maintained at 0° before use. EtOH (3~5 drops) was added to each of the quenched solution and then the samples, 2~10 μl., for the gas chromatographic analysis were injected into the GC apparatus described above being equipped with the column as shown in Table IX. The areas were determined by graphical integration.

The authors are indebted to Sankyo Co., Ltd. for the measurements of infrared absorption spectra. Thanks are also due to the members of the Central Analysis Room of this Faculty for microanalytical, infrared and ultraviolet spectral data.

Summary

The reduction of the various Schiff bases with diborane in tetrahydrofuran was smoothly proceeded, being followed by the simple treatment with alcohol, to give the corresponding amines. The relative reactivity of the Schiff bases toward diborane increased with an increasing order of their basicities determined by the infrared absorption spectral method.

(Received May 2, 1966)

[Chem. Pharm. Bull. 14(12)1399~1404(1966)]

UDC 547.92.07:547.833.9.07

189. Zen-ichi Horii, Koichi Morikawa, Yasumitsu Tamura, and Ichiya Ninomiya: Studies on Azasteroids and Related Compounds. I. The Reaction of Ethyl 2-Piperidineacetate with 2-Tetralone.

(*Faculty of Pharmaceutical Sciences, Osaka University*[*1])

The reaction of methyl 2-methyl-3-methylaminopropionate with 2-tetralone has been reported to give the rearranged compound (Ⅲ) as a major product.[1] This was explained by the thermal decomposition of the initially formed enamine (Ⅴ), followed by the recombination of the resulted enamine and methyl acrylate moieties. Therefore, if one can provide the product of type I in good yield by using the thermally stable β-aminoester, the reaction of ketone and β-aminoester can be a useful method for the preparation of the skeleton of 14-azasteroids bearing oxygen function at C_{11} position. Actually, methyl 3-methylaminopropionate, when reacted with cyclohexanone at the boiling point of toluene, yielded the normally acylated product as a major, along with the rearranged product as a minor.[1]

This paper deals with the investigation of the intramolecular cyclization of the enaminoester derived from 2-tetralone and ethyl 2-piperidineacetate,[2] which was found to be stable upon treating it under the reaction condition, suggesting the possible exclusion of the formation of the rearranged product like Ⅲ.

Heating of ethyl 2-piperidineacetate and cyclohexanone in the presence of *p*-toluenesulfonic acid gave the enamine (Ⅵ), which was then refluxed in ethylene glycol to afford the compound (Ⅶ) in 69% yield, and its structural assignment was obtained mainly from its infrared spectrum, showing peaks at 1620 and 1550 cm^{-1} characteristic

---

*1 Toneyama, Toyonaka, Osaka-fu (堀井善一, 森川浩一, 田村恭光, 二宮一弥).

1) *a*) Z. Horii, C. Iwata, Y. Tamura, N. A. Nelson, G. H. Rasmusson: J. Org. Chem., **29**, 2768 (1964).
b) Z. Horii, C. Iwata, I. Ninomiya, N. Imamura, M. Ito, Y. Tamura: This Bulletin, **12**, 1405 (1964).
2) G. R. Clemo, W. M. Morgan, R. Raper: J. Chem. Soc., **1935**, 1743.

