotation and molecular formula.

TABLE 1.  
*A comparison of Heyl's alkaloid with Corydalis B*

	Heyl's alkaloid	Corydalis B.
M. p.	$148^{\circ}$ - $149^{\circ}$	$148^{\circ}$ - $149^{\circ}$
Sp. rotation	—	$[\alpha]_D = 0^{\circ}$
Molecular formula	—	$C_{20}H_{23}O_4N$
$HNO_3$ (D 1.5)	Colourless and then faintly yellowish-red	Yellow instantly
Erdmann's reagent	Colourless	Olive green, becoming orange yellow
Froehde's reagent	Olive green, slowly becoming bluish grey	Green, then deep blue

Heyl did not mention its specific rotation and molecular formula.

Two salts of Corydalis B were prepared.

(a) *Hydrochloride*. Colourless prismatic needles were obtained by neutralizing the base with hydrochloric acid in hot water from which it can be easily recrystallised; m. p. about  $215^{\circ}$ . In cold water or alcohol it is only sparingly soluble. The hydrochloride prepared in alcoholic solution is generally more or less coloured.

(b) *Acid oxalate*. Prepared by dissolving molecular proportions of the base and oxalic acid in hot water. Well formed colourless prisms (see fig. 5) m.p.  $208^{\circ}$  with decomposition. Its aqueous solution is acid to litmus. It dissolves easily in hot water or alcohol and crystallises on cooling.

(3) *Corydalis C*.  $C_{20}H_{19}O_5N$ .

This alkaloid usually crystallises out from very dilute solutions of a mixture of chloroform and alcohol in the form of nodular masses (see fig. 6) or prisms. It melts at  $201^{\circ}$  and is readily soluble in chloroform, sparingly so in ether or alcohol, insoluble in petroleum ether. Towards the action of light and heat, it is rather stable. Its solution in chloroform is optically inactive  $[\alpha]_D=0^{\circ}$ .

Analysis:—

(i) 0.1236 gm substance gave 0.3084 gm  $CO_2$  and 0.0592 gm  $H_2O$ .  
C=68.04; H=5.30.

(ii) 0.1226 gm substance gave 0.5030 gm  $CO_2$  and 0.0580 gm  $H_2O$ .  
C=68.07; H=5.25.

(iii) 0.1146 gm substance gave 4.1 cc moist nitrogen at  $22^{\circ}$  and 774 mm pressure. N=4.11.

Calculated for the formula  $C_{20}H_{19}O_5N$ .

C=67.98; H=5.38; N=3.96.

It shows colour reactions (table 2) which may be compared with those of protopine as described by Asahina and Motigase (2). Its molecular formula, solubilities and colour reactions suggest its identity with protopine, but its m.p. remains constantly at  $201^{\circ}$  after repeated recrystallisations instead of  $207^{\circ}$  m.p. of protopine.

TABLE 2.

*A comparison of protopine with Corydalis C.*

	Protopine	Corydalis C
Conc. $HNO_3$ Conc. $H_2SO_4$	yellow violet	yellow, orange yellow yellow, greenish yellow, reddish violet
Froehde's reagent Erdmann's reagent	yellow, violet, blue violet, deep violet	violet, deep blue violet, greenish grey

The following salts of Corydalis C have been prepared.

(a) *Hydrochloride*. Crystallised out from hot water in colourless long square prisms (see fig. 7) melting at  $248^{\circ}$  with decomposition. It is easily soluble in hot water, less so in cold water or alcohol.

(b) *Hydrobromide*. Crystallised out from boiling water in prisms m.p.  $250^{\circ}$ . It is sparingly soluble in alcohol or cold water.

(c) *Acid oxalate*. Prepared by dissolving equal molecular proportions of Corydalis C and oxalic acid in hot water from which it crystallises out on cooling in prisms, m.p.  $237^{\circ}$ . Its aqueous solution is acid to litmus.

(d) *Aurichloride*. Obtained by adding a 5 per cent gold chloride solution to an aqueous solution of Corydalis C hydrochloride in the presence of dilute hydrochloric acid; reddish brown amorphous precipitate, m.p.  $195^{\circ}$ .

(4) *Corydalis D*.  $C_{19}H_{16}O_4N$  or  $C_{19}H_{17}O_4N$ .

