

Some Minor Alkaloids of Pei-Mu, *Fritillaria Roylei**

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Four minor alkaloids in addition to the two principal ones previously reported have been isolated from the Chinese drug, Pei-Mu. The procedures employed are described and the analytical data and derivatives used in the characterization of these new alkaloids are reported.

IN A PREVIOUS communication, Chou and Chu (1) reported the preparation and properties of peimine, $C_{26}H_{43}O_3N$ and peiminine, $C_{26}H_{41}O_3N$, the two principal alkaloids of the Chinese drug, Pei-Mu, identified as *Fritillaria Roylei*. From their mother liquor, there have been isolated up to present 4 other alkaloids which are named peimisine, peimiphine, peimidine, and peimitidine, respectively. Their compositions, melting points, and specific rotations are given in Table I.

remains insoluble. The aqueous solution is filtered, made alkaline with sodium carbonate, and the precipitate extracted with ether. The ethereal solution, when dried and distilled, leaves behind about 10 Gm. of a basic residue which is dissolved in acetone and neutralized with an alcoholic hydrochloric acid. On standing for a few weeks at room temperature, there separates out a crystalline deposit weighing about 1.5 Gm. and consisting of a mixture of peimisine, peimiphine, and peiminine hydrochlorides. After filtration, it is warmed on water bath for some time with 10 cc. of 93% alcohol in which about half the quantity remains insoluble. The insoluble part which consists of the peimisine hydrochloride in an almost pure state is filtered and dried, its mother liquor being reserved for working up peimiphine. It is dissolved in about 70 cc. of boiling water. The aqueous solution, when cooled to room temperature, is made alkaline with sodium carbonate and the liberated base extracted with chloroform. Peimisine is recovered from the chloroform solution by distilling off the solvent and crystallizing the residue from a little alcohol. It forms colorless rhombic

TABLE I

Name	Formula	M. P., °C.	Specific Rotation
Peimisine	$C_{27}H_{43}O_4N$	270	$[\alpha]_D^{25} -51^\circ$ in alcohol
Peimiphine	$C_{27}H_{41}O_3N$	127	$[\alpha]_D^{25} -69^\circ$ in alcohol
Peimidine	$C_{27}H_{45}O_2N$	222	$[\alpha]_D^{25} -74^\circ$ in alcohol
Peimitidine	$C_{27}H_{44}O_3N$	188	$[\alpha]_D^{25} -68^\circ$ in alcohol

All these alkaloids are found in the drug only in very small quantities, ranging from 0.001 to 0.002 per cent. Their isolation has been effected by taking advantage of the difference in the solubilities of their well-crystallized hydrobromides or hydrochlorides. Like peiminine, peimisine contains in its molecule a carbonyl group, forming easily an oxime, m. p. 196°

EXPERIMENTAL

Peimisine, $C_{27}H_{43}O_4N$.—In the isolation of peimine and peiminine as reported previously (1), 70 Kg. of the Chinese drug, Pei-Mu, were used. After the removal of these 2 principal alkaloids in the form of their hydrochloride as much as possible by fractional crystallization, all the mother liquors are united and distilled nearly to dryness and the residue taken up with water in which much resinous matter

prisms, m. p. 270° , $[\alpha]_D^{25} -51$. It is easily soluble in alcohol and chloroform, but only sparingly soluble in acetone or ether. Its hydrochloride, prepared by neutralizing the pure alkaloid with hydrochloric acid in alcohol, forms prismatic needles, m. p. 257° , and is soluble in water or alcohol with difficulty. Its aurichloride is obtained as an amorphous powder by precipitation in aqueous solution in the presence of hydrochloric acid. The analytical data obtained with the alkaloid, its hydrochloride, and aurichloride agree with the formula $C_{27}H_{43}O_4N$ as shown in Table II.

