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14. **Naokata Morita** : Studies on the Flavonoid of Sesame Leaves. II.[1] Synthesis of Demethylpedalitin.

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The assumed structure of pedaliin, the flavonoid in the leaves of sesame, was described in the preceding paper[1] and in the present series of work, the demethylated compound of pedalitin, 5,6,7,3′,4′-pentahydroxyflavone, was prepared and compared with the natural product.

In 1930, Wessely, Moser, and others[2] synthesized scutellarein (5,6,7,4′-tetrahydroxyflavone) by the route shown in Chart 1.

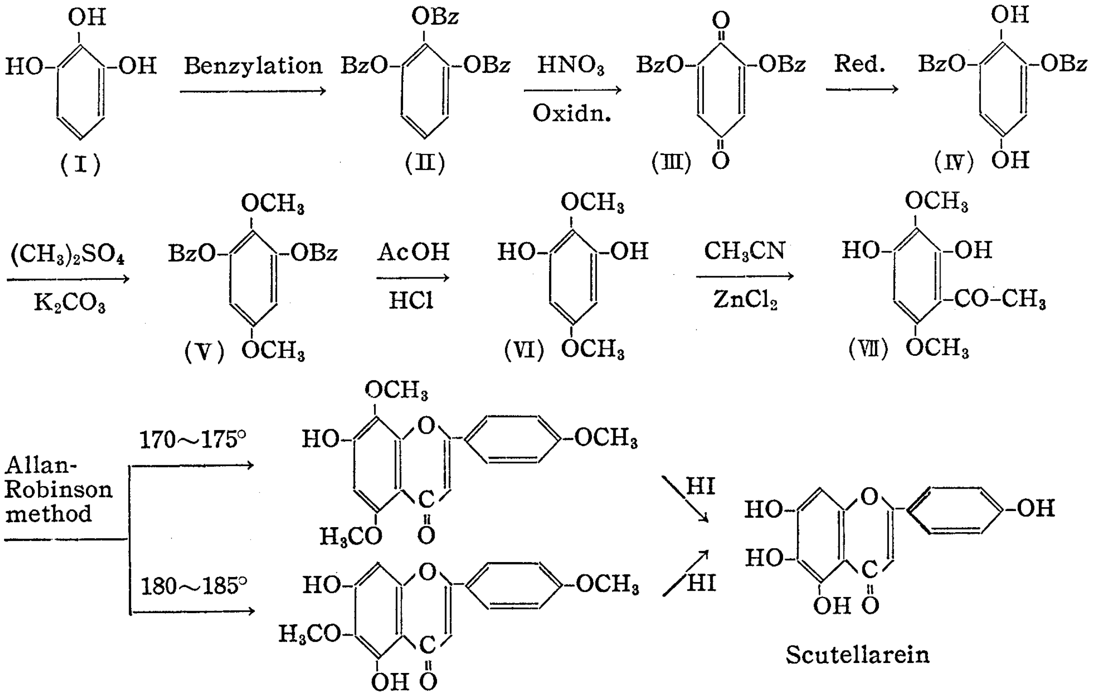

Chart 1.

In accordance with this procedure, the benzyl ether of pyrogallol was oxidized with nitric acid to the 1,4-quinone compound (III), reduced with hydrosulfite, methylated with dimethyl sulfate, and debenzylated by catalytic reduction over palladium carbon to obtain 2,5-dimethoxyresorcinol (VI). Its Hoesch reaction afforded 2,4-dihydroxy-3,6-dimethoxyacetophenone (VII).

