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142. **Hiroshi Morimoto and Seiichi Kimata :** Studies on the Components of *Fritillaria thunbergii* Miq. II.[1] On Peimine. (1).

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In the preceding work,[1] a new alkaloid, peiminoside, was obtained besides peimine from the bulbs of *Fritillaria thunbergii* Miq. and its structure was elucidated as O-β-D-glucopyranosyl-(1→3)-peimine. In the present paper will be reported some later findings on peimine.

Peimine (I) is negative to Liebermann-Burchard reaction and does not produce sparingly soluble digitonide, and the pKb of its hydrochloride is 6.1. It does not decolorize bromine in glacial acetic acid and is not reduced over platinum oxide or affected by lithium aluminium hydride, and therefore it has no double bond or a ketone group. This fact is in accord with its infrared spectrum.

As peimine affords a nitrite with nitrous acid and a methiodide with methyl iodide, its nitrogen is tertiary.[1] Treatment of the methiodide with sodium perchlorate gives methylperchlorate (II), $C_{27}H_{45}O_3N \cdot CH_3ClO_4$, m.p. 278~279°(decomp.), $[\alpha]^{22}_{D}$ $-16°$(EtOH), and acetylation of (I) with acetic anhydride and pyridine furnishes the diacetyl derivative (III), $C_{27}H_{43}ON \cdot (CH_3COO)_2$, m.p. 214°. From the infrared spectrum of (III) revealing the presence of a free hydroxyl group and from the fact that the peimine portion of penta-O-methylpeiminoside methiodide prepared by the methylation of peiminoside has also a free hydroxyl group as reported in the previous paper, it is evident that peimine possesses a tertiary hydroxyl group. Treatment with sodium perchlorate of monomethylpeimine methiodide, which was produced by acid hydrolysis of penta-O-methylpeiminoside methiodide, furnishes the methyl perchlorate (IV), $C_{28}H_{47}O_3N \cdot CH_3ClO_4 \cdot H_2O$, m.p. 202°, $[\alpha]^{22}_{D}$ $-4°$ (EtOH), and oxidation of (I) with chromium trioxide in glacial acetic acid gives in a good yield a diketone compound, peiminone (V), $C_{27}H_{41}O_3N$, m.p. 165~168°, $[\alpha]^{22}_{D}$ $-51°$(EtOH). Presence of two CO groups in peiminone is apparent from the fact that the compound shows absorption of a hydroxyl group ($3450\,cm^{-1}$) and a six-membered ring CO group ($1700\,cm^{-1}$), and that it can be led to a dioxime. From the foregoing, peimine (I) was ascertained to be a saturated tertiary base having two secondary hydroxyl groups attached to a six-membered ring and a tertiary hydroxyl group.

As reported in the preceding paper, Chou and Chen[2,3] obtained peiminine in addition to peimine from Pei-mu (*Fritillaria roylei*) produced in China and clarified the relationship between the two substances by finding that the latter can be converted into the former by oxidation of one of its two secondary hydroxyl groups by the Beckmann method and the former into the latter by reduction of the CO group with metallic sodium and ethanol. Later, Chu, Hwang, and Loh[4,5] deduced the formula (A) as the basic skeleton of peimine (I) from their studies on the dehydrogenation product of the compound. This deduction seems quite reasonable from the structural study of alkaloids of veratrum genus of the Liliaceae family.

In general, the steroids and modified steroids found in the vegetable kingdom have a hydroxyl or a substituted amino group at C-3 without exception. Therefore, it is not

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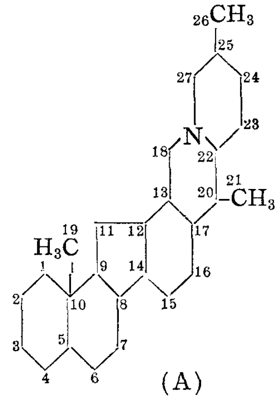
1) Part I. H. Morimoto, S. Kimata : This Bulletin, **8**, 302(1960).

