Summary

For the explanation of chemical changes and loss of dermatological activity of salicylic acid in external preparations containing salicylic acid and zinc oxide, systems composed of salicylic acid, zinc oxide, and water were investigated. By the determination of salicylic acid and zinc ion in the aqueous phase after an equilibrium state was attained, the formation of 1:1 and 2:1 salts of salicylic acid and zinc was ascertained quantitatively.

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44. Seigo Fukushima, Akira Ueno, and Yukio Akahori: Studies on Benzochromones. V.*1 Synthesis and Ring Isomerization of 2-Methyl-5,8-dimethoxy-6,7-benzochromone.*2

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The synthesis of 2-methyl-5,8-dimethoxy-6,7-benzochromone (V), in which the furan ring of khellin (Ⅵ) was replaced by a benzenoid ring, has attracted considerable interest concerning its physiological activity, and several attempts[1,2] have been made unsuccessfully. We wish to report herein the successful synthesis and the ring isomerization of this compound.

Methyl 3,4-dimethoxy-2-naphthoate which was prepared from 3-hydroxy-2-naphthoic acid, was condensed with acetone by means of sodium hydride to form 3-acetoacetyl-1,2-dimethoxynaphthalene. Cyclization of the diketone in hydriodic acid gave 2-methyl-8-hydroxy-6,7-benzochromone (I). When hydroxylation of I was carried out by means of potassium persulfate, there was obtained 2-methyl-5,8-dihydroxy-6,7-benzochromone (Ⅳ) as red prisms, m.p. 250° (decomp.), in poor yield (ca. 10%). Coupling of I with diazotized sulfanilic acid gave a red violet, water soluble azo dye which on reduction with sodium hydrosulfite was converted into yellow needles of 2-methyl-5-amino-8-hydroxy-6,7-benzochromone (Ⅱ), m.p. 252° (decomp.). Oxidation of Ⅱ with sodium nitrite in acidic medium afforded 2-methyl-4*H*-naphtho[2,3-*b*]pyrane-4,5,10(5*H*,10*H*)-trione (Ⅲ), m.p. 165° (decomp.), and Ⅲ was reduced to Ⅳ with sodium hydrosulfite. If the reduction was carried out without isolation of Ⅲ, the overall yield of Ⅳ from I was more than 30%. The compound (Ⅳ) was then converted to 2-methyl-5,8-dimethoxy-6,7-benzochromone (V), m.p. 146°, by prolonged action of ethereal diazomethane solution, in the presence of methanol. Heating of Ⅳ with hydrochloric acid on a boiling water bath gave yellow needles, m.p. 224°, which was proved to be 2-methyl-5,6-dihydroxy-7,8-bezochromone (Ⅷ) reported previously.[2] Drastic demethylation of V using hydriodic acid and acetic anhydride also produced Ⅷ. Such a ring isomerization might proceed through cleavage of γ-pyrone ring to an intermediate, 2-acetoacetyl-1,3,4-naphthalenetriol (Ⅳ'),

