C, 42.87; H, 1.80; N, 12.50. Found : C, 43.05; H, 2.08; N, 12.32.

2-(*p*-Aminophenyl)-7-bromopyrido[3,4-*d*]thiazole (XV)—To a solution of an excess $SnCl_2$ in conc. HCl solution was added (XIV) (0.5 g.) and the mixture was heated on a water bath for 2 hrs. The reaction mixture was evaporated to dryness and the residue was extracted with acetone. After evaporation of the extract, the residue was recrystallized from benzene to pale yellow crystals, m.p. 222~223°. Yield, 0.23 g. *Anal.* Calcd, for $C_{12}H_8N_3BrS$: C, 47.07; H, 2.63; N, 13.73. Found : C, 47.28; H, 2.89; N, 13.72.

Summary

1) 3-Nitro-4-chloro-5-bromopyridine (I) reacted with KSCN in glacial acetic acid to give 3-nitro-4-amino-5-bromopyridine, and 3-nitro-4-mercapto-5-bromopyridine was obtained by the reacion of (I) and KSH in methanol.

2) 7-Bromopyrido[3, 4-*d*]thiazole derivatives were synthesized from 3-nitro-4-mercapto-5-bromopyridine through reduction followed by cyclization.

(Received November 2, 1955)

U.D.C. 547.972.2 :

7. Yasuo Kishimoto : Phamaceutical Studies on Ferns. XI.* Flavonoids of Cyrtomium Species. (3). Constitution of Cyrtominetin and Cyrtopterinetin.

(*Shizuoka College of Pharmacy***)

It was shown in the previous paper of this series,[1] that two new kinds of flavanone, cyrtominetin (I) and cyrtopterinetin (II) had been isolated besides kaempferol and quercetin as flavonoid aglycones in *Cyrtomium falcatum* Presl, *C. Fortunei* J. Sm., and *C. Fortunei* J. Sm. var. *clivicola* Tagawa. Analysis agreed with the formula $C_{17}H_{16}O_6$ for (I) and $C_{17}H_{16}O_5$ for (II) and gave tetra- and triacetate, respectively. Each has optical activity and no methoxyl group.

Methylation of (I) with diazomethane gave trimethyl ether which shows a green coloration with ferric chloride, and it is presumed that one phenolic hydroxyl group is still left in the 5-position. On gentle alkali fusion of (I), 2,4-dimethylphloroglu-

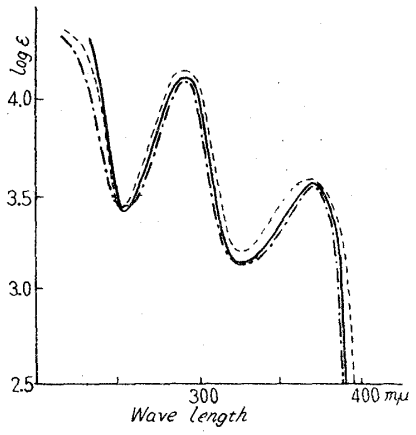


Fig. 1.

Ultraviolet Absorption Spectra
($^1/_{10000}$ *M.* EtOH solution)

.. .. Cyrtominetin trimethyl ether
—·—·— Cyrtopterinetin dimethyl ether
———— Matteucinol monomethyl ether

---

* This work constitutes a part of a series entitled "Pharmaceutcal Studies on Ferns" by Toshikazu Harada. Part X : J. Pharm. Soc. Japan, **76**, in press (1956).

** Oshika, Shizuoka (岸本安生).

1) Part IX. Y. Kishimoto : *Ibid.* **76**, in press (1956).

Table I. Degradation Products of Cyrtominetin and Cyrtopterinetin

Original compd.	Product	Rf Values A[a]	Rf Values B[b]	Color (in visible light) Untreated	Color (in visible light) D[c]	Color (in visible light) F[d]
Cyrtominetin	2,4-Dimethylphloroglucinol	0.51	0.81	P Y[e]	Bl G	D V
	Caffeic Acid	0.49	0.83	P Bl	V	C G
Cyrtopterinetin	2,4-Dimethylphloroglucinol	0.50	0.81	P Y	Bl G	D V
	p-Coumaric Acid	0.82	0.95	—	R	Y R Br
Synthetic Samples	2,4-Dimethylphloroglucinol	0.50	0.81	P Y	Bl G	D V
	Caffeic Acid	0.49	0.83	P Bl	V	C G
	p-Coumaric Acid	0.82	0.95	—	R	Y R Br

