alone and on admixture with a sample of (+)-*threo*-1-phenyl-2-dimethylaminopropan-1-ol (XVII) picrate[7]; yield, 1.251 g. *Anal.* Calcd. for $C_{17}H_{30}O_8N_4$(XVII-Picrate): C, 49.99; H, 4.95; N, 13.72. Found: C, 50.19; H, 4.91; N, 13.83.

Further concentration of the EtOH mother liquor afforded only a small crop of (XVII)-picrate, m.p. 150~151°.

Summary

In the new route to N-benzoyl-*dl*-*threo*-phenylserinol which has been reported in the previous papers, the formation of *dl*-*erythro*-1-phenyl-1,2-dibromoprop-3-yl benzimino ether is intermediately involved. In the present series acetonitrile was used instead of benzonitrile in the analogous process and the whole process was placed under consideration. It was found that in the acidic solvolysis of *dl*-*threo*-1-phenyl-1-bromo-2-amino-3-acetoxypropane hydrochloride, the displacement of C_1-Br by OH^- was effected with overall retention, particularly accompanying with the fission of O-acetyl group. In contrast with the same treatment of the O-benzoyl analog which as has been reported, resulted in inversion and retention without fission of the O-benzoyl group, the effect of the O-acetyl fission upon stereochemical results was examined and the mechanism was discussed.

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33. **Shin Matsuura**: The Structure of Cryptostrobin and Stropopinin, the Flavanones from the Heartwood of *Pinus strobus*.

(*Gifu College of Pharmacy**)

Erdtman[1] once isolated a flavanone, stropopinin (m.p. 225~227°), from the heartwood of *Pinus strobus* and proposed for its structure, C-methyl-5,7-dihydroxyflavanone. Lindstedt[2] also isolated stropopinin from the heartwood of *P. monticola* DOUGL. Later, Alvarez-Nóvoa and others[3] isolated another flavanone, cryptostrobin, m.p. 202~203°, from *P. strobus* and assumed it to be an isomer of stropopinin.

Lindstedt and others[4] obtained a mixture of stropopinin and cryptostrobin in a low yield by the condensation of 2-methylphloroglucinol and cinnamoyl chloride by Fujise's method,[5] and isolated *dl*-stropopinin, m.p. 231~233°, alone from this mixture. Methylation of this racemic compound with diazomethane afforded a monomethyl ether, m.p. 96~97°, and its further methylation with dimethyl sulfate and potassium carbonate in acetone yielded orange red 2′-hydroxy-3′-methyl-4′,6′-dimethoxychalcone (X). A mixture of chalcone and flavanone had been obtained by methylation of the monomethyl ether from natural cryptostrobin. Boiling of (X) with ethanolic sulfuric acid had afforded 5,7-dimethoxy-8-methylflavanone (XI). From these facts, they reported that stropopinin is probably 5,7-dihydroxy-8-methylflavanone (III) and its isomer, cryptostrobin, will then be the 6-methyl compound.

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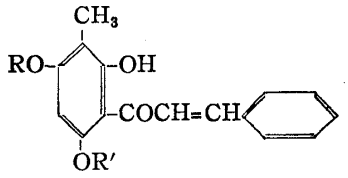
* 3 Kokonoe-cho, Gifu (松浦 信).

1) H. Erdtman: Svensk Kem. Tid., **56**, 2(1944).
2) Lindstedt: Acta Chem. Scand., **3**, 1147(1949).
3) J.C. Alvarez-Nóvoa, H. Erdtman, G. Lindstedt: *Ibid.*, **4**, 390(1950).
4) G. Lindstedt, A. Misiorny: *Ibid.*, **5**, 1(1951).
5) S. Fujise, H. Tatsuta: Ber., **74**, 275(1941).

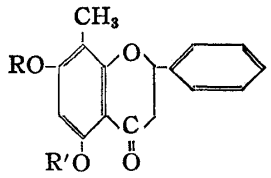
The present writer synthesized 5,7-dihydroxy-8-methylflavanone (III) by the method used for the synthesis of 4′-methoxy-5,7-dihydroxy-8-methylflavanone[6] and found it to be identical with cryptostrobin. It was thereby assumed that strobopinin would be 5,7-dihydroxy-6-methylflavanone.