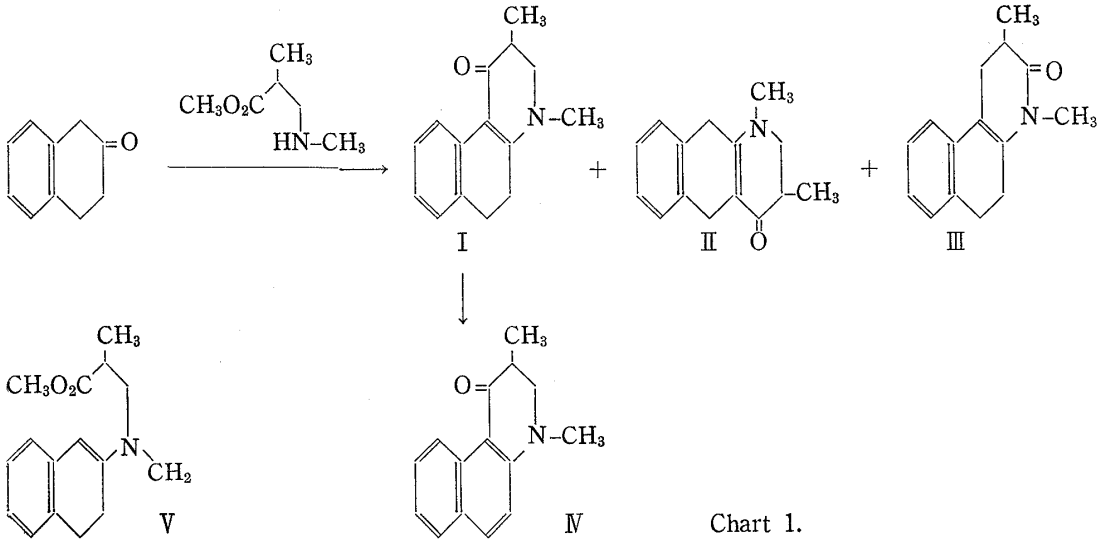


Chart 1.

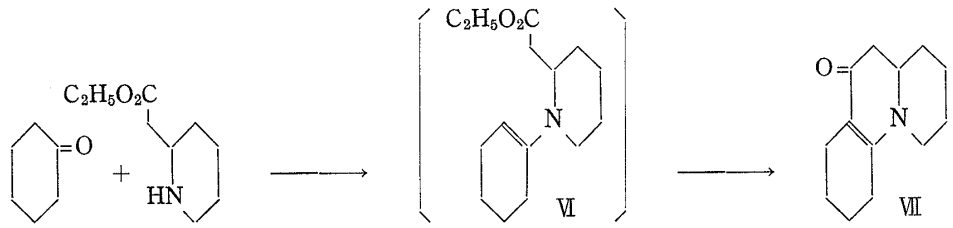


Chart 2.