This crystallises out from chloroform, by the addition of an equal volume of alcohol in prisms (see fig. 8), m.p.  $204^{\circ}$ . It is only sparingly soluble in the usual organic solvents except chloroform in which it is readily soluble. A 1 per cent solution in chloroform in a 1-dm tube gave a specific rotation  $-2.95^{\circ}$   $[\alpha]_{25/D} = -295^{\circ}$ .

Analysis:—

(i) 0.1222 gm substance gave 0.3164 gm  $CO_2$  and 0.0546 gm  $H_2O$ .  
C=70.61; H=4.96.

(ii) 0.1204 gm substance gave 0.3128 gm  $CO_2$  and 0.0566 gm  $H_2O$ .  
C=70.84; H=5.22.

(iii) 0.1123 gm substance gave 4.4 cc moist nitrogen at  $22^{\circ}$  and 774 mm pressure. N=4.48.

Calculated for the formula  $C_{19}H_{16}O_4N$  or  $C_{19}H_{17}O_4N$ .

C=70.80	C=70.58.
H=4.96	H=5.26.
N=4.34	N=4.33.

This substance may therefore have one of the above two formulae.

*Colour reactions.*

Conc.  $HNO_3$ , orange yellow; conc.  $H_2SO_4$ , greenish grey, becoming slowly violet; Froehde's reagent, green, deep green, blue; Erdmann's reagent, green, yellowish orange.

(a) *Hydrochloride*. Prepared by neutralizing a chloroform solution of Corydalis D with conc. HCl previously diluted with alcohol. The

crystals are fine needles (see fig. 9) with a m.p. about 250°. It is only slightly soluble in water or alcohol, soluble in chloroform.

(b) *Hydrobromide*. Prepared in a similar way as the hydrochloride; crystalline powder; m.p. about 260°. It is soluble in chloroform, only slightly soluble in alcohol or water.

(c) *Acid oxalate*. Crystallises out from hot water in group of prisms; m.p. about 203° with decomposition. It is soluble in hot water or alcohol, sparingly so in cold water.

(5) *Corydalis E*.

This crystallises out from a mixture of chloroform and alcohol in long silky white needles (see fig. 10), m.p. 219°. It is only slightly soluble in alcohol, insoluble in petroleum ether or water. It shows the same colour reactions as Corydalis D with the following reagents. Conc. HNO<sub>3</sub>, orange yellow; conc. H<sub>2</sub>SO<sub>4</sub>, greenish grey becoming slowly violet; Froehde's reagent, yellowish green, green, blue, Erdmann's reagent, green, orange.

On account of the small quantity of substance in hand, its specific rotation and molecular formula have not been determined. Its hydrochloride differs from that of Corydalis D in being more soluble in hot water from which it crystallises out in long needles, m.p. 246°.

Notes on the physiological action of Corydalis B and C.

CORYDALIS B

By Dr. Hung-pih Chu

The subcutaneous injection of 0.13 mg per gm body weight induced in the rat, definite depression in 5 minutes and complete somnolence in 10 minutes. The effect lasted about two hours and is followed by uneventful recovery.

Tested on scarified areas of the human arm, one drop of a 0.2 per cent solution of Corydalis B hydrochloride produced within 5 minutes complete anesthesia to pain. The anesthesia was confined to the area scarified and was not accompanied by vasoconstriction; the effect lasted about one hour.

Five to ten milligrams intravenously in cats caused augmentation of the cardiac contractions with slowing of the rate and a slight fall in blood pressure followed by a rise.

## CORYDALIS C

By Dr. Chubyung Pak

Dorsal subcutaneous injection of 0.05-0.22 mg per gm body weight in frogs produced marked nervous depression during which the righting reflex and the reflexes from the forelimbs and abdominal wall were lost; the hind leg reflexes, however, were still present. In two animals slight convulsions involving the whole body occurred. The effect was produced within 30 minutes and was completely recovered from the following day.

Subcutaneous injection of 0.06 mg per gm body weight in rats induced within 10 minutes marked excitability, restlessness and tremors followed in 15 minutes by violent convulsions affecting the head, neck and forelimbs. Following the convulsions were periods of wakeful restlessness alternating with more convulsions. Recovery occurred after about 3 hours. A second dose of 0.03 mg per gm injected at the fourth hour again induced marked convulsions, which occurred every 5-8 minutes each lasting less than 1 minute.