2′-Hydroxy-3′-methyl-4′,6′-dibenzyloxychalcone (I), obtained by the condensation of 2-hydroxy-3-methyl-4,6-dibenzyloxyacetophenone[6] and benzaldehyde, was heated with ethanolic phosphoric acid[7,8] for a long time, and 5,7-dibenzyloxy-8-methylflavanone (II) thereby obtained was catalytically reduced, yielding (III), m.p. 202~203°, undepressed on admixture with cryptostrobin.* Paper chromatography of these two substances also gave identical Rf values.[9] The action of hot nitric acid and cold sulfuric acid on (III) and its coloration to ferric chloride and bis-diazotized benzidine were all identical with those described by Alvarez-Nóvoa, *et al.*[3] Reaction of magnesium and hydrochloric acid on (III) gave yellow coloration when the sample was in a very small amount (Lindstedt and others[4] reported yellow coloration) but the color was orange when a large amount of the sample was used.

Methylation of (III) here obtained with methyl iodide and potassium carbonate afforded its 7-methyl ether (IV) and its 5-acetate formed 5-hydroxy-7-methoxy-8-methylflavone (VI) by bromination-dehydrobromination. (VI) was also obtained by demethylation of 5,7-dimethoxy-8-methylflavone (IX) which was prepared first by the condensation of 2-hydroxy-3-methyl-4,6-dimethoxyacetophenone and benzoyl chloride in pyridine to 2-benzoyloxy-3-methyl-4,6-dimethoxyacetophenone (VII), whose benzoyl group was submitted to rearrangement with sodium amide to the diketone (VIII) and finally cyclized to (IX) by conc. sulfuric acid in hot glacial acetic acid.

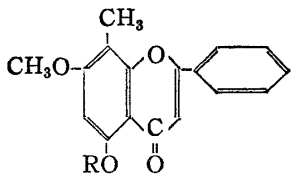


(I) R, R′=-$CH_2C_6H_5$
(X) R, R′=CH_3



(II) R, R′=-$CH_2C_6H_5$
(III) R, R′=H
(IV) R=CH_3; R′=H

(V) R=CH_3; R′=CH_3CO
(XI) R, R′=CH_3



(VI) R=H
(IX) R=CH_3

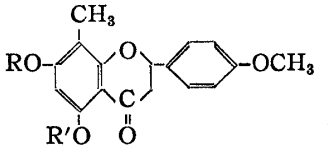
It is concluded from the foregoing results that the considerations made by Lindstedt and others had been misled on the following points : (1) That the chief product obtained by the Friedel-Crafts reaction of 2-methylphloroglucinol and cinnamoyl chloride is the 8-methylflavanone compound[4] (In this case, the use of *p*-methoxycinnamoyl chloride chiefly gives the 6-methylflavanone compound[6]). (2) That the melting points of 5,7-dihydroxy compound and its mono- and dimethyl ethers in C-methyl-5,7-dihydroxyflavanones were higher in the 8-methyl compounds than in the 6-methyl compounds[4,10] (In C-methyl-4′-methoxy-5,7-dihydroxyflavanones, the 5-methyl and 5,7-dimethyl ethers show higher melting points in the 8-methyl compound than in the 6-methyl compound but the melting points of 5,7-dihydroxy compound and its 7-methyl ether are higher in the 6-methyl compound than in the 8-methyl compound[6,11,12] (cf. Table I)). (3) That the me-

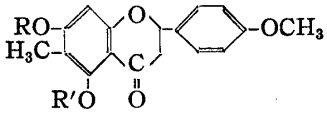
* The natural cryptostrobin would easily be racemised by heating, showing no melting point depression on admixture with the synthetic *dl*-cryptostrobin.

6) S. Matsuura : J. Pharm. Soc. Japan, **77**, 302(1957).
7) H. F. Dean, M. Nierenstein : J. Am. Chem. Soc., **47**, 1676(1925).
8) H. S. Mahal, H. S. Rai, K. Venkataraman : J. Chem. Soc., **1935**, 866.
9) G. Lindstedt : Acta Chem. Scand., **4**, 448(1950).
10) G. Lindstedt, A. Misiorny : *Ibid.*, **6**, 1212(1952).
11) K. Nakazawa, S. Matsuura : J. Pharm. Soc. Japan, **75**, 467(1955).
12) S. Matsuura : *Ibid.*, **77**, 296(1957).

thylation of their 7-methyl ethers once formed the dimethyl ether of flavanone, which then underwent cleavage of the bridged oxygen to afford the chalcones, (X) from 8-methylflavanone compound and 2′-hydroxy-4′,6′-dimethoxy-5′-methylchalcone from the 6-methylflavanone compound[4] (In fact, (X) is obtained both from the 8-methyl- and 6-methylflavanone compounds[6,12]).