In the foregoing reaction, 2,6-dibenzyloxy-1,4-hydroquinone (IV) was obtained in quantitative yield by reduction with saturated hydrosulfite solution, its methylation was effected with dimethyl sulfate and sodium hydroxide in methanol, and debenzylation by catalytic reduction over palladium-carbon in ethanol gave 2,5-dimethoxyresorcinol (VI) in quantitative yield, although the yield was low when carried out in glacial acetic acid with hydrochloric acid, due to polymerization of the phenol. For the Hoesch reaction,

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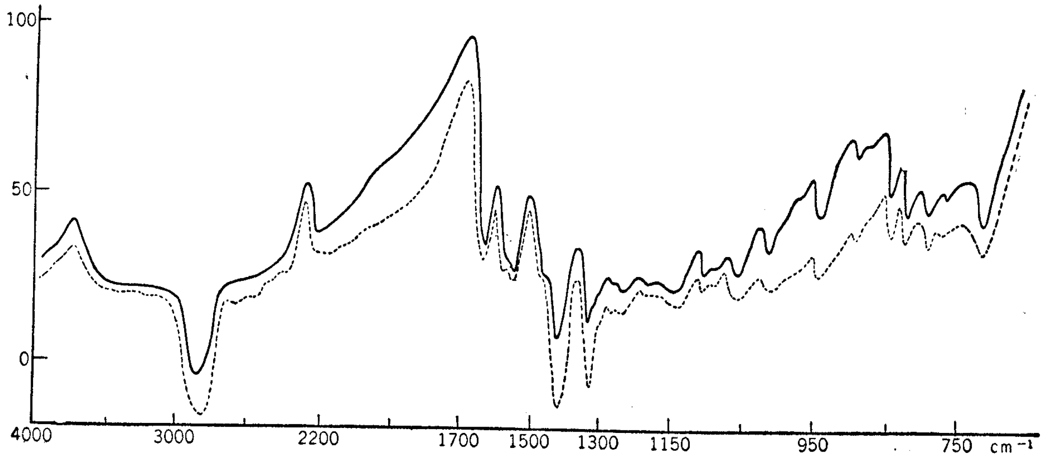
[1] Part I : This Bulletin, 8, 59(1960).

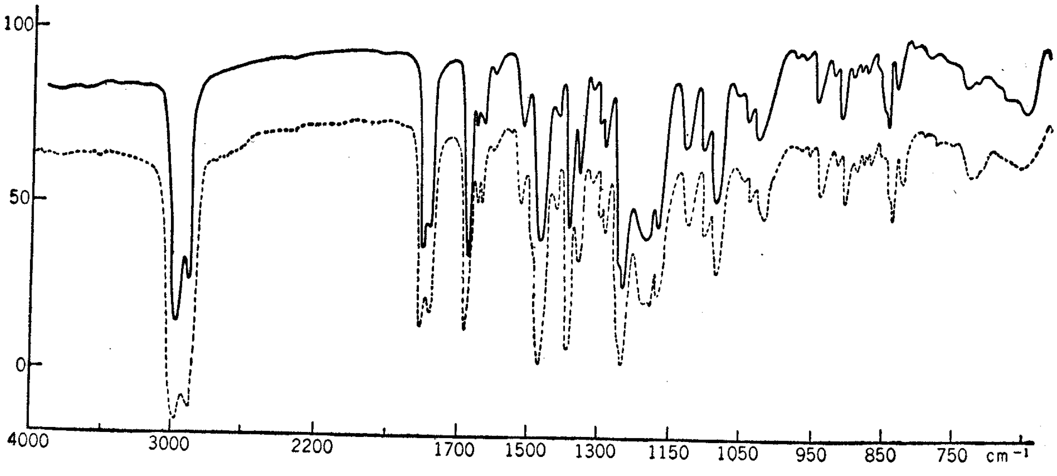
[2] F. Wessely, G.H. Moser : Monatsh., **56**, 97(1930); F. Wessely, F. Kallab : *Ibid.*, **60**, 26(1931). cf. W. Baker, R. Nodzu, R. Robinson : J. Chem. Soc., **1929**, 74; A. Geisman, G. Halsall : J. Am. Chem. Soc., **73**, 1280(1951).