*1 Part Ⅳ: This Bulletin, **9**, 127 (1961).
*2 A preliminary communication on this subject appeared in this Bulletin, **10**, 638 (1962).
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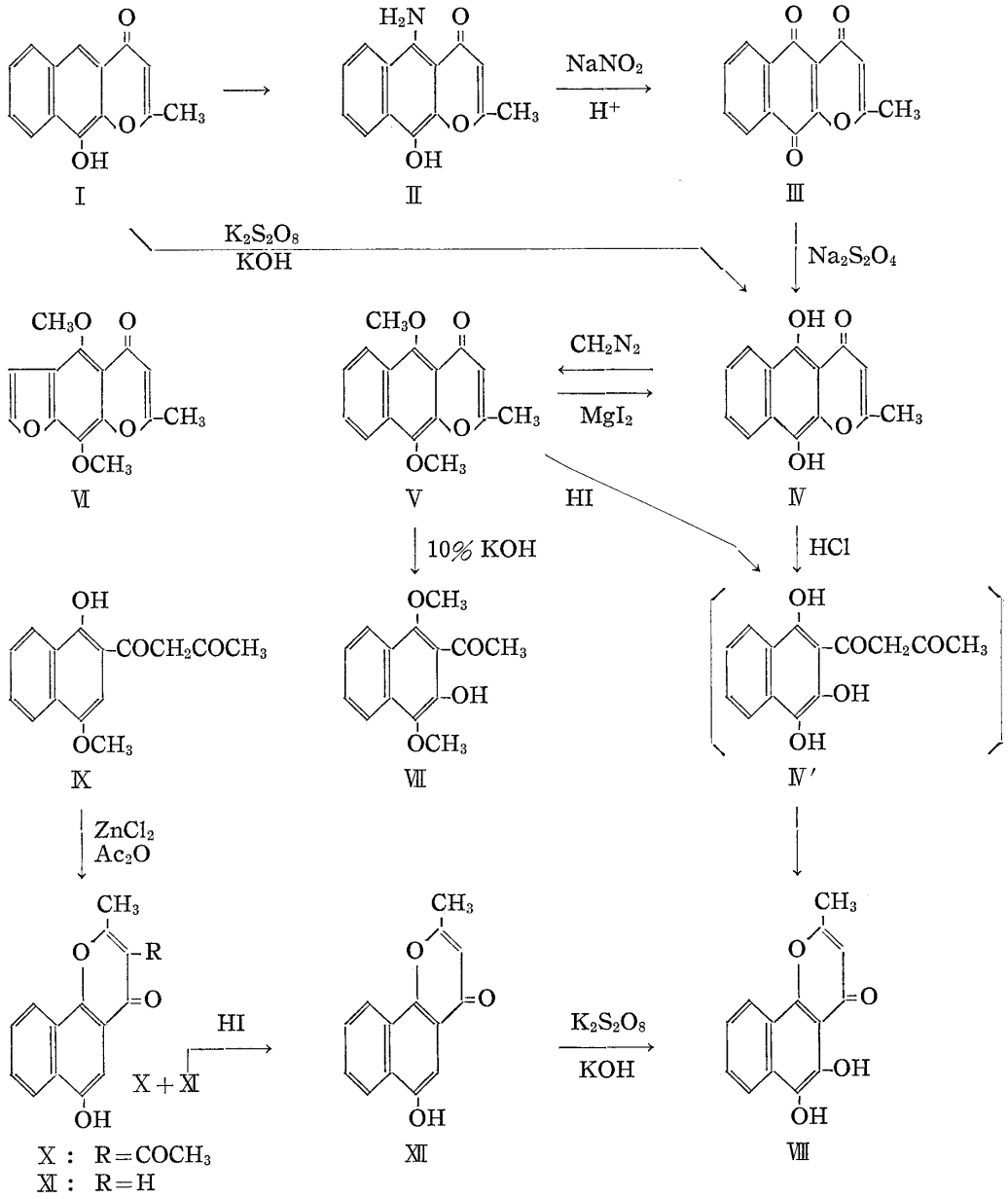
1) S. Wawzoneck, *et al.*: J. Org. Chem., **17**, 1419 (1952).
2) K. Yamaguchi, S. Fukushima, H. Yamada: This Bulletin, **8**, 1028 (1960).



followed by cyclization of the diketone to the new chromone (Ⅷ). When Ⅴ was subjected to mild demethylation with magnesium iodide, there was obtained Ⅳ as expected.

These facts indicated that the hydroxyl group was introduced undoubtedly in 5-position of I, and suggested that angular structure might be more stable than linear structure in such a dihydroxybenzochromone. This behavior is similar to that of khellin, which is isomerized to angular type isonorkhellin by demethylation with hydriodic acid.