Table I. Melting Points of 8- and 6-Methyl-4′-methoxy-5,7-dihydroxyflavanones and their Derivatives





R, R′=H	180°	217°
R=CH_3; R′=H	136°	148°
R=H; R′=CH_3	208°	196°
R, R′=CH_3	132°	119°

The writer is deeply grateful for the kind encouragements and valuable advices of Prof. Shoji Shibata of the University of Tokyo, Dr. Etsuo Miyamichi, Dean of this College, and Prof. Koichi Nakazawa of this College. He is greatly indebted to Prof. Erdtman and Dr. Lindstedt for kind gift of samples for admixture and for reprints of their work, and to Misses H. Iwata and Y. Mano of the Central Analysis Room of the University of Kyoto for microanalytical data reported in the present work.

Experimental

2′-Hydroxy-3′-methyl-4′,6′-dibenzyloxychalcone (I)—Condensation was carried out with 3.6 g. (0.01 mole) of 2-hydroxy-3-methyl-4,6-dibenzyloxyacetophenone,[6] 2 g. of benzaldehyde, 20 cc. of EtOH, 4 g. of KOH, and 6 cc. of water, and the reaction mixture was acidified with AcOH. Orange needles (from glacial AcOH), m.p. 153.5°. Yield, 3.85 g.(76.7%). *Anal.* Calcd. for $C_{30}H_{26}O_4$: C, 79.98; H, 5.82. Found: C, 80.15; H, 6.12.

5,7-Dibenzyloxy-8-methylflavanone (II)—A mixture of 3.6 g.(0.08 mole) of (I), 500 cc. of EtOH, and 10 g. of 85% H_3PO_4[7,8] was refluxed for 70 hrs. and concentrated to about 50 cc. The starting material that precipitated out on cooling was removed by filtration, the filtrate was diluted with water, and the precipitate was taken up in ether. The ether residue was recrystallized from EtOH to 0.4 g.(11.1%) of colorless needles, m.p. 128°, negative to $FeCl_3$ test and giving pink coloration with Mg+HCl. *Anal.* Calcd. for $C_{30}H_{26}O_4$: C, 79.98; H, 5.82. Found: C, 79.72; H, 5.97.

5,7-Dihydroxy-8-methylflavanone (III)—A solution of 0.23 g.(0.0005 mole) of (II) in 20 cc. of EtOH and 10 cc. of glacial AcOH was submitted to reduction with Pd-C catalyst. Colorless needles (from dil. AcOH), m.p. 202~203°. Yield, 0.1 g.(77.0%). It gave dark purple coloration to $FeCl_3$, reddish brown to hot HNO_3, yellow to cold conc. H_2SO_4, orange yellow to bis-diazotized benzidine, and orange to Mg+HCl. Admixture with natural cryptostrobin, m.p. 202~203°, kindly furnished by Prof. Erdtman, showed no depression of m.p.

Paper chromatography[9] of this (III) and natural cryptostrobin was carried out in 0.01% EtOH solution with Toyo Roshi No. 50 (3.5×40 cm.), spotted with an interval of 1.8 cm., and developed with the standard solvent (water-saturated mixture of 50 : 50 : 1 of benzene, ligroine (b.p. 85~105°), and MeOH). When immersed in a solution of bis-diazotized benzidine for 3 mins., both spots colored orange yellow and their Rf values were both 0.26 (at room temperature of 9~10°), although the spots were oblong in shape and the upper end was clear but the lower end indistinct, that the distance from the original starting line to top of the upper end of the spot was measured. (Lindstedt[9] reported Rf 0.48 at room temperature of 20°; paper, Munktell OB). *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.84; H, 5.47.

5-Hydroxy-7-methoxy-8-methylflavanone (IV)—Methylation of 0.135 g.(0.0005 mole) of (III) with CH_3I-K_2CO_3 gave 0.14 g.(quantitative) of (IV) as colorless needles (from EtOH), m.p. 143°(Lindstedt[4] reported m.p. 134~136°). Dark coloration to $FeCl_3$ and yellow to Mg+HCl. *Anal.* Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 72.09; H, 5.86.

5-Acetoxy-7-methoxy-8-methylflavanone (V)—Acetylation of 0.142 g.(0.0005 mole) of (IV) with Ac_2O-AcONa afforded 0.16 g.(quantitative) of colorless plates (from dil. EtOH), m.p. 152°, negative to $FeCl_3$ test. *Anal.* Calcd. for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 69.63; H, 5.66.