(Ⅵ) was dissolved in dehyd. ether, acetonitrile and zinc chloride were added, and the mixture was saturated with dry hydrogen chloride gas. This mixture was allowed to stand in a tightly stoppered vessel in an ice chamber and the large amount of ketimine that precipitated out was decomposed with water, affording colorless needles of m.p. 127°, in 96.46% yield. This substance is 2,4-dihydroxy-3,6-dimethoxyacetophenone (Ⅶ) which was fused with veratric anhydride and potassium veratrate at 170~175° and 180~185°, in accordance with the Allan-Robinson method, and gave 5,8,3′,4′-tetramethoxy-7-hydroxyflavone. The product recrystallized from methanol into pale yellowish white needles, m.p. 223°; giving almost no coloration to ferric chloride. Its analytical values corresponded to the molecular formula of $C_{15}H_6O_3(OCH_3)_4$. Complete methylation with dimethyl sulfate in dehyd. acetone afforded colorless needles, m.p. 193°; negative to the ferric chloride reaction, and corresponding to the molecular formula of $C_{15}H_5O_2(OCH_3)_5$.

Demethylation of this product (m.p. 223°) with hydriodic acid affords a substance corresponding to the molecular formula of $C_{15}H_{10}O_7 \cdot H_2O$, forming yellow microneedles of m.p. above 325°; coloring dark brown to ferric chloride. Complete methylation of this product with dimethyl sulfate gives a compound of the formula $C_{15}H_5O_2(OCH_3)_5$, as colorless prisms, m.p. 173~174°, negative to ferric chloride reaction. This substance is entirely different from the completely methylated product of m.p. 193° mentioned above.



—— Demethylpedalitin, m.p. >325°
------ 5,6,7,3′,4′-Pentahydroxyflavone, m.p. >325°



—— Demethylpedalitin acetate, m.p. 245~246°
------ 5,6,7,3′,4′-Pentaacetoxyflavone, m.p. 245°

Fig. 1.

It is certain, therefore, that demethylation with hydriodic acid had effected ring fission, followed by recyclization, and consequently, this product would be 5,6,7,3′,4′-pentahydroxyflavone. Acetylation of this pentahydroxyflavone by the usual process afforded a compound corresponding to the formula $C_{15}H_5O_7(CH_3CO)_5$ as colorless needles, m.p. 246°, undepressed on admixture with demethylpedalitin acetate, m.p. 245~246°. No depression in the melting point was observed also in the admixture of the completely methylated product of m.p. 173~174° and pedalitin tetramethyl ether, m.p. 172~173°.

Comparison of the synthesized 5,6,7,3′,4′-pentahydroxyflavone, m.p. above 325°, and demethylpedalitin, m.p. over 325°, and their acetates by infrared spectra are shown in Fig. 1.

In 1949, Seshadri and Sreerama[3] prepared 5,6,7,3′,4′-pentahydroxyflavone during the course of synthesis of nobiletin (5,6,7,8,3′,4′-hexamethoxyflavone) by the route shown in Chart 2.