The convulsions resulting from the second injection passed off after an hour, but the animal continued to be restless and inco-ordinate, running around until exhausted; complete recovery occurred on the following day. The convulsions were not brought about by reflex stimulation.

When 0.12 mg was injected into a rat already completely narcotized by chloral hydrate (0.3 mg per gm), the animal recovered from the narcosis within 10 minutes and within 40 minutes exhibited convulsions which continued intermittently and ultimately ceased. Complete recovery occurred on the following day.

Intravenous injection of 150 mg per kg in the rabbit induced somewhat similar symptoms.

Corydalis C apparently acts on the cerebrum as no convulsions occurred when it was injected into the decerebrated rat.

It caused a sharp fall of blood pressure (in the rabbit) which is not prevented by vagotomy or atropine. The respiration was increased.

## SUMMARY

From the tubers of Chinese *Corydalis ambigua*, Cham. et Sch. (Yen-hu-so) five alkaloids have up to now been isolated from the non-phenolic fraction. They are provisionally named Corydalis A, Corydalis

B, Corydalis C, Corydalis D and Corydalis E respectively. One of them is identical with Corydaline and the other four are new.

1. Corydalis A,  $C_{22}H_{27}O_4N$ , six-sided prisms, m.p.  $135^\circ$ ;  $[\alpha]_{25/D} = +29.5^\circ$ . Ethyl sulphate, m.p.  $162^\circ$ ; hydrochloride, m.p.  $214^\circ$ ; nitrate, m.p.  $197^\circ$ ; plantinichloride, m.p.  $227^\circ$ ; methiodide, m.p.  $228^\circ$ . It is identical with Corydaline.

2. Corydalis B,  $C_{20}H_{23}O_4N$ , six-sided plates, m.p.  $148^\circ$ - $149^\circ$   $[\alpha]_{D=0} = 0^\circ$ . Hydrochloride, m.p. about  $218^\circ$ ; acid oxalate, m.p.  $208^\circ$ . It has the same melting point as Heyl's alkaloid isolated from the roots of *Corydalis aurea*, but differs from the latter in its colour reactions towards  $HNO_3$  and Erdmann's reagent.

3. Corydalis C,  $C_{20}H_{19}O_5N$ , nodular masses or prisms, m.p.  $201^\circ$   $[\alpha]_{D=0} = 0^\circ$ . Hydrochloride, m.p.  $248^\circ$ ; acid oxalate, m.p.  $237^\circ$ ; aurichloride, m.p.  $195^\circ$ ; hydrobromide, m.p.  $250^\circ$ .

This alkaloid is similar to protopine in its molecular formula, solubilities and some colour reactions. Its m.p. however, remains constant at  $201^\circ$  instead of  $207^\circ$ , m.p. of protopine.

4. Corydalis D,  $C_{19}H_{16}O_4N$  or  $C_{19}H_{17}O_4N$ , prisms, m.p.  $204^\circ$ ;  $[\alpha]_{25/D} = -29.5^\circ$ . Hydrochloride, m.p. about  $250^\circ$ ; hydrobromide, m.p. about  $260^\circ$ .

It is the first alkaloid of Corydalis series having a very high leavo-rotatory power.

5. Corydalis E, long needles, m.p.  $219^\circ$ . Hydrochloride, m.p.  $246^\circ$ .

6. A preliminary examination of the physiological effects of Corydalis B shows that it has narcotic and local anesthetic properties and a cardiac augmentor action. Corydalis C, is apparently a cerebral stimulant.

I desire to express my thanks to Professor B. E. Read for suggesting this drug for research.

