[Chem. Pharm. Bull. 14(2) 129~139 (1966)]

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21. Akira Ueno and Seigo Fukushima : Studies on Benzochromones. IX.*1 Syntheses of Hydroxyl Derivatives of 2-Methyl-5,6-benzochromone and 2-Methyl-3-acetyl-5,6-benzochromone.

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Synthesis and reactions of hydroxyl derivatives of 2-methyl-6,7-benzochromone and 2-methyl-7,8-benzochromone as analogs of khellin were previously reported in this series.*1 The present paper deals with the syntheses of hydroxyl derivatives of 2-methyl-5,6-benzochromone and 2-methyl-3-acetyl-5,6-benzochromone.

Recently, 1-acetyl-2,3-naphthalenediol (I) was synthesized from 2,3-diacetoxynaphthalene by Prajer-Janczewska,[1] and I was obtained by the modification of his method using aluminum chloride. Methylation of I with dimethyl sulfate gave 1-acetyl-2,3-dimethoxynaphthalene (II), which was condensed with ethyl acetate using sodium hydride to form 1-acetoacetyl-2,3-dimethoxynaphthalene (III′) which could not be obtained in a pure state. Ring closure of the crude diketone (III′) with hydriodic acid and acetic anhydride gave 2-methyl-8-hydroxy-5,6-benzochromone (III) and 2-methyl-8-methoxy-5,6-benzochromone (IV), obtained by methylation of III with diazomethane.

1,3-Naphthalenediol is a starting material for the synthesis of 2-methyl-7-hydroxy-5,6-benzochromone (V). However, conversion of 1,3-naphthalenediol to 1-acetyl-2,4-naphthalenediol failed, under a variety of conditions. Therefore, 1,3-naphthalenediol was methylated with dimethyl sulfate to give 1,3-dimethoxynaphthalene, which smoothly afforded 1-acetyl-2,4-dimethoxynaphthalene (VI) by reaction with acetic anhydride in the presence of iodine[2] as a catalyst. VI underwent the required Claisen condensation with ethyl acetate, using sodium hydride to 1-acetoacetyl-2,4-dimethoxynaphthalene (VII), but this diketone (VII) failed to undergo ring closure to the chromone either in the presence of hydriodic acid or in hydrobromic acid and acetic anhydride. This difficulty is due to liberation of acetoacetyl group, since the diketone (VII) afforded 1,3-dimethoxynaphthalene in the presence of hydrobromic acid and acetic acid at room temperature.

In the selective demethylation of IV, the use of hydrohalogen acid did not give the expected compound for the same reason, but the use of "magnesium iodide etherate"[3,4] gave 1-acetyl-4-methoxy-2-naphthol (VIII) successfully. VIII was converted into 1-acetoacetyl-4-methoxy-2-naphthol (IX), undergoing the required Claisen condensation. The diketone (IX) was subjected to ring-closure in the presence of hydrochloric acid and acetic acid, and 2-methyl-7-methoxy-5,6-benzochromone (X) was produced.

On the other hand, X was also obtained from the diketone (VII) by treatment with "magnesium iodide etherate" in a poor yield, with recovering the starting material. Demethylation of X with magnesium iodide[5] gave 2-methyl-7-hydroxy-5,6-benzochromone (V).

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*1 Part VIII : This Bulletin, **14**, 121 (1966).

*2 Oshika, Shizuoka (上野 明, 福島清吾).

1) L. Prajer-Janczewska : Roczniki Chem., **35**, 553 (1961) [C. A., **56**, 11509 (1962)].
2) X. A. Dominguer, *et al.* : J. Am. Chem. Soc., **76**, 5150 (1954).
3) V. Arkley, *et al.* : J. Chem. Soc., **1962**, 1260.
4) B. W. Bycroft, J. Roberts : *Ibid.*, **1963**, 4868.
5) A. Schönberg, R. Moubasher : J. Chem. Soc., **1944**, 462.