Alkali degradation of Ⅴ afforded acetyl-1,4-dimethoxy-3-naphthol (Ⅶ). The structure of the compound (Ⅶ) was supported by the fact that Ⅶ was identical with neither 3-acetyl-2,4-dimethoxy-1-naphthol[2] nor 2-acetyl-3,4-dimethoxy-1-naphthol,[3] which corresponded to isomers of three possible isomers of 2-acetyl-1,3,4-naphthalenetriol dimethyl ether.

In order to obtain 2-methyl-3-acetyl-6-methoxy-7,8-benzochromone (Ⅹ), cyclization of 2-acetoacetyl-4-methoxy-1-naphthol (Ⅸ) with zinc chloride and acetic anhydride was

3) S. Fukushima : This Bulletin, 8, 1036 (1960),

attempted. However, the main product was found to be 2-methyl-6-methoxy-7,8-benzochromone (XI)[4] and the yield of the expected product X was very poor.

The product (XI) was demethylated to 2-methyl-6-hydroxy-7,8-benzochromone (XII) with hydriodic acid and acetic anhydride, and hydroxylation of XII by means of potassium persulfate gave 2-methyl-5,6-dihydroxy-7,8-benzochromone (VIII). This fact might provide another evidence of the angular structure of VIII.

Experimental*4

Methyl 3,4-Dimethoxy-2-naphthoate——To a suspension of 3-hydroxy-2-naphthoic acid (50 g.) in AcOH (400 ml.) and H_2O (100 ml.), a solution of $NaNO_2$ (21 g.) in H_2O (50 ml.) was slowly added in small portions at a temperature below 0° with stirring, and the mixture was stirred at 0° for 8 hr., giving orange crystals of 4-nitroso-3-hydroxy-2-naphthoic acid, m.p. 185°. The yield (50 g.) was better than that of Kostanecki's method.[5] The nitroso compound (30 g.) was dissolved into a solution of K_2CO_3 (40 g.) in H_2O (1 L.) and $Na_2S_2O_4$ (80 g.) was added thereto at 50~60°, and the mixture was kept for 30 min. under the same condition, and then cooled. An excess amount of conc. HCl was poured into the mixture to give 4-amino-3-hydroxy-2-naphthoic acid hydrochloride (26 g.). According to the method of Möhlau and Kriebel,[6] the amino compound was converted to methyl 3,4-dihydroxy-2-naphthoate, m.p. 97°. A mixture of the ester (30 g.), Me_2SO_4 (50 g.), K_2CO_3 (100 g.) and Me_2CO (600 ml.) was refluxed on a water bath with stirring for 6 hr. After removal of K_2CO_3 by filtration, the filtrate was evaporated under a reduced pressure to a small volume, and H_2O was added. The separated oil was distilled under a reduced pressure to give methyl 3,4-dimethoxy-2-naphthoate (30 g.), b.p_2 160~161°.

3-Acetoacetyl-1,2-dimethoxynaphthalene——To a stirred suspension of NaH (2 g.) in dry Et_2O (30 ml.), a mixture of methyl 3,4-dimethoxy-2-naphthoate (10 g.), Me_2CO (4 g.) and Et_2O (20 ml.) was slowly added at 0°, and stirring was continued for 30 min. at 0°, then for 1 hr. at room temperature, and finally was refluxed for 1 hr. on a water bath. After removal of the solvent, the viscous residue was heated on a boiling water bath for 1 hr., then allowed to stand overnight at room temperature and poured into ice H_2O (500 g.) containing AcOH (16 ml.). The resulting precipitate was collected, washed with H_2O and treated with 10% $KHCO_3$. The insoluble portion was recrystallized from Et_2O to yield 3-acetoacetyl-1,2-dimethoxynaphthalene (3 g.) as pale yellow prisms, m.p. 77°. *Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.46; H, 5.92.

This product was proved to be identical with the product obtained by the method of Wawzoneck, *et al.*[1]

Acidification of the soluble portion in 10% $KHCO_3$ with HCl gave 3,4-dimethoxy-2-naphthoic acid (4 g.).

