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43. **Masao Tomita and Hideo Yamaguchi** : Studies on the Alkaloids of Menispermaceous Plants. CXXXIII.⁽¹⁾ Alkaloids of *Cocculus laurifolius* DC. (Suppl. 7).⁽²⁾ Isolation of Dihydroerysodine.

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A survey of the alkaloids of *Cocculus laurifolius* DC. (Japanese name "Kohshu-uyaku") was made first by H. Kondo and the late T. Kondo,[3] and subsequently by Tomita and Kusuda,[4] who recorded the presence of seven kinds of alkaloids including the tertiary bases (coclaurine, coclanoline, trilobine, a base of m.p. 216~217°, and another base giving a picrate, m.p. 172°) and the quaternary bases (laurifoline and a base giving a picrate, m.p. 88°).

In our attempt to obtain coclaurine necessary as the starting material for a certain purpose, a necessity has recently arisen which compelled us to extraction of the alkaloids from *Cocculus laurifolius* DC. as its source. During this isolation process there was isolated a new phenolic base, m.p. 208~209°, in a small quantity besides coclaurine, whose investigations form the subject of this communication.

The plant material used was collected late in November in the districts of Ibusuki (Ohsumi Peninsula, Kagoshima Prefecture) (A) and of Nishino-omote (Tanegashima Island) (B). The new base was isolated from both of them and the yields are shown in Table I.

TABLE I.

Locale	Bark and trunk (kg.)	Crude phenolic base (g.)	Coclaurine HCl salt (g.)	New base, m.p. 208~209°	
				Crude (g.)	Pure (g.)
(A)	26	6.1	4.0	0.46	0.30
(B)	80	26.4	15.8	2.71	1.99

This base crystallized from acetone in the form of colorless needles, m.p. 208~209°, $[\alpha]_D^8$ +224.39°(MeOH), and its analytical values correspond to the composition of $C_{18}H_{23}O_3N$. With ferric chloride it produced a weak green color, which did not turn violet on the addition of alkali. It gave negative reactions to Ehrlich, Gaebel, and Gibbs reagents, and showed the presence of two methoxyls and no N-methyl group (Vieböck-Brecher method). Since this alkaloid gave a negative Liebermann's nitroso reaction and an attempt of its N-methylation with formaldehyde solution and formic acid resulted in the recovery of the original base, it seems that >NH group is not present. The methiodide of this base has m.p. 282°(decomp.) and its *d*-tartrate

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[1] Part CXXXII. M. Tomita, Y. Watanabe : This Bulletin, **4**, 124(1956).

[2] Suppl. (6). F. Kusuda : *Ibid* **1**, 189(1953).

[3] H. Kondo, T. Kondo : J. Pharm. Soc. Japan, **45**, 876(1925); **46**, 1029(1926); **48**, 324, 1156(1928); **50**, 427(1930); J. prakt. Chem., [2] **126**, 24(1930).

[4] M. Tomita, F. Kusuda : J. Pharm. Soc. Japan, **72**, 280, 793(1952); This Bulletin, **1**, 1, 5, 55, 189(1953).

formed feathers, m.p. 68~70°, which could not be submitted to analysis due to its unstability in dry state. From these experimental data, the formula may be extended as follows : $C_{18}H_{23}O_3N = C_{16}H_{16}(OCH_3)_2(OH) - \overset{|}{\underset{|}{N}}$.

The ultraviolet absorption spectrum of this base exhibits an analogous absorption having λ_{min} 256 mμ and λ_{max} 287 mμ to those of the tetrahydroisoquinoline series. The infrared spectrum shows the presence of a phenolic hydroxyl group (Fig. 1 (II)).