Filter paper : Toyo Roshi No. 50 (40×40 cm.). Ascending method.

a) *m*-Cresol : AcOH : H_2O=50 : 2 : 48.

b) BuOH : AcOH : H_2O=4 : 1 : 5.

c) After spraying 0.7% aq. $NaNO_2$ solution, sprayed with a mixture of 1 g. sulfanilic acid, 50 g. 5 *N* HCl, and 150 g. water, then alkalized with NH_3 gas.

d) Sprayed with 0.5% $FeCl_3$ aq. solution.

e) P : Pale Y : Yellow Bl : Blue G : Green D : Dark V : Violet
C : Deep R : Red Br : Brown — : No appreciable color

Table II.

	Rf Values AcOH :H_2O (3 : 2)	Rf Values *iso*-PrOH (22%)	Rf Values BuOH: AcOH:H_2O (4:1:5)	Rf Values PhOH (satd. with H_2O)	Color Untreated V[b]	Color Untreated UV[c]	Color Na_2CO_3[a] U	Color Na_2CO_3[a] UV
Cyrtopterinetin dimethyl ether	0.75	0.00	0.96	0.92	P Y	Y Br	P Y	D Br
Matteucinol monomethyl ether	0.75	0.00	0.96	0.92	P Y	Y Br	P Y	D Br

Filter paper : Toyo Roshi No. 50 (40×40 cm.). Ascending method.

a) Spraying of 3% Na_2CO_3 aq. solution.

b) Visible light

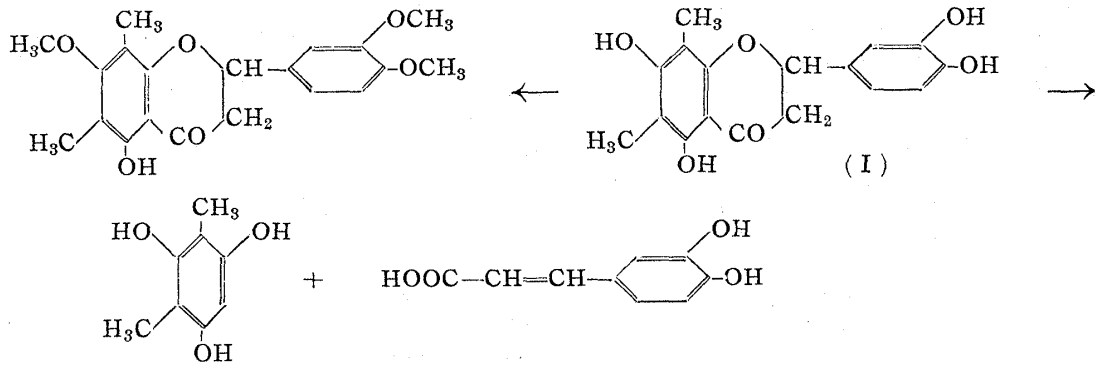
c) Ultraviolet light

cinol is obtained as phenolic fraction and caffeic acid as the acidic fraction, which were identified by mixed fusions, paper partition chromatography, and ultraviolet spectra in comparison with authentic samples.

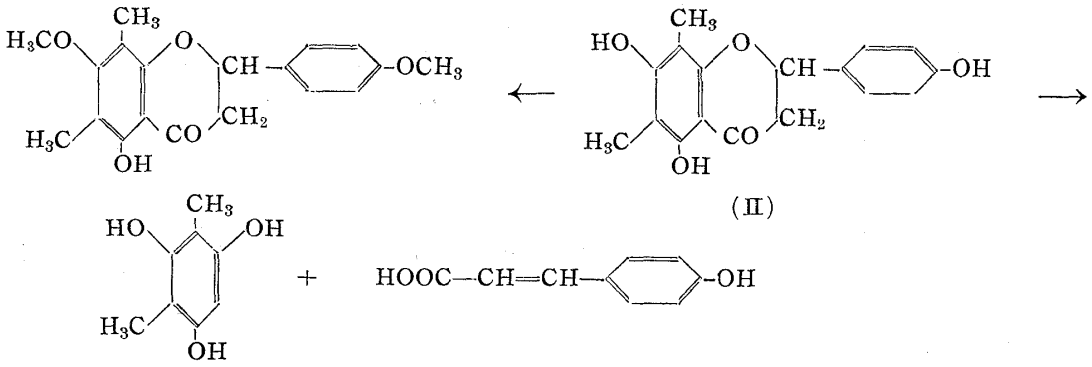
Methylation of (II) with diazomethane gave dimethyl ether which is identical with matteucinol monomethyl ether[2] in all properties and identified by mixed fusion, paper chromatography, and ultraviolet spectra. On alkali fusion of (II), 2,4-dimethylphloroglucinol and *p*-coumaric acid were obtained and identified by mixed fusions, paper chromatograpy, and ultraviolet spectras.