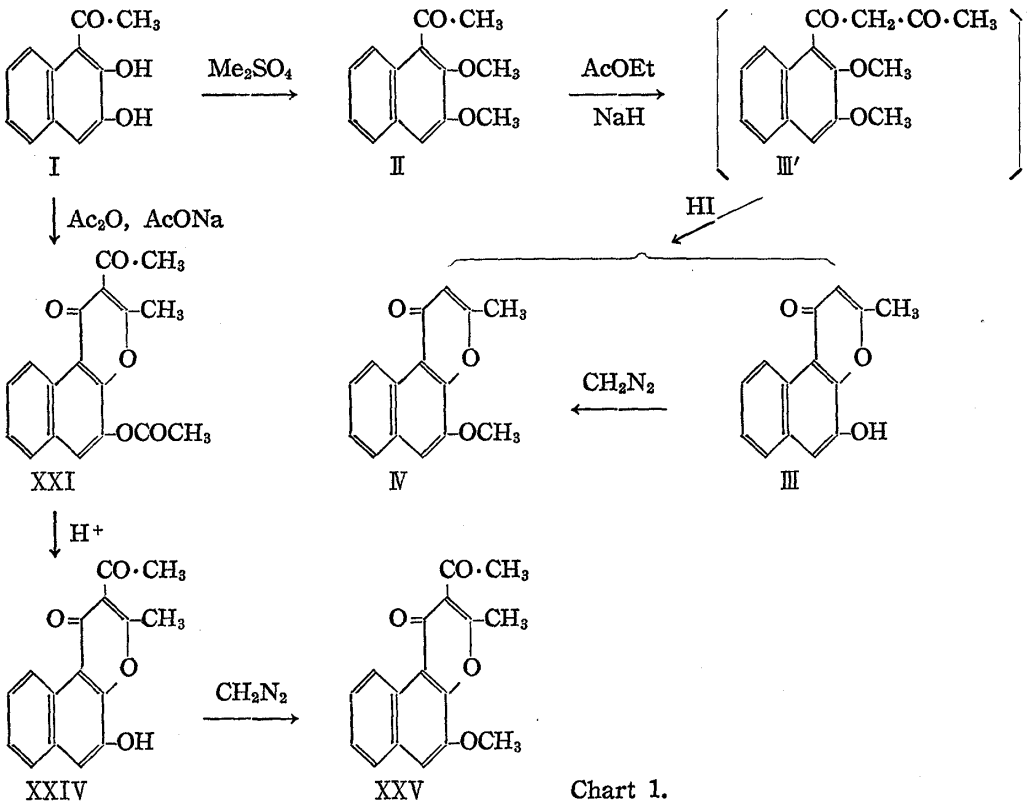


Chart 1.