2) T. Q. Chou, K. K. Chen : Chinese J. Physiol., **6**, 265 (C. A., **26**, 5703(1932)).

3) T. Q. Chou, T. T. Chu : J. Am. Chem. Soc., **69**, 1257(1947).

4) T. T. Chu, J. Y. Loh : Acta Chim. Sinica, **21**, 227(1955)(C. A., **51**, 444(1957)).

5) T. T. Chu, W. K. Hwang, J. Y. Loh : *Ibid.*, **21**, 232(1955)(C. A., **51**, 444(1957)).



(A)

unreasonable to think that peimine and peiminine have a secondary hydroxyl group at C-3. Conversion of peimine to peiminine by the Beckmann oxidation seems to be due to the easier oxidizability of the other secondary hydroxyl group. Further, from the fact that peiminone (V), a diketone compound, exhibits no property of α,β-diketone or of an acid amide and that its infrared spectrum shows only the absorption of a CO-group of a six-membered ring and not that of a five-membered ring, the possible position of the other secondary hydroxyl group of peimine seems to be one of C-6, C-7, C-15, C-16, C-23, and C-24.

If a hydroxyl group is attached to C-6 or C-7, it could be ascertained by introducing a double bond between C-4 and C-5 of (V). With this expectation, (V) was oxidized with selenium dioxide. In this case, a large amount of non-basic resinous substance formed and the yield of a basic product was very poor, but the product was purified first by chromatography on Florisil and then by recrystallization of its perchlorate, giving a small quantity of crystals (VII), $C_{27}H_{39}O_3N \cdot HClO_4$, m.p. 258°(decomp.). The ultraviolet spectrum of (VII) shows an absorption at λ_{max}^{EtOH} 225 mμ (log ε 3.58) and its infrared spectrum exhibits absorptions for hydroxyl group (3500 cm^{-1}), the CO-group of a six-membered ring (1710 cm^{-1}), a conjugated CO-group (1690 cm^{-1}), and a conjugated double bond (1620 cm^{-1}), revealing the presence of a double bond in a position adjacent to the CO-group. The product was named dehydropeiminone. There is an empirical rule about the relationship between the position of α,β-unsaturated ketones in steroids and their ultraviolet spectrum.[6] When calculated according to this rule the absorption maxima in the ultraviolet region of the α,β-unsaturated ketone against possible CO-positions in dehydropeiminone are as shown in Table I.

On the other hand, the value measured on dehydropeiminone perchlorate (VII) was λ_{max}^{EtOH} 225 mμ (log ε 3.58) as described before, which is in complete agreement with the calculated value for 1-en-3-one (λ_{max}^{EtOH} 227 mμ). This fact indicates that a double bond

Table I. Absorption Maxima of α,β-Unsaturated Ketones

λ_{max}^{EtOH} (mμ)	CO group						
	C-3	C-6	C-7	C-15	C-16	C-23	C-24
Calc.	$\Delta^{1,2}$	$\Delta^{7,8}$	$\Delta^{5,6}$	$\Delta^{8,14}$	$\Delta^{14,15}$	$\Delta^{20,22}$	$\Delta^{22,23}$
	227	244	244	259	244	>254[a)]	>244[a)]
〃	$\Delta^{4,5}$		$\Delta^{8,9}$	$\Delta^{12,14}$	$\Delta^{13,17}$	$\Delta^{24,25}$	$\Delta^{25,26}$
	244		249	249	249	239	230
〃			$\Delta^{8,14}$	$\Delta^{16,17}$	$\Delta^{17,20}$		$\Delta^{25,27}$
			259	244	254		>237[a)]

a) The absorption maximum seems to shift more to the longer wave side as the N is attached to α- or β-position.

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6) cf. L.F. Fieser, M. Fieser: "Steroids," 15(1959). Reinhold Publishing Corporation, New York.

was introduced by oxidation with selenium dioxide not in the expected Δ^4 but in Δ^1, and therefore it was impossible to confirm whether the CO-group is attached to C-6 or C-7. It is hoped that another attempt will be made to introduce a double bond into Δ^4 at a later date.