## LITERATURE

1. ASAHINA, Y. AND FUJITA, N. J. Pharmac. Soc. Japan, 1920, No. 463, 763-766.
2. ASAHINA, Y. AND MOTIGASE, S. J. Pharmac. Soc. Japan, 1920, No. 463, 766-772.
3. BIRSMANN, E. Inaug. Diss., Dorpat, 1888.
4. BIRSMANN, E. Chem. Ctralb., 1893, **1**, 35.
5. BRUCHHAUSEN, F. V. UND STIPPLER, H. Arch. d. Pharmac., 1927, **265**, 152-166.
6. DANCKWORTT, P. W. Arch. d. Pharmac., 1912, **250**, 590-346.
7. DOBBIE, J. J. AND LAUDER, A. J. Chem. Soc., 1892, **61**, 244-249.
8. DOBBIE, J. J. AND LAUDER, A. J. Chem. Soc., 1892, **61**, 605-611; with Paliatseas, P. G., J. Chem. Soc., 1901, **79**, 87-90.
9. DOBBIE, J. J. AND LAUDER, A. J. Chem. Soc., 1895, **67**, 25-30.
10. DOBBIE, J. J. AND LAUDER, A. J. Chem. Soc., 1902, **81**, 145-160.
11. FREUND, M. UND JOSEPHY, W. Ber. d. deutsch. chem. Gesellsch., 1892, **25**, 2411-2415.
12. FREUND, M. UND JOSEPHY, W. (Liebig's) Ann. d. Chem., 1893, **277**, 1-19.
13. GADAMER, J., ZEIGENBIEN, H. UND WAGNER, H. Arch. d. Pharmac., 1902, **240**, 19-52; 1911, **249**, 30-39.
14. GADAMER, J. Arch. d. Pharmac., 1911, **249**, 224-233.
15. GADAMER, J. UND BRUCHHAUSEN, F. V. Arch. d. Pharmac., 1922, **259**, 245-249.
16. HAARS, O. Arch. d. Pharmac., 1905, **243**, 154-165.
17. HEYL, G. Apoth. Ztg., 1910, No. 17, reprint.
18. LI, SHIH-CHEN. Pen Tsao Kang Mu, Shanghai, 1595.
19. MAKOSHI, K. Arch. d. Pharmac., 1908, **246**, 381-400.
20. MAKOSHI, K. Arch. d. Pharmac., 1908, **246**, 401-402.
21. MATSUMURA, J. Chinese names of plants, Tokyo, Osaka, Kyoto, and Fukuoka, 1915.
22. MERCK, E. Arch. d. Pharmac., 1893, **231**, 131-134.
23. OSADA, S. J. Pharmac. Soc. Japan, 1927, No. 547, 99-100.
24. PICTET, A. UND CHOU, T. Q. Ber. d. deutsch. chem. Gesellsch., 1916, **49**, 370-376.
25. SPÄTH, E. UND LANG, N. Ber. d. deutsch. chem. Gesellsch., 1921, **54**, B, 3974-3078.
26. SPÄTH, E., MOSETTIG, E. UND TRÖTHANDL, O. Ber. d. deutsch. chem. Gesellsch., 1923, **56**, B, 875-879.
27. STUART, G. A. Chinese materia medica, Shanghai, 1911.
28. WACKENRODER, Berzelius Jahrb., 1826, **1**, 220.
29. WICKE, H. (Liebig's) Ann. d. Chem., 1866, **137**, 274-288.

## 中國延胡索之研究

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延胡索之種類甚多，中國所產者，色深黃而扁圓（如圖一），中含要素甚多，性質不同，藥性亦異。今將提出之鹼性物質，分爲四類。第二類最多且甚重要，故先行研究之。研究之結果，得有五種結晶物，暫定名爲延胡索素甲，延胡索素乙，延胡索素丙，延胡索素丁，及延胡索素戊（參觀圖二，四，六，八及十）。

延胡索素甲，與前人所發明之考里達林（Corydaline）相同，餘則未之前聞。其提取方法，與各物之物理性質，化學性質及化學成分等，請閱西文原文。

延胡索素乙及延胡索素丙之藥性略如下述：

### 一. 延胡索素乙之藥性。

若以此物十公絲，製成溶液，注射入鼠體皮下。則發生全身麻醉而沉睡至二小時之久，且沉睡之前，並無興奮症狀。

若將臂皮之一部刮破而敷以此物之溶液，則發生局部麻醉。用貓試驗，則五至十公絲之延胡索素乙，能使其血壓稍高，同時使心之搏動速度減少而其收縮強度增加。若將貓之心竇心房，割取一薄片，以試此藥（其量爲十萬分之二至千分之一）其結果亦爲速度減而強度加。

### 二. 延胡索素丙之藥性。

此物之小量（指不到中毒量而言），對於蛙則使其中樞神經系滯鈍，或輕度搖擗對於鼠及兔，則使其頭頸背等部之肌肉，現強烈慢性搖擗。（與反射的刺激無關）但不危及生命，且仍能復元。延胡索素丙對於毀腦之鼠（指去其腦部或斷其腦與他部之連絡），無上述作用發生。由此可推知其作用之只限於大腦。