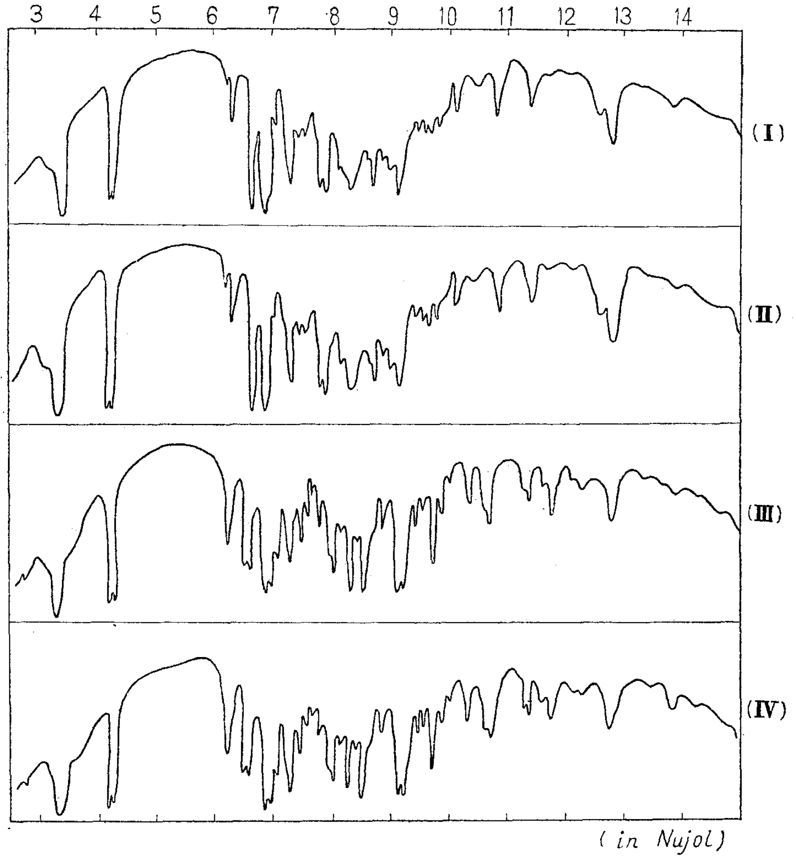

Fig. 1.

(I) Dihydroerysodine (by Prelog)

(II) The base, m.p. 208~209°, from *C. laurifolius DC.*

(III) Tetrahydroerysodine (by Prelog)

(IV) Hydrogenated product of the base of m.p. 208~209°

On methylation with diazomethane it furnished the O-methyl ether, which in spite of various attempts did not crystallize. Its picrate, however, formed microscopic yellow needles, m.p. 163~164°, and by analyses was found to possess an empirical formula, $C_{19}H_{25}O_3N \cdot C_6H_3O_7N_3$. The O-methyl ether methiodide was hygroscopic, but its picrate was obtained crystalline, $C_{20}H_{22}O_3N \cdot C_6H_2O_7N_3$, m.p. 175~176°.

When the original base was submitted to catalytic reduction with Pd-carbon catalyst, about one mole of hydrogen was absorbed and the dihydro derivative, $C_{18}H_{25}O_3N$, microscopic needles, m.p. 154.5~155°, was obtained. Analyses gave values corresponding to the composition of $C_{18}H_{25}O_3N$ and its optical rotation is $[\alpha]_D^{12}$ $-23.22°$ ($CHCl_3$).

The melting points and molecular formulae of this base and its dihydro derivative, as well as the phenomenon of inversion in their optical rotations by hydrogenation (strong dextrorotatory to weak levorotatory), suggested them to be in good accord with dihydroerysodine reported by Prelog[5] and tetrahydroerysodine by Prelog[5] and Folkers,[6] respectively (see Table II).

The ultraviolet absorption spectra of the original base and its dihydro derivative

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[5] V. Prelog, K. Wiesner, H. G. Khorana, G. W. Kenner : Helv. Chim. Acta, **32**, 453(1949).

[6] F. Koniuszy, P. F. Wiley, K. Folkers : J. Am. Chem. Soc., **71**, 875(1949).

Table II.