2-Methyl-8-hydroxy-6,7-benzochromone (I)——According to the method of Wawzoneck, *et al.*,[1] 3-acetoacetyl-1,2-dimethoxynaphthalene was cyclized to I with HI (sp. gr. 1.7) and recrystallization of the product from EtOH-AcOEt (1:1) gave pale yellow needles, m.p. 272°. *Anal.* Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.29; H, 4.51.

2-Methyl-5-amino-8-hydroxy-6,7-benzochromone (II)——To the compound (I) (1.1 g.) dissolved in a solution of KOH (1 g.) in H_2O (40 ml.) was added, with stirring under cooling, an ice (5 g.) and diazotized sulfanilic acid (prepared in the usual manner from sulfanilic acid (0.87 g.) in a solution of Na_2CO_3 (0.27 g.) in H_2O (5 ml.), $NaNO_2$ (0.37 g.) in H_2O (1 ml.) and conc. HCl (1.06 ml.) with ice (6 g.)). After standing for 1 hr. at room temperature, the red violet solution was saturated with CO_2 and filtered. To the filtrate was added $Na_2S_2O_4$ (2.3 g.) at 40~50°, and the mixture was kept for 20 min. at 70°. After cooling of the mixture, the separated yellow solid was collected, washed with H_2O containing $Na_2S_2O_4$ and immediately recrystallized from H_2O-dioxane containing a little amount of $Na_2S_2O_4$, then without delay from dil. EtOH containing $Na_2S_2O_4$ to yield 0.7 g. of yellow needles, m.p. 252°(decomp.). *Anal.* Calcd. for $C_{14}H_{11}O_3N$: C, 69.70; H, 4.59; N, 5.80. Found: C, 69.55; H, 4.71; N, 5.49. IR ν_{max}^{KBr} cm^{-1}: 1640 (C=O).

2-Methyl-4*H*-naphtho[2,3-*b*]pyrane-4,5,10(5*H*,10*H*)-trione (III)——To a suspension of II (0.5 g.) in dil. H_2SO_4 (0.55 ml. of H_2SO_4 in 200 ml. of H_2O), $NaNO_2$ (0.8 g.) was slowly added in small portions with shaking, and the mixture was warmed at 40° for 1 hr. with shaking. The cooled reaction mixture was filtered to remove a little amount of insoluble substance, and AcONa (2.5 g.) was added to the

*4 All melting points are uncorrected.

4) H. Schmid, H. Seiler: Helv. Chim. Acta, **35**, 1990 (1952).
5) S. Kostanecki: Ber., **26**, 2897 (1893).
6) R. Möhlau, F. Kriebel: *Ibid.*, **28**, 3089 (1895).

filtrate. The mixture was saturated with KCl, then extracted with AcOEt. The extract was evaporated to dryness and the residue was recrystallized twice from MeOH to yield 100 mg. of golden-yellow needles, m.p. 165°(decomp.). *Anal.* Calcd. for $C_{14}H_8O_4$: C, 70.00; H, 3.36. Found: C, 70.05; H, 3.60. IR ν_{max}^{KBr} cm^{-1}: 1673, 1640 (C=O).

2-Methyl-5,8-dihydroxy-6,7-benzochromone (IV)——a) Elbs oxidation of I: To a solution of I (1.1 g.) in H_2O (100 ml.) containing KOH (1.4 g.) and pyridine (5 ml.) was added dropwise a solution of $K_2S_2O_8$ (1.4 g.) in H_2O (30 ml.) at a temperature below 0° with stirring over a period of 2 hr. After standing overnight in a refrigerator, the reaction mixture was rendered faintly acid to congo-red, filtered to remove the ensuing brown solid and shaken with Et_2O. The aqueous layer was heated with conc. HCl (1 ml.) on a boiling water bath for 15 min. and then cooled. The separated solid was collected, washed with H_2O and recrystallized from EtOH to red prisms or from EtOH–AcOEt (1:1) to orange needles, m.p. 250°(decomp.). Yield, 100 mg. *Anal.* Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.24; H, 4.21. IR ν_{max}^{KBr} cm^{-1}: 3050 (broad), 1675 (weak), 1640, 1618.