延胡索素丙對於兔之血壓，先則使之降低。繼則使之增高。對於呼吸，則使之加速。

## EXPLANATION OF PLATES II AND III.

- Fig. 1. Fruit of Chinese *Corydalis ambigua*, Cham. et. Sch.  
(Yen-hu-so).
- Fig. 2. *Corydalis* A. (Corydaline), m.p. 135°C;  $[\alpha]_{25/D}$   
= +295°.
- Fig. 3. *Corydalis* A. Ethyl sulphate, m.p. 162°C.
- Fig. 4. *Corydalis* B. (New alkaloid), m.p. 148°-149°C.  
 $[\alpha]_D=0^\circ$ .
- Fig. 5. *Corydalis* B. Oxalate, m.p. 208°C.
- Fig. 6. *Corydalis* C. (New alkaloid), m.p. 201°C.  $[\alpha]_D=0^\circ$ .
- Fig. 7. *Corydalis* C. Hydrochloride, m.p. 248°C.
- Fig. 8. *Corydalis* D. (New alkaloid), m.p. 204°C.  $[\alpha]_{25/D}$   
= -295°.
- Fig. 9. *Corydalis* D. Hydrochloride, m.p. 250°C.
- Fig. 10. *Corydalis* E. (New alkaloid), m.p. 219°C.

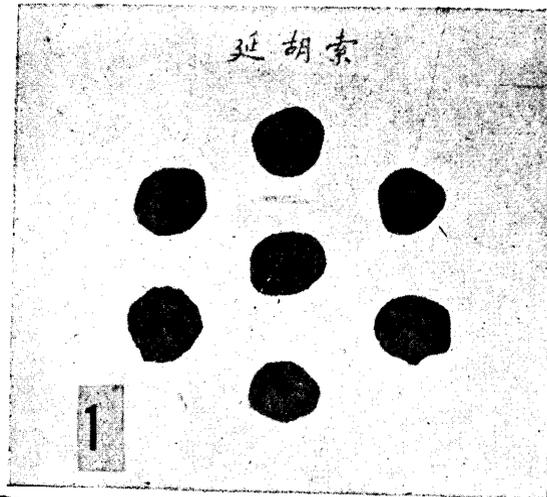


Fig. 1.

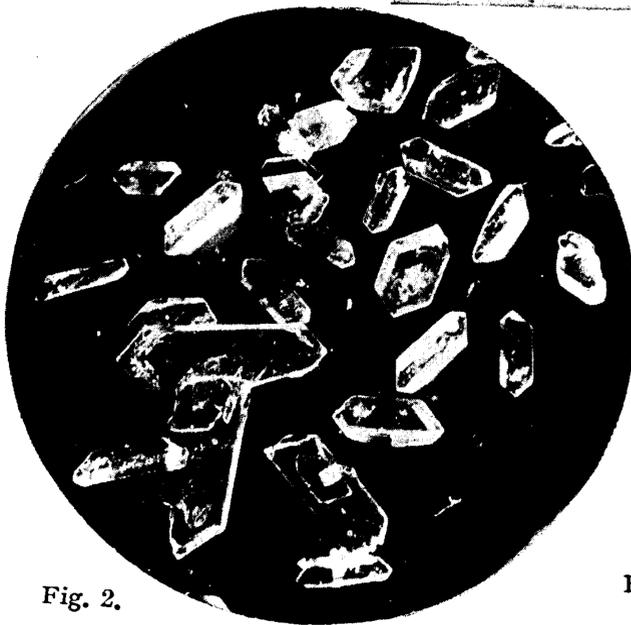


Fig. 2.