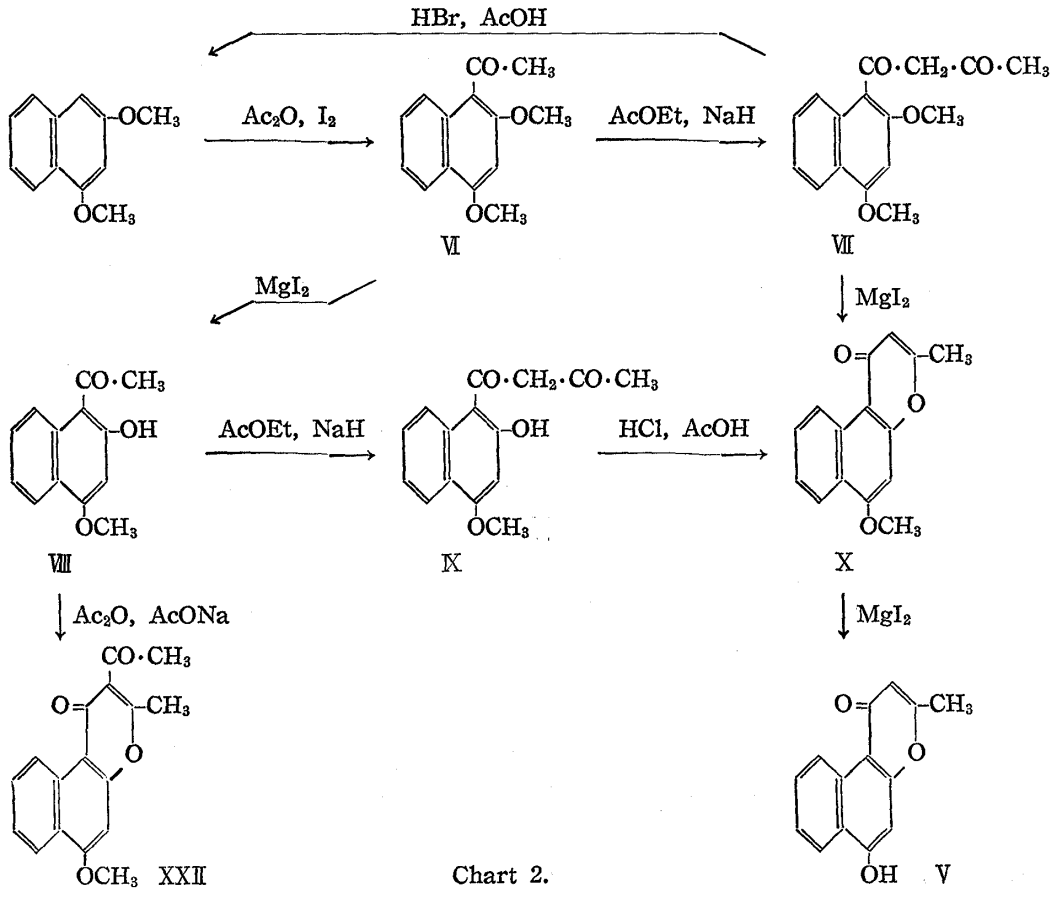


Chart 2.