As a result of above reactions, (I) is considered to be 6,8-dimethyl-5,7,3′,4′-tetrahydroxyflavanone and (II) 6,8-dimethyl-5,7,4′-trihydroxyflavanone.

(I) was synthesized by reacting 2,4-dimethylphloroglucinol with diethoxycarbonyl



2) S. Hujise : J. Chem. Soc. Japan, **50**, 500(1929).



ether of caffeic acid chloride in nitrobenzene solution, catalyzed by powdered aluminum chloride, and (II) by reacting 2,4-dimethylphloroglucinol and ethoxycarbonyl ether of *p*-coumaric acid chloride under the same conditions, and proved they and their acetates are identical* with the racemic (I), (II), and their acetates, derived by Hujise's method[3] from (I) and (II).

The author takes this opportunity to extend his deep gratitude to Prof. T. Kariyone of Kyoto University for his constant guidances and encouragements during the course of this work. The author is indebted to Mr. Y. Saiki and Miss K. Yamamoto for their assistances in this work and to Miss H. Iwata for microanalysis.

Experimental

Methylation of Cyrtominetin—80 mg. of cyrtominetin was dissolved in 2 cc. of MeOH and 10 cc. of diazomethane in ether solution which was prepared from 1 g. nitrosomethylurea was added. After standing over night, the ether was distilled off and the residual methanolic solution was placed in an ice box. The separated crystals were recrystallized from methanol to almost colorless needles, m.p. 110~110.5°, $[\alpha]_D^{25}$: −7.2° (in acetone, c=0.84). Coloration by Mg+HCl: reddish violet in MeOH solution. *Anal.* Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.02; H, 6.39.

Alkali Fusion of Cyrtominetin—0.6 g. of cyrtominetin was added to the fused mixture of 1 g. KOH and 0.5 cc. water, then fused at 150~160° for 20 mins. in H_2 current. After cooling, 1 cc. of 50% KOH aq. solution was added and fused for 10 mins. under the same conditions. The solid mixture thus obtained was dissolved in little water and phenolic substance, that separated after bubbling of CO_2, was extracted with ether. Its mother liquor was acidified with 25% H_2SO_4 and the separated acidic substance was extracted with ether.

From the phenolic fraction, after drying with Na_2SO_4, ether was distilled off and the residue was recrystallized from water, then from AcOEt-xylene mixture to almost colorless needles, m.p. 161~162°. Its aqueous solution became red violet with $FeCl_3$. Mixed fusion with 2,4-dimethylphloroglucinol, which was synthesized by Hujise's method,[4] did not show any depression of melting point. *Anal.* Calcd. for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.38; H, 6.58.

From the acidic fraction, after drying, ether was distilled off and the residue was recrystallized from dil. EtOH to pale yellow needles, m.p. 211°(decomp.). Its aq. solution colored green with $FeCl_3$ and further to red on adding a little aq. Na_2CO_3. By its mixed fusion with caffeic acid, which was synthesized by Vorsatz's method,[5] no depression was recognized. *Anal.* Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 59.75; H, 4.69.

Racemization of Cyrtominetin—After refluxing a mixture of 50 mg. cyrtominetin, 1.5 cc. EtOH, and 1.5 cc. conc. H_2SO_4 on a water bath for 2 hrs., the solution was poured into ice water and the crystals obtained were recrystallized from dil. EtOH to almost colorless needles, m.p. 234~235°, $[\alpha]_D^{28}$: ±0° (in acetone). On admixture with the starting material, it melted at 232.5~233.5°, but other properties agreed with those of cyrtominetin. *Anal.* Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.34; H, 5.22.

* Rf values and ultraviolet spectra of racemic (I) and (II) and synthetic (I) and (II) have been omitted because they were almost the same as those of (I) and (II) (c.f. part IX).

3) S. Hujise, T. Kobota: J. Chem. Soc. Japan, **55**, 1027(1934).
4) S. Hujise, S. Maruyama: *Ibid.* **55**, 1018(1934).
5) Vorsatz: J. prakt. Chem., [2], **145**, 265(1936).