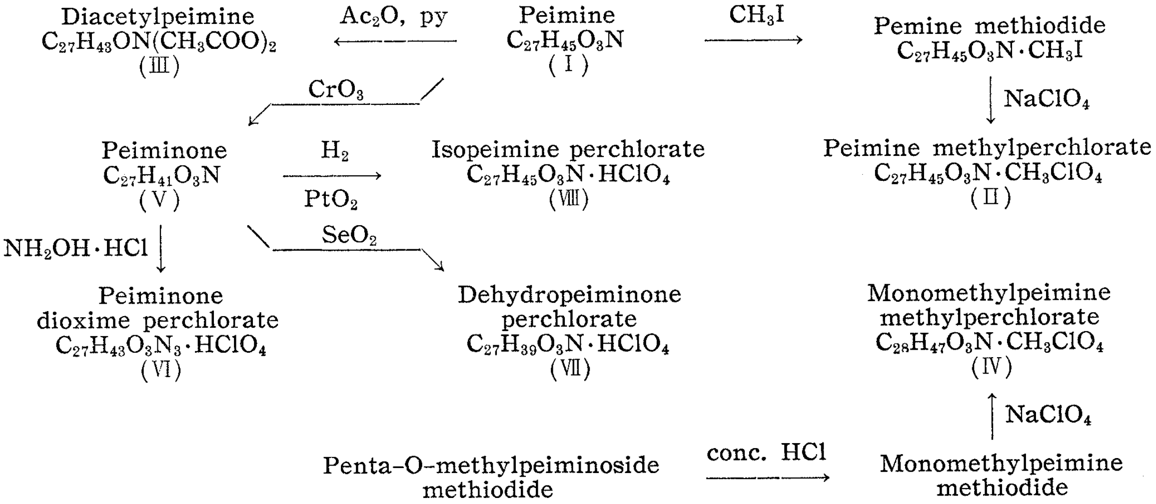
When (V) was reduced in ethanol in the presence of platinum oxide, 2 moles of hydrogen was absorbed, giving an isomer of (I), which was confirmed as its perchlorate (VIII), $C_{27}H_{45}O_3N \cdot HClO_4 \cdot H_2O$, m.p. 263° (decomp.), $[\alpha]_D^{20}$ $-47°$ (EtOH).[*2] As (VIII), whose OH-group formed by the reduction is different from that of (I) in configuration, is a stereoisomer of (I), it was named isopeimine perchlorate.

Experimental[*3]

Peimine Methylperchlorate (II)—To a solution of 260 mg. of peimine methiodide in 10 cc. of water, 100 mg. of $NaClO_4$ was added when crystals separated out. After heating for 2 hr., the crystals were collected (195 mg.) and recrystallized from water to colorless prisms, m.p. 278~279° (decomp.), $[\alpha]_D^{22}$ $-16°$ (c=1.0, EtOH). *Anal.* Calcd. for $C_{27}H_{45}O_3N \cdot CH_3ClO_4$: C, 61.58; H, 8.86; N, 2.56. Found: C, 61.67; H, 8.84; N, 2.52.

Diacetylpeimine (III)—To a solution of 200 mg. of (I) in 3 cc. of Ac_2O 3 drops of pyridine were added and the mixture was heated for 3 hr. The solvent was distilled off under a reduced pressure, a solution of the residue in a small quantity of water was made alkaline, and the resulting precipitate was recrystallized from MeOH to colorless needles, m.p. 214°.

Hydrochloride: Crystallized from 50% EtOH in colorless needles, m.p. 295° (decomp.), $[\alpha]_D^{14}$ $-18.9°$ (c=0.26, H_2O). *Anal.* Calcd. for $C_{27}H_{43}ON(CH_3COO)_2 \cdot HCl$: C, 67.43; H, 9.13; N, 2.54. Found: C, 67.71; H, 8.78; N, 2.77.