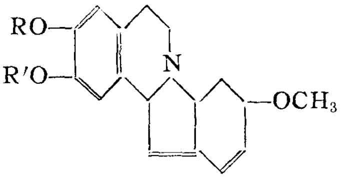
	m.p. (°C)	[α]D
New base from *C. laurifolius*	208∼209	+224°(MeOH)
Dihydroerysodine	212∼214(Prelog[5])	+239°(EtOH)
Hydrogenated new base	154.5∼155	−23°($CHCl_3$)
Tetrahydroerysodine	158∼159(Prelog[5]) 152∼153(Folkers[6])	−25°($CHCl_3$)

Table III. Ultraviolet Spectrum

	in 0.01*N* EtOH-NaOH			in 0.01*N* EtOH-HCl		
	λ_{max} (mμ)	λ_{min} (mμ)	log ε	λ_{max} (mμ)	λ_{min} (mμ)	log ε
New base from *C. laurifolius*		239	3.758	235		3.839
	253		3.776		257	2.687
		275	3.388	285		3.529
	293		3.559			
Dihydroerysodine (Prelog[5])		233	3.75	235		3.9
	252		3.9		257	<2.8
		276	3.35	285		3.5
	300		3.7			
Hydrogenated new base	245		3.712		251	2.536
		267	3.139	283		3.615
	293		3.552			
Tetrahydroerysodine (Prelog[5])	245		3.9		255	3.0
		270	3.1	282		3.7
	300		3.7			

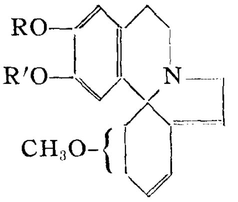
were further measured in 0.01*N* ethanolic sodium hydroxide and hydrogen chloride solutions following the procedures adopted by Prelog and the results are compared in Table III along with Prelog's data. It is seen that although a slight difference is observed in the molecular extinction coefficient between the two series, the locations of absorption are almost identical. Slight difference in their molecular extinction coefficients would be due to the pH of the solutions. Through the generosity of Prof. Dr. Prelog, the samples of dihydroerysodine and tetrahydroerysodine were made available, which enabled us to make a direct cmparison by infrared spectra and mixed melting point determinations. As a result, it was confirmed that this new base and its dihydro derivative are identical with dihydroerysodine and tetrahydroerysodine, respectively (see Fig. 1. for infrared spectra).

The occurrence of alkaloids having analogous structure from taxonomically unrelated families is a rare example and it is noteworthy that the dihydro derivative of erysodine peculiar to Erythrina plants (Legminosae) was isolated from *Cocculus laurifolius* DC.(Menispermaceae). Although dihydroerysodine was previously derived by Prelog from erysodine, this is the first instance that this alkaloid was discovered in nature.



(I)

R=H; R'=CH_3
or
R=CH_3; R'=H



(II)

R=H; R'=CH_3
or
R=CH_3; R'=H

For the structure of erysodine, Folkers[7] first offered formula (I), but later Prelog[8] gave formula (II), which Robinson[9] also supported. However, there is no confirm-

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[7] K. Folkers, F. Koniuszy, J. Shavel : J. Am. Chem. Soc., **73**, 589(1951).

[8] M. Carmak, B. C. McKusick, V. Prelog : Helv. Chim. Acta, **34**, 1601(1951); G. W. Kenner, H. G. Khorana, V. Prelog : *Ibid.*, **34**, 1969(1951).

[9] R. Robinson : "The Structural Relations of Natural Products," Clarendon Press, Oxford, 89 (1955).

atory experimental proof, which must await further work, but the amount of this alkaloid available was too small to permit further investigations.