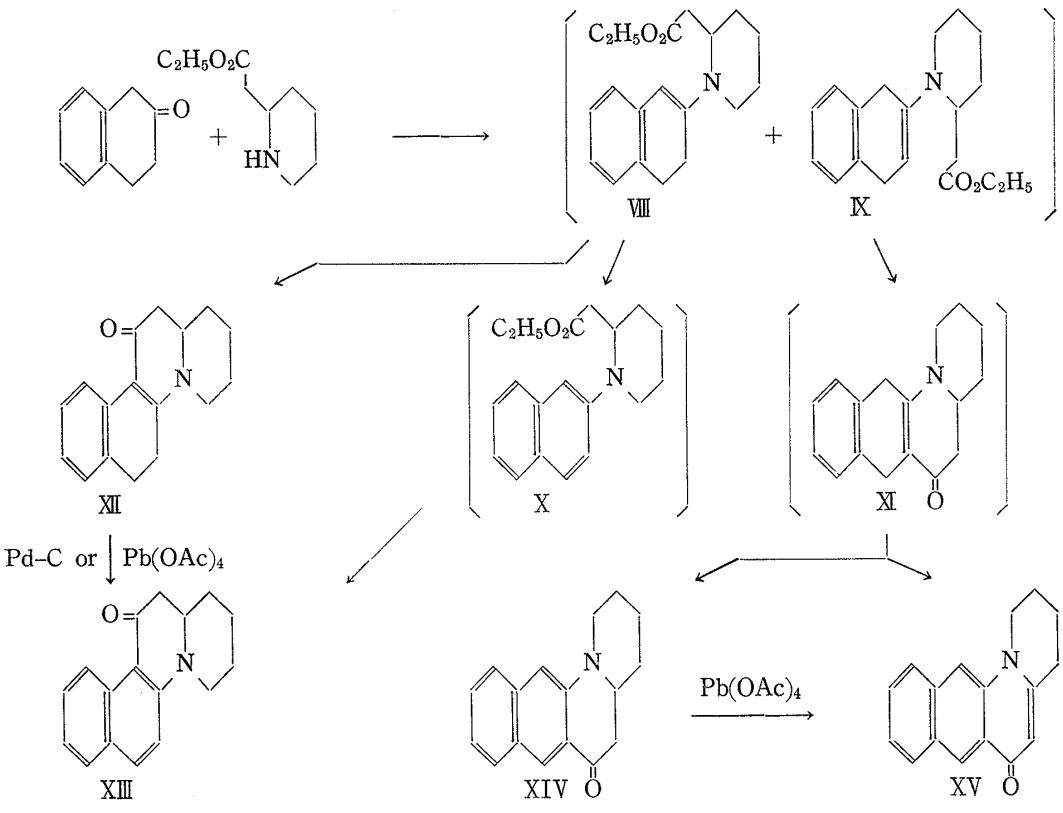


Chart 3.

for the vinylogous lactam grouping[1,3] and ultraviolet spectrum, which showed a bathochromic shift on the addition of hydrochloric acid,[1,4] as shown in Table I.

Then, we applied this reaction to the synthesis of the tetracyclic compound containing a nitrogen atom at the bridgehead position. Ethyl 2-piperidineacetate and 2-tetralone were condensed in xylene in the presence of *p*-toluenesulfonic acid and cyclized by heating it in ethylene glycol to give XII in 13.5%, XIII in 1.6%, XIV in 21%, and XV in 9% yields, respectively. The structures of these compounds (XII, XIII, XIV and XV) were determined by their infrared, ultraviolet and NMR spectra as discussed below (Table I).

Table I.

Compod. No.	Appearance	M.p. (°C)	Yield (%)	IR ν_{max} : cm^{-1}		UV λ_{max} : mμ(log ε)		NMR τ (signal for aromatic protons)
				in $CHCl_3$	KBr-tablet	in EtOH	in EtOH–HCl	
VII	almost colorless needles	72~73	69.4	1620(s) 1550(vs)	1630(s) 1570(s)	334(4.13)	340(3.94)	—
XII	pale yellow needles	137~138	13.5	1621(vs) 1597(s) 1522(vs) 1493(s)	1625(vs) 1600(m) 1522(vs) 1495(m)	277(4.16) 360(4.03)	260(4.34) 362(3.81)	1.70(**d**) 2.75(m)
XIII	yellow needles	128~129	1.6	1640(vs) 1615(s) 1600(m) 1555(m) 1515(s)	1645(vs) 1622(s) 1600(m) 1552(m) 1515(s)	218(4.43) 262(4.52) 322(3.70) 407(3.72)	218(4.44) 262(4.51) 322(3.72) 407(3.73)	1.70(**d**) 2.75(m)
XIV	brilliant yellow needles	150.5~151.0	20.6	1680(s) 1630(s) 1595(m) 1500(m)	1685(s) 1628(s) 1595(s) 1500(m)	241(4.44) 272(4.69) 437(3.97)	241(4.45) 252(4.43) 272(4.59) 437(3.88)	1.50(sgl.) 2.51(m)
XV	pale yellow needles	218~221	8.8	1643(s) 1615(vs) 1590(vs) 1577(s) 1558(m)	1645(s) 1620(vs) 1590(vs) 1577(s) 1558(m)	226(4.25) 253(4.85) 262(4.80)	224(4.32) 229(4.34) 263(5.09)	—
IV[a)]	almost colorless needles	97~98	—	1643(vs) 1616(s) 1600(m) 1558(m) 1525(s)	—	217(4.39) 263(4.57) 322(3.78) 407(3.61)	217(4.36) 262(4.52) 320(3.81) 406(3.61)	—

a) See ref. 1*b*)

Two characteristic bands in the region of 1630 to 1550 cm^{-1} for the vinylogous lactam grouping[1,3,5] were important clue for elucidation of the structures. The compound (XII) had two similar bands at 1621 (vs) and 1522 (vs) cm^{-1} and its ultraviolet spectrum showed maximum at 277 and 360 mμ in ethanol solution. The former band was hypsochromically shifted to 260 mμ on adding hydrochloric acid, as observed in the compound (I). All these data were consistent with the structure of the N-C=C-C=O grouping, conjugated with benzene ring for this compound, represented by XII.

3) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, D. J. Wallace : J. Am. Chem. Soc., **71**, 3337 (1949).
4) C. Weissmann, H. Schmid, P. Karrer : Helv. Chim. Acta, **43**, 2201 (1960).
5) F. Bohlmann, E. Winterfeld, O. Schmidt, W. Reusche : Chem. Ber., **94**, 1774 (1961); F. Bohlmann, O. Schmidt : *Ibid.*, **97**, 1354 (1964); G. O. Dudek : J. Org. Chem., **30**, 548 (1965); W. Sobota, W. N. Beverung, G. G. Munoz, J. C. Sircar, A. I. Meyers : *Ibid.*, **30**, 3667 (1965).

As for the compound (XIII), which was obtained by the dehydrogenation of the compound (XII) with palladium on charcoal in tetraline or with lead tetraacetate in acetic acid, its infrared and ultraviolet spectra were well resembled with those of the compound IV (Table I). Therefore, the structure of this compound should be represented by XIII.

The infrared spectrum of the compound (XIV) showed three peaks at 1680, 1630 and 1595 cm^{-1}, but lacked peaks characteristic for N-C=C-C=O grouping. A peak at 1680 cm^{-1}, attributable for a carbonyl group having aromatic ketone character, might be the reason for the absence of the contribution of the vinylogous lactam chromophore.

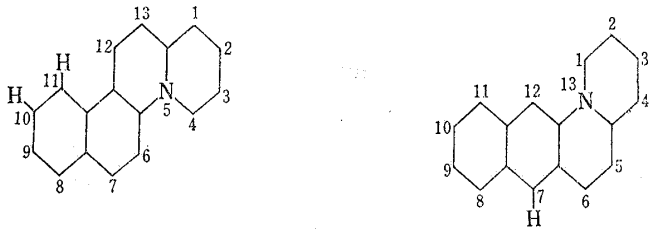


Fig. 1.

The compound (XV) was also obtained by dehydrogenation of the compound (XIV) with lead tetraacetate in acetic acid, and its infrared spectrum showed three absorptions in the carbonyl region, one at 1643 cm^{-1}, attributed to the γ-pyridone structure and two at 1615 and 1558 cm^{-1} to the vinylogous lactam grouping, which were absent in the compound (XIV).

The NMR spectra of XII, XIII, and XIV gave further firm information about their structures, especially whether they were cyclized at α- or β-position of the naphthalene ring. In the compounds (XII) and (XIII), a signal corresponding to a proton at C_{11} appeared as doublets centered at 1.70 τ, which showed coupling with a proton at C_{10}. On the other hand, of six aromatic protons in the compound (XIV), a proton at C_7 appeared at 1.50 τ as a singlet, showing the absence of any neighboring proton (Fig. 1).

In addition to the results reported previously, the confirmation of the structures (XII, XIII, XIV and XV) have now provided the whole aspect of the reactions between 2-tetralone and β-aminoesters, as shown in Chart 3.

In this particular case, the condensation of ethyl 2-piperidineacetate with 2-tetralone in xylene might give a mixture of two enamines, the one conjugated (VIII) and the other nonconjugated (IX). The enamine (VIII) might be directly cyclized to give the compound (XII), and also might be subject to dehydrogenation to the intermediate (X), which is converted to the compound (XIII) by cyclization in ethylene glycol, whereas the possibility to form XIII directly from XII could be excluded by the fact that the prolonged heating of the compound (XII) in ethylene glycol recovered the starting material. The compound (XIV) and (XV) might be resulted from dehydrogenation of the intermediate lactam (XI) which might be formed by the cyclization of IX in the linear fashion.