Acetylation of *rac*-Cyrtominetin—25 mg. of *rac*-cyrtominetin was suspended in 0.5 cc. Ac_2O and one drop of conc. H_2SO_4 was added. After standing for 15 mins. the mixture was poured into ice water and the crystals were recrystallized from MeOH to colorless needles, m.p. 173~174°. *Anal.* Calcd. for $C_{25}H_{24}O_{10}$ (Tetraacetyl-*rac*-cyrtominetin) : C, 61.98; H, 4.99. Found : C, 61.81; H, 5.01.

Synthesis of *rac*-Cyrtominetin—A mixture of 2.3 g. diethoxycarbonylcaffeic acid, synthesized by Shinoda's method,[6] and 6 g. $SOCl_2$ was warmed at 60° for 1.5 hrs. The reaction product, after distilling off excess $SOCl_2$ under reduced pressure, was dissolved in 60 cc. of abs. nitrobenzene and some dehyd. ether with 1 g. dehyd. 2,4-dimethylphloroglucinol, and 2.5 g. powdered $AlCl_3$ were added to the mixture and allowed to stand at room temperature. 1.5 g. each of additional powdered $AlCl_3$ was added after 2 and 4 days. After 6 days, ether was distilled off on warming at 60° for 1 hr. and nitrobenzene was removed by steam distillation. Dark brown, resinous solid thus obtained, after decanting from hot aq. mother liquor, was dissolved in 100 cc. of 5% KOH aq. solution saturated with H_2 by gentle warming on water bath in H_2 current. After cooling and filtering, the solution was acidified with HCl and extracted with ether. The ethereal solution was washed with 1% $NaHCO_3$, then with water. After distilling off ether, the residue was repeatedly extracted with boiling water, its aq. solution was cooled, and extracted with ether again, then dried. The crystalline residue, after distilling off the solvent, was recrystallized from dil. EtOH to almost colorless needles, m.p. 237~238, $[\alpha]_D^{21}$: ±0° (in acetone). Mixed fusion with *rac*-cyrtominetin showed no depression. *Anal.* Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.27; H, 5.20.

Acetylation of Synthetic *rac*-Cyrtominetin—After acetylation of 50 mg. of the material with 1 cc. Ac_2O and 1 drop conc. H_2SO_4 at room temperature, the product treated under the same conditions as in the acetylation of *rac*-cyrtominetin and the crystals were recrystallized from MeOH. Mixed fusion with *rac*-tetraacetylcyrtominetin showed no depression. *Anal.* Calcd. for $C_{25}H_{24}O_{10}$: C, 61.98; H, 4.99. Found : C, 62.15; H, 4.85.

Methyation of Cyrtopterinetin—50 mg. of cyrtopterinetin was dissolved in 1.5 cc. of MeOH and added with 10 cc. of CH_2N_2 in ether solution prepared from 1 g. nitrosomethylurea. After treating under the same conditions as in the case of cyrtominetin, the crystals were recrystallized from MeOH to almost colorless needles, m.p. 100.5~101°. $[\alpha]_D^{25}$: −7.5° (in acetone, c=0.81). Coloration with Mg+HCl : red violet in MeOH solution. Mixed fusion with matteucinol monomethyl ether showed no depression. *Anal.* Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14; Found: C, 69.27; H, 6.34.

Matteucinol Monomethyl Ether—Prepared from 30 mg. of matteucinol by Hujise's method.[2] Almost colorless needles, m.p. 100.5~101°. $[\alpha]_D^{21}$: −7.7° (in acetone, c=0.73). *Anal.* Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found : C, 69.16; H, 6.34.

Alkali Fusion of Cyrtopterinetin—0.6 g. of cyrtopterinetin was added to the fused mixture of 1 g. KOH and 0.5 cc. water, then fused at 150~160° for 30 mins. in H_2 current. After cooling, 1 cc. of 50% KOH was added and fused for 10 mins. at 160°±3°. The solid mixture so obtained was treated under the same conditions as in alkali fusion of cyrtominetin. As a phenolic fraction, almost colorless needles, m.p. 161~162°, were obtained by recrystallization from AcOEt-xylene mixture. No melting point depression was observed with synthetic 2,4-dimethylphloroglucinol. *Anal.* Calcd. for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found : C, 62.17; H, 6.56.