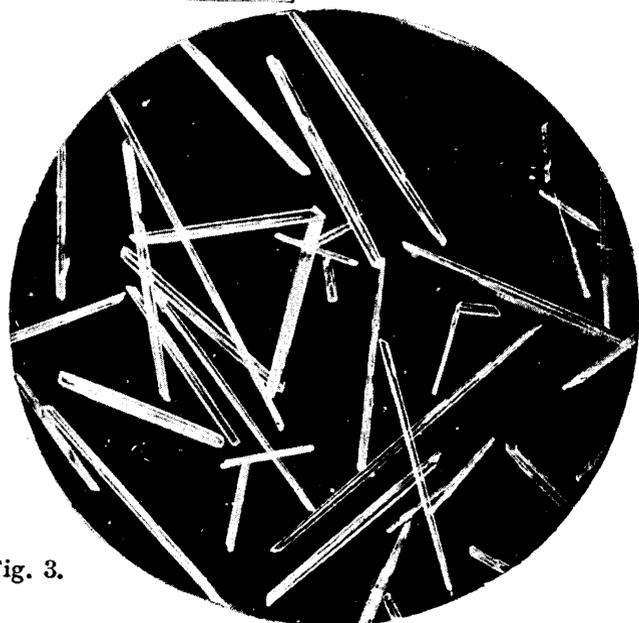


Fig. 3.

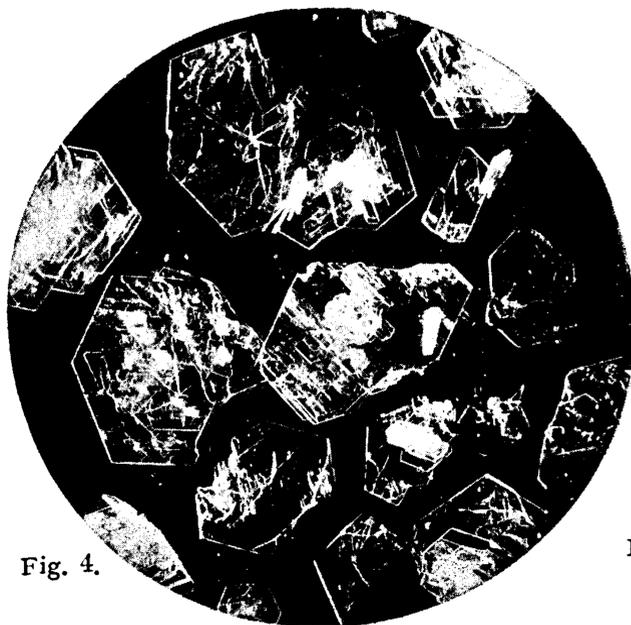


Fig. 4.



Fig. 5.

Figs. 1-5. Alkaloids of Corydalis Ambigua.

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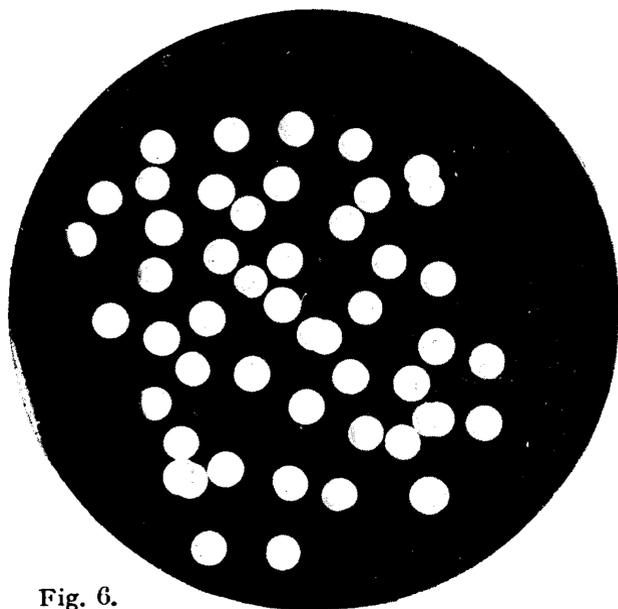


Fig. 6.

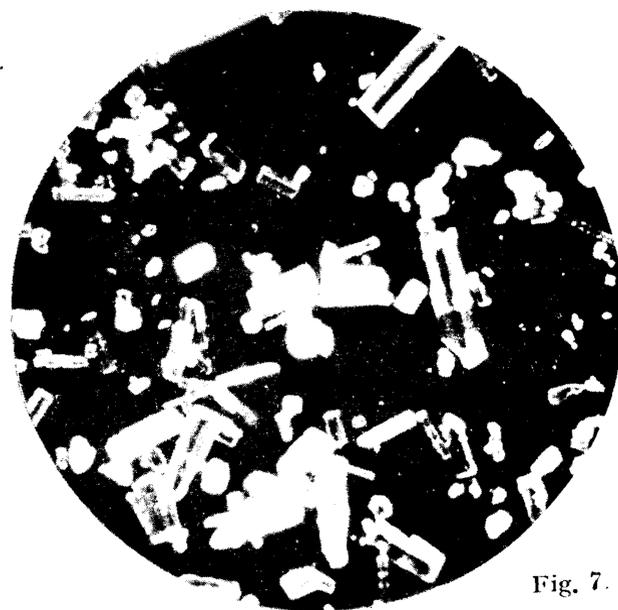


Fig. 7.