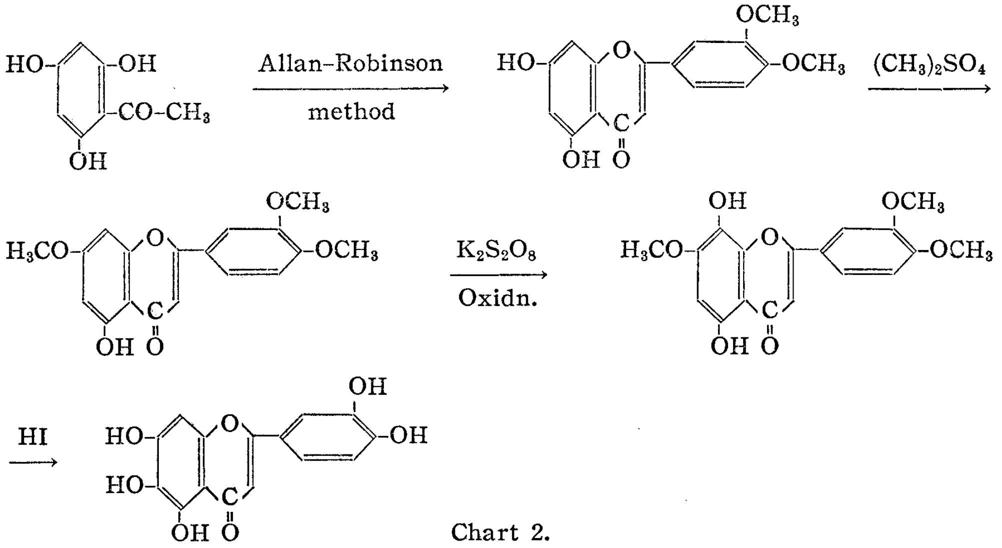


Chart 2.

Comparison of the product obtained by Seshadri by the procedure given above and that obtained in the present series of experiments, including their derivatives, is given in Table I.

Table I.

	5,6,7,3′,4′-Pentahydroxyflavone m.p. (°C)	Acetate m.p. (°C)	Methyl ether m.p. (°C)
Seshadri, *et al.*	315	225~226	142~143
Morita	>325	246	173~174

As will be seen from this Table, there is a fair amount of difference between the two values. The procedure of Seshadri and others was therefore reëxamined and the 5,6,7,3′,4′-pentahydroxyflavone thereby obtained came as yellow microneedles, m.p. above 325°, coloring dark brown to ferric chloride. This flavone showed a spot on the paper chromatogram at the same Rf value as that of the product obtained in the present series of experiments, starting with pyrogallol. The acetate obtained from this product came as colorless needles, m.p. 243~244°, undepressed on admixture with the acetate of m.p. 246°, obtained in the present synthesis described above. These facts have proved that the two kinds of pentahydroxyflavone are identical substances and the melting points given by Seshadri should be corrected.

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3) V. V. Sreerama, T. R. Seshadri : Proc. Ind. Acad. Sci., **27A**, 217(1948)(C. A., **43**, 4263(1949)); K. Visweswara Rao, T. R. Seshadri, N. Viswanadham : Proc. Ind. Acad. Sci., **29A**, 72(1949).

Experimental

1,2,3-Tribenzyloxybenzene (I)—A mixture of 50 g. (0.396 mole) of pyrogallol, 240 g. of anhyd. K_2CO_3, and 300 cc. of dehyd. Me_2CO was stirred on a water bath at 70~75° in N_2 stream, 210 g. of benzyl chloride was added slowly, and the mixture was refluxed for 22~23 hr. After cool, Me_2CO was removed by decantation, the residue was washed thoroughly with Me_2CO, and the combined Me_2CO solution was evaporated, leaving a reddish brown, syrupy substance. Water was added to this residue and extracted several times with Et_2O. The Et_2O extract was washed with 10% NaOH and water, Et_2O was evaporated, and the residue was steam-distilled to remove excess of benzyl chloride. The residue was again extracted with Et_2O and the reddish brown syrupy residue obtained on evaporation of Et_2O was recrystallized from a large quantity of MeOH to colorless, long needles, m.p. 70°. Yield, 56 g. (36.16%).

2,6-Dibenzyloxy-1,4-benzoquinone (II)—A solution of 80 g. of (I) dissolved in 800 cc. of glacial AcOH was stirred on a water bath at 40° and 40 cc. of 30% HNO_3 was added dropwise, when 5-nitro-1,2,3-benzyloxybenzene separated out as colorless needles, m.p. 138~139°. The mixture was allowed to stand for 3 hr. at room temperature, the crystals were collected by filtration, and the filtrate was again warmed on a water bath of 40°. Dropwise addition of 30% HNO_3 to the warmed solution under stirring gradually precipitated yellow needle crystals. After leaving this mixture to stand over night, the crystals were collected by filtration, washed with water, and recrystallized from Me_2CO to yellow, long needles, m.p. 200~201°. Yield, 28 g. (42.42%).