Monomethylpeimine Methylperchlorate (IV)—A solution of 1.23 g. of penta-O-methylpeiminoside methiodide in 45 cc. of a mixture of MeOH and conc. HCl (8:1) was refluxed for 4 hr. and the reaction mixture, after addition of 57 cc. of water, was concentrated to about 40 cc. The concentrate was refluxed with 3.3 cc. of conc. HCl for 2.5 hr., treated with decolorizing carbon, and shaken with ten 15-cc. portions of $CHCl_3$. The aqueous solution was evaporated to dryness under a reduced pressure, leaving 730 mg. of a residue. The residue was dissolved in 10 cc. of water, 230 mg. of $NaClO_4$ was added, and the mixture, after heating on a water bath for 2 hr., was evaporated to dryness under a reduced pressure. The residue was recrystallized from water to colorless fine needles, m.p. 202° (sint. 164°), $[\alpha]_D^{22}$ $-4°$ (c=1.0, EtOH). *Anal.* Calcd. for $C_{28}H_{47}O_3N \cdot CH_3ClO_4 \cdot H_2O$: C, 60.24; H, 9.06; N, 2.42. Found: C, 59.82; H, 9.02; N, 2.37.

Peiminone (V)—A solution of 150 mg. of (I) in 3 cc. of AcOH was heated with a solution of 70 mg. of CrO_3 in 7 cc. of AcOH on a water bath for 1 hr. The solvent was distilled off under a reduced pressure, the residue was dissolved in 30 cc. of $CHCl_3$ and the solution, after washing with $NaHCO_3$ solution, was extracted with 15 cc. of 5% H_2SO_4. The extract was made alkaline with NH_4OH, and shaken with three 10-cc. portions of $CHCl_3$. The $CHCl_3$ solution was dried over K_2CO_3 and evaporated, leaving 110 mg. of a product. After recrystallization from MeOH, the product was obtained as

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[*2] Peimine perchlorate, $[\alpha]_D^{20}$ $-17°$ (EtOH).

[*3] All m.p.s are uncorrected.

colorless needles, m.p. 165~168°, $[\alpha]_D^{22}$ $-51°$(c=1.0, EtOH). IR ν_{max}^{KBr} cm^{-1} : 1700 (CO in a six-membered ring), 3450 (OH). *Anal.* Calcd. for $C_{27}H_{41}O_3N$: C, 75.83; H, 9.67; N, 3.28. Found : C, 75.52; H, 9.72; N, 3.19.

Perchlorate : Crystallized from water in colorless fine needles, m.p. 216°, after coloring from about 176°. *Anal.* Calcd. for $C_{27}H_{41}O_3N \cdot HClO_4 \cdot H_2O$: C, 59.39; H, 8.12; N, 2.57. Found : C, 59.60, 59.06; H, 8.37, 8.04; N, 2.63.

Thiocyanate : Colorless prisms (from water), m.p. 251°(decomp.) (sint. 160°). *Anal.* Calcd. for $C_{27}H_{41}O_3N \cdot HCNS \cdot H_2O$: C, 66.63; H, 8.79; N, 5.55. Found : C, 66.04; H, 8.61; N, 5.31.

Peiminone Dioxime Perchlorate (VI)—A solution of 110 mg. of (V), 110 mg. of $NH_2OH \cdot HCl$, and 220 mg. of anhyd. AcOK in 9 cc. of 65% EtOH was refluxed for 1 hr. and the reaction mixture was evaporated to dryness under a reduced pressure. The residue was dissolved in 20 cc. of 5% H_2SO_4, the solution was washed with $CHCl_3$, and made alkaline with NH_4OH. The solution was extracted with three 10-cc. portions of $CHCl_3$ and the $CHCl_3$ solution, after drying over K_2CO_3, was evaporated to leave 110 mg. of a residue. A solution of the residue in 3 cc. of 20% AcOH was heated with 50 mg. of $NaClO_4$ for 30 min., the solvent was distilled off, and the residue was recrystallized from 20 cc. of water to colorless fine needles, m.p. 242°(decomp.), after coloring from about 225°. *Anal.* Calcd. for $C_{27}H_{43}O_3N_3 \cdot HClO_4 \cdot H_2O$: C, 56.29; H, 8.05; N, 7.29. Found : C, 56.25, 56.52; H, 8.46, 8.23; N, 6.89, 6.89.