Experimental

Ethyl 2-Piperidineacetate——Ethyl 2-piperidineacetate was prepared by hydrogenation of ethyl 2-pyridineacetate with PtO_2 in AcOH containing small amount of 70% $HClO_4$ in 87% yield,[2] $b.p_{17}$ 105°.

1,2,3,4,4a,5,7,8,9,10-Decahydro-6*H*-benzo[*c*]quinolizin-6-one (VII)——A mixture of 5.0 g. (0.29 mole) of ethyl 2-piperidineacetate and 10 ml. of cyclohexanone was refluxed for 20 hr. under N_2 atmosphere in the presence of a few crystals of *p*-TsOH. After evaporation of cyclohexanone under reduced pressure, 60 ml. of ethylene glycol was added to the dark brown residue which showed peaks at 1705 (ester) and 1615 cm^{-1} (C=C) in its infrared spectrum. The resulting solution was refluxed for 10 hr. under N_2 atmosphere. After cooling, 150 ml. of H_2O and 50 ml. of benzene were added, and the mixture was shaken well. The benzene layer was separated, and the aqueous layer was extracted with benzene (50 ml × 3). The benzene layer and extract were combined, washed three times with H_2O and dried over anhydrous Na_2SO_4. After evaporation of benzene, 7.3 g. of a dark brown paste was obtained. Chromatography of the residue on alumina (240 g.) eluted by benzene gave 4.20 g. (69.4%) of a viscous oil, 1,2,3,4,4a,5,7,8,9,10-decahydro-6*H*-benzo[*c*]quinolizin-6-one (VII), $b.p_{0.07}$ 160~170°, which crystallized on standing and was recrystallized from *n*-hexane to give

almost colorless needles, m.p. 72~73°. *Anal.* Calcd. for $C_{13}H_{19}ON$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.92; H, 9.00; N, 6.67. Picrate: m.p. 143~144°(from iso-PrOH). *Anal.* Calcd. for $C_{19}H_{22}O_8N_4$: C, 52.53; H, 5.10; N, 12.90. Found: C, 52.34; H, 5.20; N, 13.09.

Reaction of Ethyl 2-Piperidineacetate with 2-Tetralone——A solution of 8.5 g. (0.05 mole) of ethyl 2-piperidineacetate and 7.3 g. (0.05 mole) of 2-tetralone in 100 ml. of dry xylene containing a few crystals of *p*-TsOH was refluxed under N_2 stream with Dean-Stark water separator in order to remove water as it formed for 10 hr. After evaporation of xylene, 80 ml. of ethylene glycol was added and refluxed for another 7 hr. After cooling, an equal amount of H_2O was added, and the mixture was extracted with benzene (60 ml. × 5). The benzene extract was washed with H_2O, and dried over anhydrous Na_2SO_4. After evaporation of benzene, a residual dark brown paste was chromatographed on alumina (300 g.). The first elution by 9 liters of benzene gave 2.7 g. (20.6%) of brilliant yellow crystals, 1,2,3,4,4a,5-hexahydro-6*H*-naphtho[2,3-*c*]quinolizin-6-one (XIV), m.p. 145~148°, which was recrystallized from EtOH to give brilliant yellow fine needles, m.p. 150.5~151°. *Anal.* Calcd. for $C_{17}H_{17}ON$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.50; H, 6.79; N, 5.54.

The second elution by 2 liters of benzene-chloroform (1:1) gave 0.2 g. (1.6%) of 1,2,3,4,13,13a-hexahydro-12*H*-naphtho[1,2-*c*]quinolizin-12-one (XIII), as yellow needles, m.p. 128~129°, upon recrystallization from benzene. *Anal.* Calcd. for $C_{17}H_{17}ON$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.26; H, 6.59; N, 5.19.