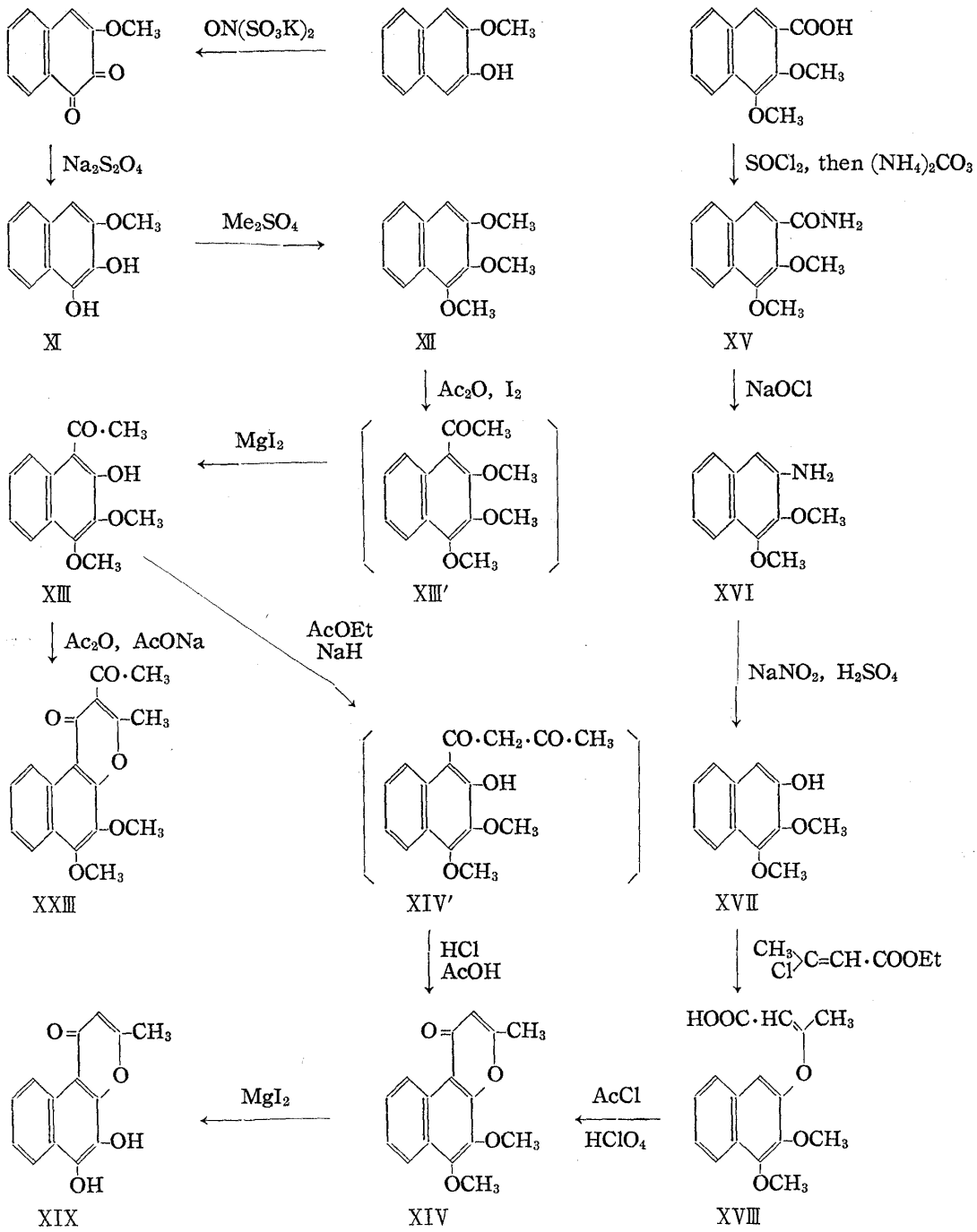


Chart 3.

Synthesis of 2-methyl-7,8-dimethoxy-5,6-benzochromone (XIV) was attempted in several ways, and was accomplished by the two routes shown in Chart 3 and by the Elbs persulfate oxidation of III and V.

In the first course, 3-methoxy-2-naphthol was converted into 3-methoxy-1,2-naphthoquinone by the method of Teuber and Götz,[6] and the resulting product was reduced to 3-methoxy-1,2-naphthalenediol (XI) with sodium hydrosulfite. Methylation of XI with dimethyl sulfate gave 1,2,3-trimethoxynaphthalene (XII). Acetylation of XII using acetic anhydride in the presence of iodine gave a viscous oil, b.p_2 160~170°,

6) H. Teuber, N. Götz : Chem. Ber., **87**, 1236 (1954).

whose infrared spectrum showed the presence of acetyl group at 1685 cm^{-1} and it was assumed to be 1-acetyl-2,3,4-trimethoxynaphthalene (XIII'), but this product could not be purified from the contamination of XII. Demethylation of this product with "magnesium iodide etherate" and alkali treatment of the resulting product gave a viscous oil, b.p_2 171~172°, and a small amount of XII which was assumed to have remained in XIII'. The main product, soluble in aqueous 2% potassium hydroxide solution, showed a dark violet color with ferric chloride in ethanolic solution and it was difficult to assign the absorption band of acetyl group in its infrared spectrum. Its analytical values agreed with $C_{14}H_{14}O_4$, and infrared spectrum of its acetylated product exhibits the absorption of O-acetyl group at 1770 cm^{-1} and the presence of aryl-acetyl group at 1690 cm^{-1}. These facts showed that this product must be 1-acetyl-3,4-dimethoxy-2-naphthol (XIII). Condensation of XIII with ethyl acetate using sodium hydride led to the diketone (XIV') which could not be obtained in a purified oil or crystalline state. 2-Methyl-7,8-dimethoxy-5,6-benzochromone (XIV), m.p. 119°, was obtained in a poor yield by heating the crude diketone (XIV') with hydrochloric acid in acetic acid.