Peimisine Oxime, $C_{27}H_{44}O_4N_2$.—A mixture of 0.1 Gm. of peimisine, 0.1 Gm. of hydroxylamine hydrochloride, and 0.2 Gm. of potassium acetate is dissolved in 20 cc. of water in the presence of one drop of acetic acid and warmed on the water bath for about one hour. After standing overnight the clear aqueous solution is made alkaline with potassium carbonate and the precipitate extracted with a mixture of ether and chloroform. The ether-chloroform extract, when dried and distilled, leaves behind the required oxime which separates from acetone as a crystalline powder, m. p. 196° . Its hydrochloride crystallized from alcohol in prismatic

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TABLE II.—CHEMICAL COMPOSITION OF THE COMPOUNDS DESCRIBED IN THIS PAPER

Name	Formula	Percentage Composition									
		Carbon		Hydrogen		Nitrogen		Chlorine		Platinum or Gold	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Peimisine	$C_{27}H_{46}O_3N$	72.75	72.78	9.73	9.81	9.89	9.89	7.36	7.43	25.10	24.93
Peimisine Hydrochloride	$C_{27}H_{46}O_3N \cdot HCl$
Peimisine Aurichloride	$C_{27}H_{46}O_3N \cdot HCl \cdot AuCl_3$
Peimisine Oxime	$C_{27}H_{46}O_3N_2$	6.08	6.07
Peimisine Oxime Hydrochloride	$C_{27}H_{46}O_3N_2 \cdot HCl$
Peimiphine	$C_{27}H_{46}O_3N$	74.93	74.75	10.72	9.99	10.71	8.23	7.56	7.75	25.53	25.70
Peimiphine Hydrochloride	$C_{27}H_{46}O_3N \cdot HCl$
Peimiphine Aurichloride	$C_{27}H_{46}O_3N \cdot HCl \cdot AuCl_3$
Peimidine	$C_{27}H_{46}O_3N$	78.00	77.93	10.92	11.24	11.37	3.37	7.85	7.85	15.72	15.61
Peimidine Hydrochloride	$C_{27}H_{46}O_3N \cdot HCl$
Peimidine Platrichloride	$(C_{27}H_{46}O_3N \cdot HCl)_2 \cdot PtCl_4$
Peimitidine	$C_{27}H_{46}O_3N$	75.29	75.38	10.30	9.89	10.01	3.25	7.59	7.68	25.59	25.64
Peimitidine Hydrochloride	$C_{27}H_{46}O_3N \cdot HCl$
Peimitidine Aurichloride	$C_{27}H_{46}O_3N \cdot HCl \cdot AuCl_3$

needles, m. p. 256°. Analysis confirms its composition as indicated in Table II.

Peimiphine, $C_{27}H_{46}O_3N$.—After filtering off the insoluble peimisine hydrochloride, the alcohol-soluble part of the crystalline deposit obtained above is evaporated to dryness and converted into its free base again by dissolving in water, making alkaline with sodium carbonate, and extracting with ether. The ethereal solution is dried and distilled and the residue neutralized with hydrobromic acid in a little alcohol. On addition of a sufficient quantity of ether, peimiphine hydrobromide crystallizes out in rhombic prisms. Peimiphine is liberated from its hydrobromide by action of sodium carbonate and recrystallizes from a mixture of acetone and petroleum ether. It forms hard prisms, m. p. 127°, $[\alpha]_D^{25} - 69$. It is easily soluble in chloroform and alcohol, but much less so in ether. Its hydrochloride, prepared by neutralizing the pure alkaloid with hydrochloric acid in acetone, forms orthorhombic prisms, m. p. 287°, and is easily soluble in water or alcohol. Its aurichloride is obtained as a yellow amorphous powder in a similar way as peimisine aurichloride. The composition of peimiphine is determined to be $C_{27}H_{46}O_3N$ according to the analytical results given in Table II.

Peimidine, $C_{27}H_{46}O_3N$.—After the removal of peimisine and peimiphine hydrochlorides as a crystalline deposit as described above, the mother liquor is distilled to almost dryness and the residue taken up with water and filtered. The aqueous solution is made alkaline with sodium carbonate and the free base extracted with ether. The ethereal solution is dried and distilled and the basic residue neutralized with concentrated hydrobromic acid in a little alcohol. On addition of ether, peimidine hydrobromide crystallizes out in rhombic prisms, m. p. over 300°. It is soluble in cold water with difficulty. Peimidine is obtained from its hydrobromide by action of sodium carbonate in an aqueous solution and extraction with chloroform. When crystallized pure from 95% alcohol, peimidine forms orthorhombic prisms, m. p. 222°, $[\alpha]_D^{26} - 74$ °. It is only sparingly soluble in ether or acetone but easily soluble in chloroform or alcohol. Its hydrochloride forms rhombic prisms, m. p. 318°, easily soluble in alcohol or water. Its platinichloride is obtained as an orange amorphous powder by precipitation in aqueous solution in the presence of one drop of hydrochloric acid. The analytical data as given in Table II indicate its formula to be $C_{27}H_{46}O_3N$.