The third elution by 400 ml. of chloroform gave 1.8 g. (13.5%) of pale yellow needles, 1,2,3,4,6,7,13,13a-octahydro-12*H*-naphtho[1,2-*c*]quinolizin-12-one (XII), m.p. 137~138°, upon recrystallization from benzene-*n*-hexane. *Anal.* Calcd. for $C_{17}H_{19}ON$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.80; H, 7.60; N, 5.50.

The fourth elution by one liter of chloroform gave a dark brown solid, which was recrystallized from benzene to give 1.1 g. (8.8%) of 1,2,3,4-tetrahydro-6*H*-naphtho[2,3-*c*]quinolizin-6-one (XV), as pale yellow needles, m.p. 218~221°.) *Anal.* Calcd. for $C_{17}H_{15}ON$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.87; H, 6.11; N, 5.51.

Dehydrogenation Reaction of 1,2,3,4,6,7,13,13a-Octahydro-12*H*-naphtho[1,2-*c*]quinolizin-12-one (XII)——a) With 10% Pd-C in tetraline: A mixture of 140 mg. of 10% Pd-C and 360 mg. of XII in 10 ml. of tetraline was refluxed for 3 hr. After removal of tetraline *in vacuo*, a brown pasty residue was chromatographed on alumina (20 g.) to give 70 mg. (19.5%) of yellow fine needles, m.p. 128~129°, which was found to be identical with XIII on the comparison of the mixed melting point and their IR spectra. $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640, 1615, 1600, 1555 and 1515.

b) With $Pb(OAc)_4$ in AcOH: A solution of 100 mg. (0.39 mmole) of XII in 10 ml. of AcOH was added to a solution of 170 mg. (0.40 mmole) of $Pb(OAc)_4$ in 20 ml. of AcOH, and the solution was warmed at 80~90° with stirring for 3 hr. After neutralizing with 10% NaOH, the solution was shaken with chloroform (20 ml. × 3), and the chloroform extract was washed with H_2O and dried over anhydrous Na_2SO_4. The solvent was removed to give 90 mg. of a dark brown viscous residue, which was chromatographed on alumina (5 g.). The first elution by 120 ml. of benzene gave 15 mg. of yellow crystals, m.p. 126~128°, which was found to be identical with a sample of XIII on the comparison of their IR spectra. $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640, 1615, 1600, 1555 and 1515.

The second elution by 300 ml. of benzene-chloroform (3:1) gave 40 mg. of the starting material. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1621, 1597, 1522 and 1493.

c) With chloranil in dry benzene: A solution of 100 mg. (0.39 mmole) of XII and 90 mg. (0.37 mmole) of chloranil in 30 ml. of dry benzene was refluxed for 3 hr. After cooling, the solution was washed with 10% NaOH and then with H_2O and dried over anhydrous Na_2SO_4. Evaporation of benzene gave 90 mg. of a dark brown solid. Recrystallization from benzene gave pale yellow needles, m.p. 135~137°, which was found to be identical with the starting material on the comparison of their IR spectra. $\nu_{max}^{CHCl_3}$ cm^{-1}: 1621, 1597, 1522 and 1493.

Dehydrogenation Reaction of 1,2,3,4,4a,5-Hexahydro-6*H*-naphtho[2,3-*c*]quinolizin-6-one (XIV) with $Pb(OAc)_4$ in AcOH——To a solution of 790 mg. (1.6 mmole) of $Pb(OAc)_4$ in 10 ml. of AcOH was added a solution of 300 mg. (1.2 mmole) of XIV in 20 ml. of AcOH and the resulting solution was warmed on a steam bath at 80~90° with stirring for 1.5 hr. After cooling, the solution was made alkaline with K_2CO_3, and extracted with chloroform (20 ml. × 3). The chloroform extract was washed with H_2O and dried over anhydrous Na_2SO_4. Evaporation of chloroform gave 250 mg. of a crystalline residue which was chromatographed on alumina (5 g.). The first elution by 300 ml. of benzene gave a starting material, 120 mg. (40.5%). The second elution by 300 ml. of benzene gave 80 mg. (26.7%) of yellow needles, m.p. 217~220°, which was found to be identical with XV, prepared above, on the comparison of the mixed melting point and their IR spectra. $\nu_{max}^{CHCl_3}$ cm^{-1}: 1643, 1615, 1590, 1577 and 1558.