When the foregoing aqueous solution was heated with a larger quantity of HCl than that described above, the product was obtained as yellow needles, m.p. 224°, after recrystallization from EtOH, which was confirmed to be identical with an authentic sample of 2-methyl-5,6-dihydroxy-7,8-benzochromone by a mixed fusion and comparison of the IR spectra.

b) Reduction of III: To a warm solution of III (30 mg.) in EtOH (2.5 ml.), a solution of $Na_2S_2O_4$ (50 mg.) in H_2O (1 ml.) was added. After warming the mixture for several minutes, H_2O (3 ml.) was added. The separated red crystals were collected, and recrystallized from EtOH to form 20 mg. of red prisms, m.p. 250°(decomp.).

To a filtered reaction mixture prepared from II (0.2 g.), H_2SO_4 (0.22 ml.), H_2O (200 ml.) and $NaNO_2$ (0.3 g.) as described in the preparation of III, AcONa (1 g.) was added. Without isolation of III, the mixture was heated with $Na_2S_2O_4$ (0.5 g.) on a boiling water bath for 10 min. and cooled. The separated solid was collected and recrystallized from EtOH to yield 0.1 g. of red prisms, m.p. 250°(decomp.).

c) Demethylation of V with MgI_2: A solution of V (150 mg.) in benzene (1 ml.) was added to an Et_2O–benzene solution of MgI_2[7] prepared from I_2 (200 mg.) and Mg (40 mg.) in Et_2O (1 ml.). The solvent was removed under a reduced pressure, and the residue was kept at 130° in vacuum and then heated at 160~165° for 1.5 hr. After cooling, the solid was triturated with dil. H_2SO_4, and the resulting precipitate was collected, followed by washing with H_2O, aq. $NaHSO_4$ and H_2O, successively. The product was recrystallized from EtOH to form red prisms, m.p. 250°(decomp.).

The products obtained by the methods a), b), and c) were proved to be identical with each others by admixture and comparison of the IR spectra.

2-Methyl-5,8-dimethoxy-6,7-benzochromone (V)——A suspension of powdered IV (1 g.) in MeOH (20 ml.) and Et_2O (50 ml.) was treated with an Et_2O-solution of CH_2N_2 (prepared from 20 g. of N-methyl-N-nitrosourea). After standing for 4 days at room temperature, the excess of CH_2N_2 was evaporated together with Et_2O. The residue was recrystallized twice from 50% EtOH to yield 0.7 g. of colorless needles, m.p. 146°, which showed negative tests for phenol by color reactions. *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.89; H, 5.16. IR ν_{max}^{KBr} cm^{-1}: 1663 (C=O).

Ring Isomerization of IV and V——a) A mixture of conc. HCl (25 ml.) and H_2O (85 ml.) was added to a solution of IV (100 mg.) in pyridine (1 ml.). The resulting suspension was heated on a boiling water bath for 1 hr. and then cooled. The separated solid was collected, washed with H_2O and dried. Yield, 60 mg. Two recrystallization from EtOH gave yellow needles, m.p. 224~226°. *Anal.* Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.16; H, 4.15.

b) To a cold suspension of V (26 mg.) and Ac_2O (1 ml.), HI (sp. gr. 1.7; 2 ml.) was slowly added and the mixture was refluxed for 30 min. After cooling, the mixture was poured into ice H_2O containing $NaHSO_3$, and the separated solid was collected, washed with H_2O and dried. Recrystallization from EtOH gave 15 mg. of yellow needles, m.p. 223°. The products obtained by methods a) and b) were proved to be identical with VIII by admixture and comparison of the IR spectra.

2-Acetyl-1,4-dimethoxy-3-naphthol (VII)——A mixture of V (0.2 g.) and 10% KOH (4 ml.) was boiled gently for 1 hr. on an oil bath, the resulting red brown mixture was filtered to remove a little amount of dark solid, and the filtrate was acidified with 10% HCl. The separated solid was recrystallized twice from 50% EtOH to yield 60 mg. of orange yellow plates, m.p. 80°. Its EtOH-solution showed a green color with $FeCl_3$. *Anal.* Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 67.87; H, 5.80. IR ν_{max}^{KBr} cm^{-1}: 1638 (C=O).