On the other hand, 3,4-dimethoxy-2-naphthoic acid was converted into 3,4-dimethoxy-2-naphthoyl chloride by treatment with thionyl chloride and was led to 3,4-dimethoxy-2-naphthamide (XV) without isolation of the chloride. This amide (XV) was converted into 3-amino-1,2-dimethoxynaphthalene (XVI) by the Hoffmann reaction using sodium hypochlorite, and 3,4-dimethoxy-2-naphthol (XVII) was obtained from XVI through the diazo compound. In the application of the Dann chromone synthesis,[4,7] XVII was reacted with ethyl 3-chlorocrotonate, followed by hydrolysis of the product, and 3-(3,4-dimethoxy-2-naphthoyloxy)crotonic acid (XVIII) was formed. Cyclization of XVIII using perchloric acid in acetyl chloride gave XIV which was identified with the product (XIV) prepared as above. XIV was demethylated with magnesium iodide to 2-methyl-

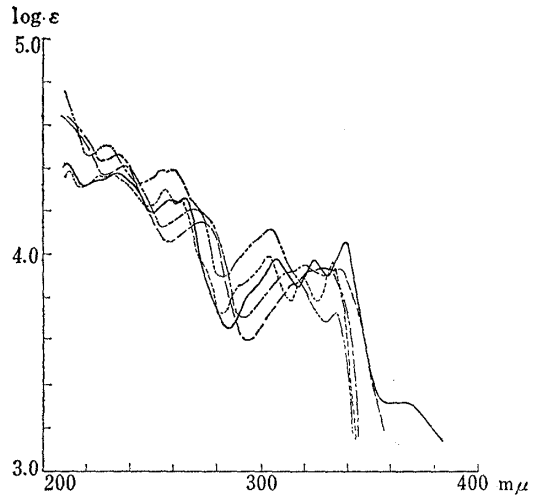


Fig. 1. Ultraviolet Spectra of Derivatives of 2-Methyl-5,6-benzochromone (XXVI)

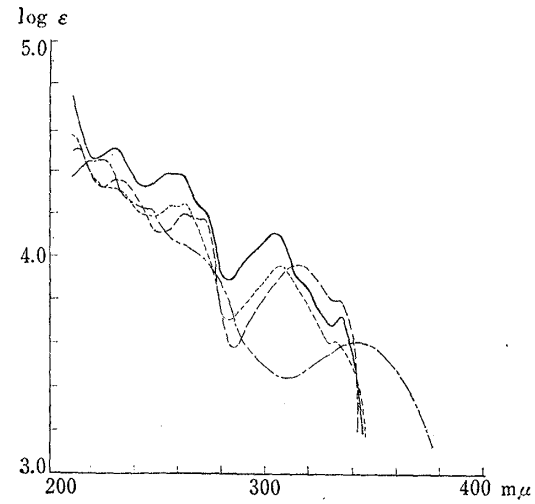
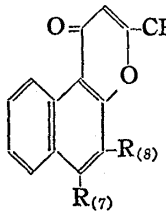


Fig. 2. Ultraviolet Spectra of Derivatives of 2-Methyl-5,6-benzochromone (XXVI)



Compound		$R_{(7)}$	$R_{(8)}$
III :	– – – –	H	OH
IV :	– – – –	H	OCH_3
V :	———	OH	H
X :	.....	OCH_3	H
XXVI :	– · – · –	H	H

Compound		$R_{(7)}$	$R_{(8)}$
XX :	.....	$O\text{-}COCH_3$	$O\text{-}COCH_3$
XIV :	– – – –	OCH_3	OCH_3
XIX :	– – – –	OH	OH
XXVI :	———	H	H

7) O. Dann, G. Illing : Ann., **605**, 158 (1957).

7,8-dihydroxy-5,6-benzochromone (XIX), which was led to 2-methyl-7,8-diacetoxy-5,6-benzochromone (XX).

In order to obtain XIX by the hydroxylation of Ⅲ or Ⅴ, these were oxidized by potassium persulfate and the products were acetylated because of difficulty of their recrystallizations. The product in each case was confirmed to be XX. This fact demonstrated that XIX was produced from Ⅲ or Ⅴ by the Elbs persulfate oxidation.

On the basis of these facts, structure of all the newly synthesized derivatives of 2-methyl-5,6-benzochromone and 1-acetyl naphthols reported here was established unequivocally.