2,6-Dibenzyloxy-1,4-hydroquinone (III)—Saturated aqueous solution of $Na_2S_2O_4$ was added dropwise into 10 g. of (II) suspended in water and stirred at 70~80°. The reduction was effected instantaneously and 10 g. of the product was obtained as colorless small plates, m.p. 113~114°.

2,6-Dibenzyloxy-1,4-dimethoxybenzene (IV)—A solution of 12 g. of (III) dissolved in 120 cc. of MeOH was stirred while adding 16 g. of Me_2SO_4, the reaction mixture was warmed on a water bath to around 60°, and 19 g. of NaOH solution (60 g. of NaOH in 150 cc. of H_2O) was added dropwise during 2 hr., by which prismatic crystals began to precipitate out on the wall of the vessel. After allowing the mixture to stand over night, the crystals were collected by filtration and recrystallized from MeOH to colorless needles, m.p. 80~81°. Yield, 12 g.

2,5-Dimethoxyresorcinol (V)—A solution of 4 g. of (IV) dissolved in 150 cc. of EtOH and added with 5% Pd-C was submitted to catalytic reduction. The residue obtained on evaporation of EtOH was recrystallized from benzene to colorless columnar crystals, m.p. 60~61°; easily soluble in cold water and giving violet coloration to the pine-splinter reaction. Yield, 1.5 g.

2,4-Dihydroxy-3,6-dimethoxyacetophenone (VI)—To a solution of 2.5 g. of (V), and 1.8 g. of dehyd. MeCN dissolved in 40 cc. of dehyd. Et_2O, 1 g. of fused $ZnCl_2$ powder was added, and dry HCl gas was passed thorugh this mixture for 1 hr. at a fast rate. After 40 min., the mixture became emulsified and colorless crystals began to separate out on the wall of the vessel after 1 hr. HCl gas was bubbled for further 30~40 min., the vessel was tightly closed with a rubber stopper, and allowed to stand over night in an ice chamber. The ketimide that precipitated out on the bottom of the vessel was collected, washed twice with Et_2O, and the solvent was completely evaporated under a reduced pressure. The ketimine was dissolved completely by addition of water in small portions, while cooling in ice water, and 200 cc. of water was added. The mixture was maintained on a boiling water bath to decompose the ketimide and the solution was filtered while warm. The colorless needle crystals that precipitated out from the filtrate were collected and recrystallized from 5~10% EtOH to colorless needles, m.p. 128°. *Anal.* Calcd. for $C_{10}H_{12}O_5$ (VI): C, 56.58; H, 5.71; $3CH_3O$, 29.23. Found: C, 56.47; H, 5.81; CH_3O, 29.27.

5,8,3′,4′-Tetramethoxy-7-hydroxyflavone (VII)—i) A mixture of 1.3 g. of (VI), 8.3 g. of veratric anhydride, and 4 g. of potassium veratrate was triturated thoroughly in a mortar and the mixture was fused for 1.7 hr. in an oil bath at 170~175°. After cool, the solidified mass was pulverized in a mortar, extracted with 120 cc. of EtOH, and the EtOH solution was boiled on a water bath for 30 min. with KOH solution (4 g. of KOH in 15 cc. of H_2O) to effect saponification. EtOH was distilled off under a reduced pressure, 50 cc. of water was added to the residue, and CO_2 was bubbled through this solution for 2 hr. The mixture was allowed to stand over night, the yellow crystals that precipitated out were collected, and recrystallized from MeOH to pale yellowish white needles, m.p. 223~224°. Yield, 110 mg. This substance showed almost no coloration to $FeCl_3$. Paper partition chromatography of this substance gave a spot at Rf 0.68 ($BuOH:AcOH:H_2O=4:1:5$) or Rf 0.77 (60% AcOH), which appeared yellowish brown under ultraviolet rays. *Anal.* Calcd. for $C_{19}H_{18}O_7$ (VII): C, 63.68; H, 5.02; $4CH_3O$, 34.63. Found: C, 63.62; H, 5.02; CH_3O, 33.77.

