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The Alkaloids of Fritillaria Roylei. I. Isolation of Peimine[1]

BY YUOH-FONG CHI, YEE SHENG KAO AND KOU JEN CHANG

Previous contributions on the alkaloidal content of the plant *Fritillaria Roylei* (Pei-Mu) by Fukuda[2] and Chou[3,4] have shown that it contains the following alkaloids: (A) verticin, $C_{18}H_{33}O_2N$ or $C_{19}H_{30}O_2N$; (B) verticilin, $C_{19}H_{33}O_2N$; (C) peimine, $C_{19}H_{30}O_2N$; (D) peiminine, $C_{18}H_{28}O_2N$; (E) fritimine, $C_{38}H_{62}O_3N_2$; and (F) fritillarin, $C_{19}H_{33}O_2N$. The properties of these alkaloids are recorded in Table I.

TABLE I

Name	Formula	M. p., °C.	Rotation	Pei-Mu source
Peimine	$C_{19}H_{30}O_2N$	223	0°	Chekiang
Peiminine	$C_{18}H_{28}O_2N$	135	−62.5°	Chekiang
Fritimine	$C_{38}H_{62}O_3N$	167	−50°	Szechuen
Verticin	$C_{18}H_{33}O_2N$ $C_{19}H_{35}O_2N$	224–224.5	−10.66°	Japanese
Verticillin	$C_{19}H_{33}O_2N$	Sinters at 130, melts at 148–150, resolidifies at 157–159, decomposes at 212–213		Japanese
Fritillarin	$C_{19}H_{33}O_2N$	130–131		Japanese

This interesting drug (Pei-Mu) finds wide application in medicine and is prescribed in fevers, coughs, dysuria, hemorrhages, deficiency of milk, threatened mammary abscess, lingering labor, rheumatism and diseases of the eye. This plant was identified as *Fritillaria Roylei* by Stuart[5] or *Fritillaria verticillata* by Read and Liu.[6] The part of the plant used in medicine is the starchy corm of this liliaceous plant growing in different parts of China, especially in Chekiang and Szechuen. The material used for this investigation was a Chekiang variety known by the commercial name "Ta Pei," and was obtained from a local drug store or pharmacy. The pharmacological properties of peimine, peiminine and fritimine have been described by Chen.

The alkaloid A, (verticin) recently isolated by us, had the same melting point as C (peimine); but the results of our analyses of the free bases and its salts proved it to have the formula $C_{26}H_{43}O_3N$, instead of $C_{19}H_{30}O_2N$ assigned to peimine by Chou. Judging from the analytical data already known, we conclude this was probably the same alkaloid as peimine, to which the present authors have assigned a different formula.

Experimental Part

Ninety-eight kilograms of the starch corms of *Fritillaria Roylei*, known under the commercial name "Ta Pei" was powdered, and percolated with 95% alcohol. When the solvent had been removed from the alcoholic extract under diminished pressure at 40–45°, the residue was dissolved in 2% hydrochloric acid, and the solution filtered. The crude alkaloid was then liberated from the acid extract with sodium carbonate, and extracted with ether and then with chloroform. After distilling the solvent from the ethereal solution, the ether-soluble alkaloid weighed 48 g., which represented about 0.05% of the total quantity of the crude drug. This crude alkaloid dissolved in benzene, to which some petroleum ether was added just to turbidity, whereupon peimine separated as an amorphous powder. It was then purified by recrystallization from an alcohol–petroleum ether mixture, from which peimine separated in needles, melting at 223–224°.

In some cases, it was better to convert the ether-soluble alkaloids, after solution in dry ether, into their hydrochlorides by passing in dry hydrogen chloride. The mixed hydrochlorides were then separated into peimine hydrochloride and peiminine hydrochloride (to be described in our next paper) by fractional crystallization from an alcohol–ether mixture.

Pure peimine was recovered from its hydrochloride by action of sodium carbonate. It was recrystallized from a mixture of alcohol–petroleum ether, and separated in needles melting at 224°. The yield of pure peimine was 3 g. For analysis, the alkaloid was dried over phosphorus pentoxide at 80° in a vacuum, $[\alpha]^{13}_{D}$ 0°.

The hydrochloride and hydrobromide of peimine were prepared by dissolving in each case 100 mg. of the pure alkaloid in ether, passing in hydrogen chloride or bromide and recrystallizing from an alcohol–ether mixture. The acid sulfate was prepared in similar fashion except that dilute sulfuric acid was employed. The different products were dried for analysis over phosphorus pentoxide at 80° in a vacuum.

The platinichloride and aurichloride were prepared by precipitation in aqueous solution. The former salt was recrystallized from water and the latter from dilute hydrochloric acid. The products were dried for analysis over phosphorus pentoxide at 110° in a vacuum. The results of analyses of the alkaloid and its different salts are recorded in Table II.