One of the plant material (Tanegashima) used in this work was collected by Mr. H. Shiba of Nishino-omote, Tanegashima, Kagoshima Prefecture, through the good offices of Dr. T. Okanishi of the Research Laboratory, Shionogi & Co., Ltd., and the other (Ibusuki) by Mr. T. Tanigawa, priest of Hirakiki Shrine, Ibusuki, Kagoshima Prefecture. We are indebted to Prof. Dr. V. Prelog for the generous gift of samples of dihydro- and tetrahydroerysodine, and to Drs. Kato and Hiyama, and Mr. Tanno and members of the Dainippon Pharmaceutical Industries, and to Mr. Sato and his associates of the Research Laboratory, Shionogi & Co., Ltd., for according us facilities in the extraction of the plant material. Our thanks are also offered to Messrs. Matsui and Narisada of the Research Laboratory, Shionogi & Co., Ltd., for infrared determinations. This work was supported partly by a Grant in Aid for Fundamental Scientific Research from the Ministry of Education, to which we are also grateful.

Experimental[10]

Isolation of Dihydroerysodine from ***Cocculus laurifolius*** **DC.**—The isolation of the alkaloids of *Cocculus laurifolius* DC. was carried out according to the procedure employed by Kusuda.[4] From the phenolic portion, coclaurine was removed as the hydrochloride, and its mother liquor was diluted with water and made alkaline with Na_2CO_3. The deposited base was extracted with ether and partitioned between acid and ether. The ether extract was dried over anhyd. K_2CO_3 and the ether removed, yielding a slightly yellowish amorphous powder. This was dissolved in acetone, the insoluble portion was removed by filtration, and the filtrate concentrated. On being kept in an ice chest, aggregates of colorless needles, m.p. 202~208°, appeared. From the mother liquor there was recovered a small amount of the above base, m.p. 202~208°.

Dihydroerysodine—The above crude base, m.p. 202~208°, after recrystallization from acetone, formed colorless needles, m.p. 208~209°. *Anal.* Calcd. for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69; N, 4.65; OCH_3, 20.59. Found : C, 71.31, 71.54; H, 7.57, 7.67; N, 5.06, 5.10; OCH_3, 19.71, 20.90. $[\alpha]^{8}_{D}$ +224.39° ($c=0.41$ in MeOH, $l=0.5$ dm.). This substance did not depress the melting point of dihydroerysodine[11] on admixture. It gave negative tests with Ehrlich, Gaebel, and Gibbs reagents. Liebermann's nitroso reaction was also negative. With ferric chloride it produced a slightly greenish color, which on addition of alkali, did not turn violet. The N-methylation with formaldehyde solution and formic acid resulted in recovering the starting material. U.V. λ^{EtOH}_{max} 287 mμ(log ε 3.57), λ^{EtOH}_{min} 256 mμ(log ε 2.59); in solution of 0.01*N* EtOH-NaOH and of 0.01*N* EtOH-HCl (cf. Table II). Infrared absorption spectrum is given in Fig. 1 (II).

Dihydroerysodine Methiodide—(a) A portion of the base, m.p. 208~209°, was refluxed in MeOH with MeI, yielding the methiodide. It was recrystallized from MeOH to microscopic needles, m.p. 282°(decomp.). *Anal.* Calcd. for $C_{18}H_{23}O_3N \cdot CH_3I$: C, 51.47; H, 5.91. Found : C, 51.26; H, 5.97. (b)[12] 30 mg. of the base, m.p. 208~209°, was dissolved in MeOH, followed by 0.2 cc. of MeI. The mixture was allowed to stand in an ice chest and the methiodide deposited as pillars. Recrystallization from MeOH showed m.p. 282°(decomp.).

Dihydroerysodine *d*-Tartrate—To an EtOH solution of the base, m.p. 208~209°, was added the calculated amount of *d*-tartaric acid, and the mixture was allowed to stand at room temp. Dihydroerysodine *d*-tartrate deposited as feathers, m.p. 68~70°. It seems that this substance becomes stable when it holds water of crystallization and in a dry state, it was too unstable to submit to analysis.