As the acidic fraction, pale yellow brown needles, m.p. 212~213° (decomp.), were obtained by recrystallization from dil. EtOH. Its aq. solution colored orange red with $FeCl_3$. Mixed fusion with *p*-coumaric acid which was synthesized by Furst's method[7] showed no depression. *Anal.* Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found : C, 65.63; H, 5.13.

Racemization of Cyrtopterinetin—After refluxing a mixture of 70 mg. cyrtopterinetin, 2 cc. EtOH, and 2 cc. conc. H_2SO_4, it was treated under the same conditions as for cyrtominetin. Recrystallized from HOAc to pale yellow needles, m.p. 211~212°. $[\alpha]_D^{23}$: ±0° (in acetone). On admixture with cyrtopterinetin, it melted at 209~210°, but other properties agreed with those of cyrtopterinetin. *Anal.* Calcd. for $C_{17}H_{16}O_5$ (after dehydration) : C, 67.99; H, 5.37. Found : C, 67.71; H, 5.36.

Acetylation of *rac*-Cyrtopterinetin—After acetylation of 40 mg. *rac*-cyrtopterinetin with 1 cc. Ac_2O and 1 drop conc. H_2SO_4 at room temperature, the product was worked up as before and the obtained crystals were recrystallized from MeOH to colorless needles, m.p. 186~186.5°. *Anal.* Calcd. for $C_{23}H_{22}O_8$ (Triacetyl-*rac*-cyrtopterinetin) : C, 64.78; H, 5.20. Found : C, 64.83; H, 5.42.

---

*) Extracted from *Pentarhiziudim japonicum* Hayata (*Matteucia orientalis* Trev.) by Hujise's method.[3] m.p. 174°. *Anal.* Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found : C, 68.52; H, 5.82.

6) J. Shinoda, S. Sato : J. Pharm. Soc. Japan, **49**, 71(1929).

7) A. Furst, *et al.* : Archiv Biochem. Biophys., **31**, 190(1951).

Synthesis of *rac*-Cyrtopterinetin—A mixture of 2 g. ethoxycarbonyl-*p*-coumaric acid, synthesized by Shinoda's method,[8] and 5 g. $SOCl_2$ was warmed at 60° for 2 hrs. The reaction product, after distilling off excess $SOCl_2$ under reduced pressure, was dissolved in 40 cc. of dehyd. nitrobenzene and some dehyd. ether with 1 g. dehyd. 2,4-dimethylphloroglucinol, and added to a mixture of 2.5 g. powdered $AlCl_3$ and stood at room temperature. Next day, 1.5 g. additional powdered $AlCl_3$ was added and after further standing over night, ether and nitrobenzene were removed as before. Dark brown resinous solid thus obtained, after decanting from aq. mother liquor, was dissolved in 100 cc. of 3% KOH by gentle warming on a water bath. After cooling and filtering, the solution was bubbled with CO_2 and the deposited precipitation was recrystallized from HOAc to pale yellow needles, m.p. 211~212°. $[\alpha]_D^{21}$: ±0°(in acetone). Mixed fusion with *rac*-cyrtopterinetin did not show any depression of the melting point. *Anal.* Calcd. for $C_{17}H_{16}O_5$(after dehydration): C, 67.99; H, 5.37. Found : C, 67.78; H, 5.54.

Acetylation of Synthetic *rac*-Cyrtopterinetin—Acetylation of 50 mg. material was made with 1 cc. Ac_2O and 1 drop conc. H_2SO_4 at room temperature and the product was worked up as before. Recrystallized from MeOH to colorless needles, m.p. 186~186.5°. The mixed melting point with triacetyl-*rac*-cyrtopterinetin showed no depression. *Anal.* Calcd. for $C_{23}H_{22}O_8$: C, 64.98; H, 5.20. Found : C, 64.74; H, 5.02.

Summary

Cyrtominetin and cyrtopterinetin, isolated from *Cyrtomium falcatum* Presl. and other Cyrtomium species as flavonoid aglycones, were proved to be 6,8-dimethyl-5,7,-3′,4′-tetrahydroxyflavanone and 6,8-dimethyl-5,7,4′-trihydroxyflavanone, respectively, by their methylation and alkali fusion. Their syntheses were achieved by Shinoda's method and the products proved to be identical with racemic cyrtominetin and cyrtopterinetin.

(Received November 10, 1955)

8) J. Shinoda, S. Sato : J. Pharm. Soc. Japan, **48**, 935(1928).