a) Demethylation of (VII): A mixture of 80 mg. of (VII), 12 cc. of HI (b.p. 125°), and 0.1 g. of phenol was boiled in an oil bath at 160~170° for 6 hr. to effect demethylation, cooled, and poured into water. The yellow, gel-like precipitate was collected by filtration, washed with $NaHSO_3$ solution and water, dried, and recrystallized from MeOH, forming yellow microneedles, m.p. above 325°; coloring dark brown to $FeCl_3$. *Anal.* Calcd. for $C_{15}H_{10}O_7 \cdot H_2O$: C, 56.25; H, 3.75; $1H_2O$, 5.63. Found : C, 56.65; H, 3.68; H_2O, 5.16.

Admixture of this substance with demethylpedalitin, m.p. above 325°, showed no depression in m.p. Paper partition chromatography of the two substances gave identical spots at Rf 0.47 (BuOH:AcOH:H_2O=4:1:5) and at Rf 0.315 (60% AcOH), which appeared brown under ultraviolet rays.

Acetylation of this product by the usual process and recrystallization of the product from MeOH afforded colorless needles, m.p. 246°, undepressed on admixture with demethylpedalitin acetate, m.p. 245~246°. *Anal.* Calcd. for $C_{25}H_{20}O_{12}$: C, 58.60; H, 3.93. Found : C, 58.62; H, 3.80.

b) Complete methylation of (VII) : A mixture of 80 mg. of (VII), m.p. 223~224°, 0.5 g. of Me_2SO_4, 1 g. of K_2CO_3, and 25 cc. of Me_2CO was refluxed in an oil bath for 20 hr. K_2CO_3 was removed by filtration, Me_2CO was evaporated from the filtrate, and the residue was dissolved in water. This solution was shaken with Et_2O and extracted with $CHCl_3$, and the latter fraction was recrystallized from MeOH, affording colorless needles of m.p. 192~193°, negative to the $FeCl_3$ test. *Anal.* Calcd. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.37; $5CH_3O$, 41.66. Found : C, 64.37; H, 5.33; CH_3O, 40.96.

c) Complete methylation of the demethylated product : A mixture of 100 mg. of the demethylated product of m.p. above 325°, 0.7 g. of Me_2SO_4, 1.2 g. of K_2SO_3, and 35 cc. of Me_2CO was refluxed in an oil bath for 22 hr. Me_2CO was evaporated and the residue was recrystallized from MeOH, forming colorless prisms, m.p. 173~174°, negative to $FeCl_3$ reaction, and showing no depression in m.p. on admixture with pedalitin tetramethyl ether, m.p. 172~173°. *Anal.* Calcd. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.37; $5CH_3O$, 41.66. Found : C, 64.46; H, 5.31; CH_3O, 41.14.

ii) A mixture of 1.8 g. of (VI), 14 g. of veratric anhydride, and 5 g. of potassium veratrate was fused in an oil bath at 180~185° for 8 hr., cooled, and the solid mass that formed was pulverized in a mortar. This solid was boiled with 120 cc. of EtOH, filtered, and the filtrate was boiled gently on a water bath for 30 min. with a solution of 5 g. of KOH dissolved in 15 cc. of water. EtOH was distilled off under a reduced pressure, the residue was dissolved in 100 cc. of water, and CO_2 was bubbled through this solution for 2~3 hr. On allowing this mixture to stand over night, yellow crystals precipitated out and were recrystallized from MeOH to pale yellowish white needles, m.p. 216~217°, remaining almost colorless to $FeCl_3$ test. Paper partition chromatography of this substance showed a spot at Rf 0.675 (BuOH:AcOH:H_2O=4:1:5) or at Rf 0.77 (60% AcOH), which appeared yellowish brown under ultraviolet rays. The substance was identified with the product obtained as described in (i). *Anal.* Calcd. for $C_{19}H_{18}O_7$: C, 63.68; H, 5.02; $4CH_3O$, 34.63. Found : C, 63.36; H, 5.03; CH_3O, 33.64.