Summary

Condensation and cyclization of ethyl 2-piperidineacetate with cyclohexanone gave a vinylogous lactam, 1,2,3,4,4a,5,7,8,9,10-decahydro-6*H*-benzo[*c*]quinolizin-6-one (VII). The

same reaction with 2-tetralone gave four compounds, all having the vinylogous lactam grouping. The structures of these compounds were assigned by their infrared, ultraviolet and nuclear magnetic resonance spectra.

(Received May 2, 1966)

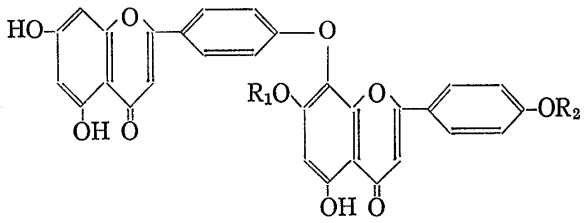
[Chem. Pharm. Bull. 14(12)1404~1408(1966)]

UDC 581.19 : 547.972.2.02 : 582.477

190. Hiroshi Miura, Nobusuke Kawano,*1 and Anthony C. Waiss, Jr.*2 : Cryptomerin A and B, Hinokiflavone Methyl Ethers from the Leaves of *Cryptomeria japonica*.*3

(*Faculty of Pharmaceutical Sciences, Nagasaki University*[*1] *and Western Regional Research Laboratory*[*2])

Hinokiflavone (I) was reported[1] to be contained in the leaves of *Cryptomeria japonica* D. Don (Japanese name, sugi). However, further investigations disclosed that this reported hinokiflavone was still a mixture of hinokiflavone and its methyl ethers (II and III), new compounds. This paper deals with the isolation and structure of cryptomerin A (II) and cryptomerin B (III).



I : $R_1=R_2=H$
II : $R_1=H$, $R_2=CH_3$
III : $R_1=R_2=CH_3$

As cryptomerin A and B are more hardly soluble in methanol than hinokiflavone considerable loss of these compounds was inevitable on extraction when the solution was filtered after cooling as reported formerly.[1] The deposits appeared when it was filtered while hot and cooled for standing were impure cryptomerin B mixed with cryptomerin A. Along the procedure shown in Chart 1 and described in the experimental part cryptomerin A, $C_{31}H_{20}O_{10}$, m.p. 308~310° (decomp.) and cryptomerin B, $C_{32}H_{22}O_{10}$, m.p. 302~303° (decomp.) were isolated as yellow prisms. Hinokiflavone was also obtained as its pentaacetate, m.p. 236~237° (reported m.p. 239~240°[2] and 240~242°[1]). In course of separation of bisflavones silica gel thin-layer chromatography[3] is useful to confirm its purity using toluene-ethyl formate-formic acid (5:4:1)[4] (Rf : I, 0.26; II, 0.37; III, 0.41). The total bisflavones in the leaves were examined by means of densitometer for thin-layer chromatography showing that the ratio I:II:III are 12:32:56 and that the over-all contents of bisflavones are 0.18% in the air-dried leaves.

---

*1 4-23, Bunkyo-cho, Nagasaki (三浦博史, 河野信助).
*2 Albany, California, U.S.A., A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U.S. Department of Agriculture.
*3 The preliminary report of this paper published in Chem. & Ind. (London), **1964**, 2020.

1) N. Kawano : Yakugaku Zasshi, **80**, 1647 (1960).
2) T. Kariyone, Y. Fukui : *Ibid.*, **80**, 746 (1960).
3) N. Kawano, H. Miura, H. Kikuchi : *Ibid.*, **84**, 469 (1964).
4) E. Stahl, P. J. Schorn : Z. physiol. Chem., Hoppe-Seyler's, **325**, 265 (1961).