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[2] Fukuda, *Science Reports, Tôhoku Imp. Univ., Japan*, 1, 18, 323 (1929). Also *Chem. Zentr.*, 1, 988 (1930).

[3] Chou and Chen, *Chinese J. Physiol.*, 6, 265 (1932).

[4] Chou and Chen, *ibid.*, 7, 41 (1933).

[5] Stuart, Chinese Materia Medica, 178 (1911).

[6] Read and Liu, "Plantae Medicinalis Sinensis," No. 630, 1927, pp. A-I, 51.

TABLE II

Compound		Peimine (P)	Hydrochloride	Hydrobromide	Acid sulfate	Platinchloride	Aurichloride
M. p., °C.		224	295, dec.	293.5–294	278–280	233–235, dec.	164–165
Formula		$C_{26}H_{43}O_3N$	P·HCl	P·HBr	$P\cdot H_2SO_4$	$P_2\cdot H_2PtCl_6$	$P\cdot HAuCl_4$
Carbon, %	Calcd.	74.75	68.74	62.61	60.53		
	Found[a,b]	74.65[c]	69.07, 68.77	62.92, 62.88, 63.13[a]	60.28, 60.27		
Hydrogen, %	Calcd.	10.38	9.77	8.90	8.80		
	Found[a,b]	10.42[d]	9.84, 9.85	9.04, 8.86, 8.77[a]	8.81, 8.64		
Nitrogen, %	Calcd.	3.35		2.81			
	Found[a,b]	3.56[e]		2.72[a]			
%	Calcd.			Br 16.04		Pt 15.68	Au 26.03
	Found			Br 15.55[a]		Pt 15.45 15.36	Au 24.9 25.09

Molecular weight determination (Rast); 0.288 mg. in 3.520 mg. camphor. ΔT, 9.2°. 0.268 mg. in 3.810 mg. camphor; ΔT, 7.7°. Calcd. for $C_{26}H_{43}O_3N$, 417.3. Found; 336,[a] 365.[2]

[a] Analyses made by Dr. Ing. A. Schoeller, Toelzestrasse 19, Berlin-Schmargendorf, Germany. [b] Analyses made by Dr. Carl Tiedcke, Bismarckstrasse, Hamburg 19, Germany. [c] Average: 74.75, 74.85,[a] 74.67,[a] 74.76, 74.58,[b] 74.39,[b] 74.53.[b] [d] Average: 10.30, 10.15, 10.49,[a] 10.54,[a] 10.43,[b] 10.53,[b] 10.51.[b] [e] Average: 3.52, 3.60, 3.77, 3.38,[a] 3.36,[a] 3.72.[b]

Summary

Peimine, melting at 224°, has been obtained in a more pure condition. Its formula is $C_{26}H_{43}O_3N$, instead of $C_{19}H_{30}O_2N$, which was assigned to it by Chou. The present formula is substantiated by the results of analysis of several salts; namely, the hydrochloride, bromide, acid sulfate, platinichloride and aurichloride.

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NOTES

An Apparatus for the Determination of the Absorption of Small Quantities of Gas by Solutions

BY H. E. BENT, W. F. GRESHAM AND N. B. KEEVIL

The apparatus illustrated in the figure is designed to measure the absorption of small amounts of gas by solutions contained in sealed glass capsules. The apparatus allows one to break and empty the capsule, measure the amount of oxygen absorbed and make a correction for the amount of oxygen dissolved in the solvent. The sample is contained in a capsule "G" and the oxygen to be introduced is measured in a capillary by means of the scale "B," a small slug of mercury in the capillary serving to confine the gas.

The particular problem which necessitated the construction of this apparatus was the determination of the purity of small quantities of organic free radicals by measuring the quantity of oxygen absorbed. Samples of a half gram or larger may conveniently be studied in the apparatus developed for measuring the heat of the reaction.[1] Frequently, however, it is desirable to analyze with a precision of about 1% a dilute solution of a free radical which will not absorb more than about 1 cc. of oxygen. The details of breaking the capsule and measuring the absorption of oxygen together with typical experimental results are given in the following paragraphs.

The manipulation of the apparatus will be evident from the figure and the following description. "A" is a stopcock through which the apparatus may be evacuated after the capsule containing the solution of the free radical has been placed in the apparatus. "B" is a scale placed behind the capillary (diameter 4 mm.) in order that the volume of oxygen introduced into the absorption bulb may be accurately measured. "C" is a three-way stopcock which connects the capillary tube to the supply of oxygen and to the

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(1) Bent, Cuthbertson, Dorfman and Leary, THIS JOURNAL, 58, 165 (1936); Bent and Cuthbertson, *ibid.*, 58, 170 (1936).