3-Acetoxy-2-acetyl-1,4-dimethoxynaphthalene——A mixture of VII (30 mg.), Ac_2O (1 ml.) and pyridine (1 drop) was allowed to stand overnight at room temperature, and the mixture was poured into ice H_2O. Two recrystallization of the separated product from 50% EtOH gave colorless prisms, m.p. 47°. *Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.67; H, 5.59.

7) A. Schönberg, R. Moubasher: J. Chem. Soc., **1944**, 462.

2-Methyl-3-acetyl-6-methoxy-7,8-benzochromone (X) and 2-Methyl-6-methoxy-7,8-benzochromone (XI)——2-Acetoacetyl-4-methoxy-1-naphthol, m.p. 110°,(1 g.) obtained according to the method of Schmid and Seiler[4] was added to a warm solution of $ZnCl_2$(1 g.) in Ac_2O(1.5 ml.). The mixture was boiled for 4 min. and H_2O was added. The separated solid was dissolved in benzene, and the solution was passed through a column of Al_2O_3. The first eluate with benzene was evaporated to dryness and two recrystallization of the residue from EtOH yielded 50 mg. of X as colorless needles, m.p. 180°. *Anal.* Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found : C, 72.10; H, 4.93.

The second eluate with additional benzene gave 0.2 g. of colorless needles, m.p. 170°, after recrystallization from EtOH. *Anal.* Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.30. Found : C, 74.98; H, 5.11. This compound was found to be identical with the authentic sample which was prepared by the method of Schmid and Seiler,[4] on admixture and comparison of the IR spectra.

2-Methyl-6-hydroxy-7,8-benzochromone (XII)——To a suspension of XI (1 g.) in cold Ac_2O(10 ml.), HI (sp. gr. 1.7; 10 ml.) was added dropwise with shaking, and the mixture was boiled for 30 min. on an oil bath. After cooling, the mixture was added to ice H_2O containing $NaHSO_3$, and the resulting solid was collected, washed with H_2O and dried. Two recrystallization of the product from EtOH–AcOEt (1:1) gave 0.6 g. of almost colorless needles, m.p. 218°. *Anal.* Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found : C, 74.54; H, 4.46.

Hydroxylation of 2-Methyl-6-hydroxy-7,8-benzochromone (XII)——XII (200 mg.) was dissolved in a solution of KOH(0.3 g.) and pyridine (6 ml.) in H_2O(30 ml.), and oxidized with a solution of $K_2S_2O_8$(0.3 g.) in H_2O(6 ml.) in the same manner as described in the case of Elbs oxidation of I. XII (150 mg.) was recovered when the mixture was slightly acidified. The mixture was heated with conc. HCl (1 ml.) on a boiling water bath for 15 min., then cooled and extracted with Et_2O. The Et_2O-extract was washed with H_2O and dried over anhyd. Na_2SO_4. After removal of the solvent the residue was recrystallized twice from EtOH to afford 5 mg. of yellow needles, m.p. 224°, which was identified with an authentic sample of VIII.

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Summary

2-Methyl-5,8-dihydroxy-6,7-benzochromone (IV) was obtained by means of either hydroxylation of 2-methyl-8-hydroxy-6,7-benzochromone (I) or reduction of 2-methyl-4*H*-naphtho[2,3-*b*]pyrane-4,5,10(5*H*,10*H*)-trione (III), and synthesis of 2-methyl-5,8-dimethoxy-6,7-benzochromone (V), in which the furan ring of khellin (VI) was replaced by a benzenoid ring, was accomplished by means of methylation of IV. It was found that V underwent irreversible ring isomerization to form 2-methyl-5,6-dihydroxy-7,8-benzochromone (VII) during demethylation of V with hydriodic acid.

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