2-Benzoyloxy-3-methyl-4,6-dimethoxyacetophenone (VII)—To a solution of 1.05 g.(0.005 mole) of 2-hydroxy-3-methyl-4,6-dimethoxyacetophenone[11] in 5 cc. of hot dehyd. pyridine, 2.1 g. of BzCl was

added and the mixture was heated in an oil bath of 110° for 2 hrs. To this hot solution, 5 cc. of EtOH and 5 cc. of conc. HCl were added, cooled somewhat, 5 cc. of water added, and the mixture was allowed to stand. Colorless plates (from dil. EtOH), m.p. 131°. Yield, 1.4 g.(89.2%). Negative to $FeCl_3$ test. *Anal.* Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.56; H, 6.03.

ω-Benzoyl-2-hydroxy-3-methyl-4,6-dimethoxyacetophenone (VIII)—A mixture of 1.6 g. (0.005 mole) of (VII) and $NaNH_2$ in dehyd. xylene was heated in an oil bath of 110° for 30 mins. to effect rearrangement and the sodium salt of (VIII) that precipitated out was triturated with 5% AcOH, affording 1.2 g.(75.0%) of pale yellow needles (from dil. EtOH), m.p. 127°. $FeCl_3$ test yellowish green. *Anal.* Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.93; H, 6.07.

5,7-Dimethoxy-8-methylflavone (IX)—To a hot solution of 1.6 g. (0.005 mole) of (VIII) in 15 cc. of glacial AcOH, 2 cc. of hot glacial AcOH solution containing 1 cc. of conc. H_2SO_4 was added, the mixture was allowed to stand at room temperature for 5 mins., and diluted with water. Colorless needles (from MeOH), m.p. 231°. Yield, 1.38 g.(93.2%). $FeCl_3$ test negative and wine red coloration to Mg+HCl. *Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.66; H, 5.30.

5-Hydroxy-7-methoxy-8-methylflavone (VI)—a) By Demethylation of (IX): A mixture of 0.6 g. (0.002 mole) of (IX) and 0.55 g.(0.004 mole) of anhyd. $AlCl_3$ in 20 cc. of nitrobenzene was heated in an oil bath of 110° for 1 hr., decomposed with dil. HCl, and submitted to steam distillation. The distillation residue was recrystallized from EtOH to 0.42 g.(74.3%) of pale yellow needles, m.p. 230~230.5°. $FeCl_3$ test dark green. Mg+HCl test brown. *Anal.* Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72,56; H, 5.28.

b) By Bromination-Dehydrobromination of (V): A solution of 0.163 g.(0.0005 mole) of (V) dissolved in 5 cc. of $CHCl_3$ was brominated with $CHCl_3$ solution of 80 mg.(0.0005 mole) of Br_2, $CHCl_3$ was distilled off, and the residue was dissolved in 5 cc. of EtOH. To this, cold solution of 60 mg.(0.001 mole) of KOH was added and the mixture was allowed to stand at room temperature for 3 hrs., by which (VI) precipitated out. The reaction mixture was acidified with AcOH and the crystals that separated out were collected. Pale yellow needles (from EtOH), m.p. 229~230°. Yield, 60 mg.(42.9%). No depression of m.p. occurred on admixture with the product, m.p. 230~230.5°, obtained by the a) method.

Summary

Of the flavanones contained in the heartwood of *Pinus strobus*, cryptostrobin (m.p. 202~203°) and strobopinin (m.p. 225~227°), the former was synthesized and its structure was determined as 5,7-dihydroxy-8-methylflavanone. It was thereby clarified that strobopinin, its isomer, would be its 6-methyl compound. In this synthesis, 2'-hydroxy-3'-methyl-4',6'-dibenzyloxychalcone was prepared from 2-hydroxy-3-methyl-4,6-dibenzyloxyacetophenone, boiled with ethanolic phosphoric acid for a long time, and 5,7-dibenzyloxy-8-methylflavanone thereby obtained was reduced with palladium-carbon catalyst to 5,7-dihydroxy-8-methylflavanone, m.p. 202~203°, which was proved to be identical with cryptostrobin by a mixed fusion and by a comparison of their Rf-values. The acetate of 7-methyl ether of this flavanone afforded 5-hydroxy-7-methoxy-8-methylflavone by bromination-dehydrobromination. On the other hand, this flavone was found to be identical with partially demethylated compound of 5,7-dimethoxy-8-methylflavone prepared from 2-hydroxy-3-methyl-4,6-dimethoxyacetophenone by the Baker-Venkataramann method.

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