Dehydropeiminone Perchlorate (VII)—A solution of 514.9 mg. of (V) in 15.5 cc. of *tert*-AmOH was boiled with 115 mg. of SeO_2 for 3 hr. The solvent was distilled off under a reduced pressure, the residue, after addition of a small amount of water, was extracted with $CHCl_3$ and, after removal of the resulting precipitate by filtration, the $CHCl_3$ layer was separated. The aqueous layer was made alkaline with K_2CO_3, extracted with $CHCl_3$, and this was dried over anhyd. K_2CO_3 and evaporated, leaving 37 mg. of a residue (Fraction A). The $CHCl_3$ layer separated first was extracted with five 10-cc. portions of 5% HCl, washed with water, dried over anhyd. Na_2SO_4, and evaporated, leaving 154.8 mg. of a residue (Fraction B). The aqueous acid solution was made alkaline with K_2CO_3 and shaken with $CHCl_3$. The $CHCl_3$ solution was dried over anhyd. K_2CO_3 and evaporated to yield 162.7 mg. of a residue (Fraction C). Fraction C was chromatographed on 10 cc. of Florisil to give the result shown in Table II.

TABLE. II.

Fraction No.	Solvent	cc.	mg.	Perchlorate	
				mg.	m.p. (°C) (decomp.)
1	$CHCl_3$	200	31.2	19.3	201~208°
2	$CHCl_3$-MeOH (99:1)	400	45.2	27.9	196~208°
3	〃	450	7.9		
4	$CHCl_3$-MeOH (50:50)	300	30.7	2.4	
5	〃	400	14.7		
6	MeOH	500	27.3		

As the perchlorates obtained from Fraction 1, 2, and 4 were found to be identical from their IR spectra, they were combined and recrystallized from water to colorless prisms, m.p. 258°(decomp.). UV λ_{max}^{EtOH} 225 mμ (log ε 3.58). IR ν_{max}^{Nujol} cm^{-1} : 1620 (conjugated double bond), 1690 (conjugated CO), 1710 (CO in a six-membered ring), 3500 (OH). *Anal.* Calcd. for $C_{27}H_{39}O_3N \cdot HClO_4$: C, 61.63; H, 7.67; N, 2.66. Found : C, 61.58; H, 7.96; N, 2.67.

Isopeimine Perchlorate (VIII)—A solution of 100 mg. of (V) in 10 cc. of EtOH was subjected to catalytic reduction over PtO_2, when 12.5 cc. of H_2 was absorbed (theoretical amount for 2 moles of H_2, 10.49 cc.). After filtering off the catalyst, the filtrate was evaporated under a reduced pressure, the residue was dissolved in 10 cc. of 20% AcOH, and boiled with 60 mg. of $NaClO_4$ for 1 hr. The solvent was distilled off and the residue was recrystallized from 20 cc. of water to colorless prisms, m.p. 263°(decomp.), after coloring from 245°, $[\alpha]_D^{20}$ $-47°$(c=1.0, EtOH). *Anal.* Calcd. for $C_{27}H_{45}O_3N \cdot HClO_4 \cdot H_2O$: C, 58.94; H, 8.79; N, 2.55. Found : C, 58.89; H, 8.29; N, 2.91.

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Summary

Judging from the properties of some its derivatives, peimine (I) was found to be a saturated tertiary base having two secondary and one tertiary hydroxyl groups. Oxidation of (I) with chromium trioxide gave a diketone, peiminone (V), and an oxidation of the product (V) with selenium dioxide afforded dehydropeiminone. Dehydropeiminone was assumed to have a 1-en-3-one structure from the ultraviolet spectrum of its perchlorate (VII).

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