Peimitidine, $C_{27}H_{44}O_3N$.—The mother liquor of peimidine hydrobromide as described above is evaporated to dryness and the residue taken up with water and filtered. The free base is regenerated from the aqueous solution with sodium carbonate and extracted with ether. The ethereal solution is dried and distilled and the residue neutralized with concentrated hydrochloric acid in acetone. On long standing, peimitidine hydrochloride crystallizes out in rhomboid prisms. When recrystallized repeat-

edly from a mixture of alcohol and acetone, it has a melting point of 291° with decomposition, easily soluble in absolute alcohol or water. Peimitidine is obtained from its pure hydrochloride in a usual way and crystallizes from a mixture of acetone and petroleum ether in hard prisms, m. p. 188°, $[\alpha]_D^{20} -68^\circ$. It is easily soluble in most organic solvents, but much less so in ether. Its platinichloride is very soluble in water, but its aurichloride is easily obtained as an amorphous powder by precipitation in an aqueous solution. It has the composition of $C_{27}H_{44}O_3N$ as shown in Table II.

SUMMARY

From the mother liquor of peimine and peiminine, two principal alkaloids isolated

from the Chinese drug, Pei-Mu, identified as *Fritillaria Roylei*, there have been isolated four other minor alkaloids to which the names peimisine, peimiphine, peimidine, and peimitidine are respectively assigned. Their formulas, melting points, and specific rotations are given in Table I. They are present in the drug only to the extent of 0.001 to 0.002 per cent. Peimisine easily forms an oxime, m. p. 196°.

REFERENCE

(1) Chou, T. Q., and Chu, T. T., *J. Am. Chem. Soc.*, **63**, 2936(1941).

The Comparative Chronic Toxicities of Fumaric, Tartaric, Oxalic, and Maleic Acids*

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Data are given on the effects of the oral administration of fumaric, tartaric, oxalic, and maleic acids. The results of the study indicate a low degree of toxicity for fumaric, oxalic, and tartaric acids. The oxalic and tartaric acids were not toxic in concentrations as high as 1.2% and fumaric acid was toxic only at the 1.5% concentration. Maleic acid was toxic at concentrations of 0.5% or more.

THE SIMILAR laxative action produced by the salts of fumaric and tartaric acids suggested a comparative survey of the chronic toxicities of these acids. Because of a low acute toxicity of fumarates to animals and of their efficacy as compared with salts of tartaric acid, recent investigators (1-6) have proposed a substitution of fumarates for tartrates in laxative preparations. The nephropathic action of large acute doses of tartaric acid (7) does not appear to occur in animals given similar doses of fumaric acid (1); however, no lifetime study has

been conducted with either of these acids. The presence of large amounts of oxalates in certain foods (8-12) and the isomerism of maleic and fumaric acids suggested the inclusion of oxalic and maleic acids in a two-year study of the chronic toxicities of these 4 dicarboxylic acids. The many experiments reported in the literature on the toxicity of oxalic acid have been either acute or short-term chronic experiments.

EXPERIMENTAL

Two experiments were conducted in which groups of weanling rats (twenty-one days) from our colony of Osborne-Mendel strain were started on diets containing one of the above-named dicarboxylic acids. A total of 420 rats was used in these experiments. In the first experiment 12 groups of 24 rats, equally divided between the sexes, were fed on diets containing 0.1, 0.5, 0.8, and 1.2% tartaric, fumaric, and oxalic acids, respectively. In a second experiment, in order to compare more closely the toxicities of fumaric and maleic acids, 6 groups of 12 male rats were fed on diets containing 0.5, 1.0, and 1.5% fumaric and maleic acids, respectively. There were 48 control animals for the first experiment and 12 con-

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