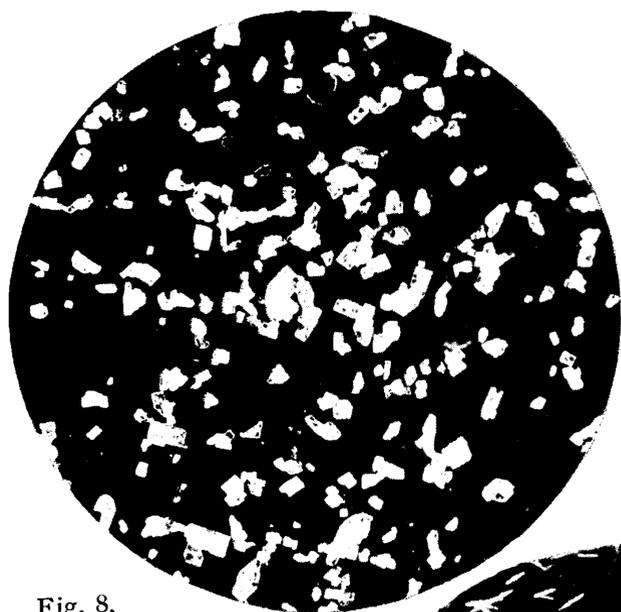


Fig. 8.

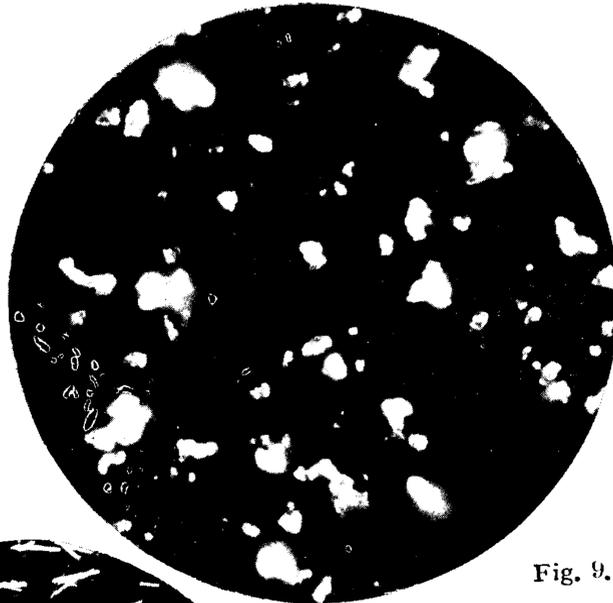


Fig. 9.

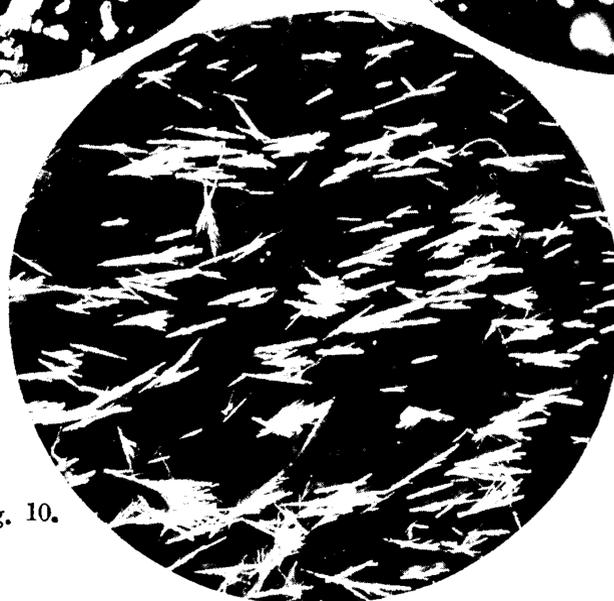


Fig. 10.

Figs. 6—10. Alkaloids of *Corydalis Ambigua*.

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