O-Methyldihydroerysodine—0.1 g. of the base, m.p. 208~209°, was dissolved in a small portion of MeOH and an ethereal CH_2N_2 prepared from 2.5 g. of nitrosomethylurea was added. The mixture was set aside for 48 hrs., after which the solvent was removed and the residue was treated with dil. HCl. After being washed with ether, the aq. solution was made alkaline with NaOH and extracted with ether. The ether extract was shaken with 10% aq. NaOH to remove unreacted material and then dried over anhyd. K_2CO_3. After removal of the ether, the residue was dissolved in benzene and purified by chromatography on alumina. The colorless oil thus

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10) All melting point are uncorrected. We are indebted to Mr. K. Hozumi and the members of the Central Analysis Room of this Institute for the microanalyses.

11) The sample of dihydroerysodine provided by Prof. Dr. Prelog was labeled m.p. 212~214°, but as determined by us, it melted at 209°.

12) This experiment was carried out in order to confirm that the base, m.p. 208~209°, was not identical with erysodine. The literature[6] records that when erysodine was kept standing in MeOH solution with MeI in an ice chest, erysodine methiodide was obtained as crystals, m.p. 229~229.5°.

obtained was dissolved in a small portion of dil. HCl and treated with an aq. Na picrate solution. The picrate, after recrystallization from acetone-EtOH, formed yellow microscopic needles, m.p. 163~164°. *Anal.* Calcd. for $C_{19}H_{25}O_3N \cdot C_6H_3O_7N_3$: C, 55.14; H, 5.18; OCH_3, 17.09. Found : C, 55.55; H, 5.14; OCH_3, 16.54.

O-Methyldihydroerysodine Methiodide—The methiodide was obtained by refluxing the above oily O-methyl ether with MeI in MeOH solution. This substance is very hygroscopic and it solidifies while kept in a desiccator, but when exposed to air, it tends to separate as an oil. The picrate was obtained by dissolving it in a little water and treating with an aq. Na picrate. It was recrystallized first from acetone-water and then from MeOH to show m.p. 174~175°. *Anal.* Calcd. for $C_{20}H_{28}O_3N \cdot C_6H_2O_7N_3$: C, 55.91; H, 5.41; OCH_3, 16.66; NCH_3, 2.69. Found : C, 56.10; H, 5.65; OCH_3, 16.24; NCH_3, 3.06.

Tetrahydroerysodine—The Pd catalyst prepared from 3.5 cc. of $PdCl_2$ (1%) in dil. HCl and 70 mg. of purified charcoal was suspended in 10 cc. of water and a solution of 150 mg. of the base, m.p. 208~209°, in 14 cc. of 1% AcOH added. The catalytic reduction proceeded smoothly, and after 2 hrs., the absorption of H_2 ceased with the total amount of 16.4 cc. The catalyst was then filtered and washed several times with warm water. The filtrate and washings were combined, basified with Na_2CO_3, and extracted with ether. The aq. layer was made acidic with H_2SO_4, then made alkaline with Na_2CO_3, and extracted with ether. The ether extracts were combined, dried over anhyd. K_2CO_3, and evaporated, yielding 100 mg. of colorless crystalline residue. Recrystallization was effected from acetone. Microscopic needles, m.p. 154.5~155°. *Anal.* Calcd. for $C_{18}H_{25}O_3N$: C, 71.25; H, 8.31. Found : C, 70.88; H, 8.30. $[\alpha]_D^{12}$ $-23.22°$(c=0.516 in $CHCl_3$, l=0.5 dm.). On admixture with the sample of tetrahydroerysodine supplied by Prof. Dr. Prelog, no melting point depression was observed. Ultraviolet absorption spectra in 0.01*N* EtOH-NaOH and 0.01*N* EtOH-HCl are given in Table II, and infrared absorption spectrum in Fig. 1 (IV).

Summary

Besides seven alkaloids so far isolated from *Cocculus laurifolius* DC. there was obtained another phenolic base of the composition, $C_{18}H_{23}O_3N$, m.p. 208~206°, $[\alpha]_D^8$ +224.39°, which as a result of detailed examinations, was confirmed to be dihydroerysodine.

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