Demethylation of this product with HI as in the case of (a) afforded yellow microneedles, m.p. above 325°. Its acetylation and recrystallization of the product from MeOH gave colorless needles, m.p. 246°, undepressed on admixture with the acetate, m.p. 246°, obtained as in (a). Further, complete methylation of the foregoing product of m.p. 216~217° afforded colorless needles of m.p. 193~194°, and that of the demethylated product gave colorless prisms, m.p. 173~174°. These derivatives all showed no depression in their m.p. on admixture with the corresponding derivatives described in (a).

Reëxamination of the Formation of 5,6,7,3′,4′-Pentahydroxyflavone (VIII) reported by Seshadri[2)] —i) Formation of 5,8-Dihydroxy-7,3′,4′-trimethoxyflavone : A solution of 2 g. of luteolin 7,3′,4′-trimethyl ether and 30 cc. of pyridine dissolved in KOH solution (2 g. of KOH in 20 cc. of H_2O) was maintained at 15~20° and a solution of 2.5 g. $K_2S_2O_8$ dissolved in 100 cc. of water was added dropwise under stirring during 3 hr. The mixture was allowed to stand at room temperature for 30 hr., the solution was acidified with HCl, and the unreacted substance that precipitated out was filtered off The filtrate was washed several times to remove unreacted material, 40 cc. of conc. H_2SO_4 was added, and the mixture was boiled over a direct flame for 30 min. The yellow substance that precipitated out on standing this mixture over night was collected by filtration, washed with water, and crystallized from pyridine to yellow minute plates, m.p. 248~249° (reported[2)] m.p. 254~255°); coloring deep reddish brown to $FeCl_3$. Yield, 0.2 g. This substance dissolves in 5% alkali to form a deep reddish brown solution.

ii) Formation of 5,6,7,3′,4′-Pentahydroxyflavone : Demethylation of the above product was effected by refluxing 0.5 g. of it in a mixture of 6 cc. of Ac_2O and 10 cc. of HI for 2 hr. The reaction mixture was poured into water, the yellow gel-like precipitate was collected by filtration, dried, and crystallized from MeOH into yellow microneedles, m.p. above 325° (reported[2)] m.p. 315° (decomp.)); coloring dark brown to $FeCl_3$. Yield, 0.2 g. *Anal.* Calcd. for $C_5H_{10}O_7 \cdot H_2O$: C, 56.25; H, 3.75; $1H_2O$, 5.63. Found : C, 56.21; H, 3.84; H_2O, 5.46. This substance was compared with (VII) by Rf values in paper partition chromatography and both showed spots at Rf 0.36 (60% AcOH) and at Rf 0.41 (BuOH:AcOH:H_2O=4:1:2), the spots appearing yellowish brown under ultraviolet rays.

The substance hereby obtained was acetylated by the usual method and the product was recrystallized from MeOH, forming colorless needles, m.p. 243~244°, undepressed on admixture with the acetate, m.p. 246°, of (VII). *Anal.* Calcd. for $C_{25}H_{20}C_{12}$: C, 58.60; H, 3.93. Found : C, 58.51; H. 3.86

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Summary

The structure of the demethylated product of pedalitin, the aglycone of pedaliin, the flavonoid from sesame leaves, was unequivocally established by the synthesis of 5,6,7,3′,4′-pentahydroxyflavone.

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