Hydroxyl derivatives of 2-methyl-3-acetyl-5,6-benzochromone were expected to be obtained from the corresponding derivatives of 1-acetyl-2-naphthol by the method of Menon and Venkataraman,[8] and derivatives of 1-acetyl-2-naphthol, which was prepared for the synthesis of 2-methyl-5,6-benzochromones, were subjected to reaction with acetic anhydride and sodium acetate. In this way, 2-methyl-3-acetyl-8-acetoxy-5,6-benzochromone (XXI) was obtained from I, 2-methyl-3-acetyl-7-methoxy-5,6-benzochromone (XXII) from Ⅷ, and 2-methyl-3-acetyl-

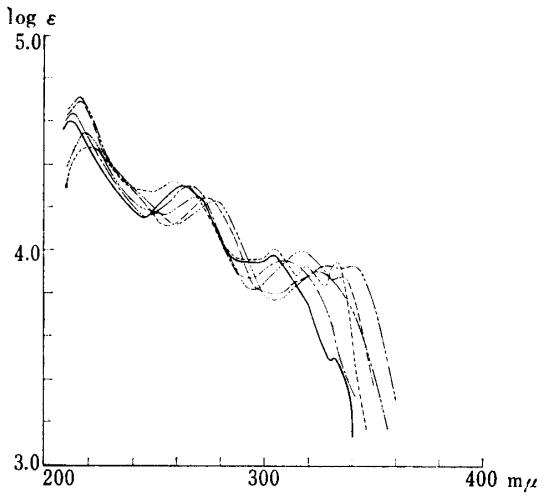
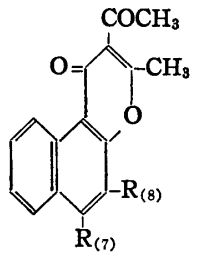


Fig. 3. Ultraviolet Spectra of Derivatives of 2-Methyl-3-acetyl-5,6-benzochromone (XXVII)



Compound		$R_{(7)}$	$R_{(8)}$
XXI :	------	H	O-$COCH_3$
XXIV :	--------	H	OH
XXV :	-----	H	OCH_3
XXII :	.....	OCH_3	H
XXIII :	--------	OCH_3	OCH_3
XXVII :	———	H	H

Table I. Ultraviolet Spectra of Derivatives of 2-Methyl-5,6-benzochromone (XXVI) and 2-Methyl-3-acetyl-5,6-benzochromone (XXVII)

Compound	$\lambda_{max}^{99\%\ EtOH}$ (log ε)					
XXVI[a]	225[b] (4.48)	230 (4.50)	253[b] (4.38)	261 (4.39)	305 (4.10)	320[b] (3.85)
	335 (3.73)					
Ⅳ	211[b] (4.64)	235 (4.46)	269 (4.21)	312[b] (3.91)	321 (3.95)	334 (3.91)
Ⅲ	236 (4.41)	272 (4.15)	314[b] (3.85)	327 (3.93)	337 (3.93)	
X	212 (4.39)	226 (4.37)	232 (4.37)	257 (4.30)	265 (4.25)	290[b] (3.86)
	304 (3.99)	320 (3.91)	334 (3.97)			
Ⅴ	212 (4.43)	225[b] (4.35)	234 (4.38)	258 (4.27)	265 (4.26)	295[b] (3.82)
	308 (3.98)	325 (3.98)	340 (4.06)	367[b] (3.32)		
XX	211[b] (4.56)	231[b] (4.32)	256 (4.24)	262 (4.24)	307 (3.96)	333 (3.61)
XIV	214 (4.50)	233 (4.53)	263 (4.20)	272 (4.17)	316 (3.96)	334 (3.80)
XIX	218[b] (4.44)	225 (4.45)	246[b] (4.22)	266[b] (4.04)	344 (3.61)	
XXVII[a]	213 (4.60)	264 (4.30)	272[b] (4.25)	305 (3.97)	320[b] (3.76)	333 (3.51)
XXV	216 (4.69)	275 (4.24)	312[b] (3.85)	324 (3.91)	337 (3.88)	
XXIV	216 (4.71)	278 (4.24)	330 (3.93)	341 (3.93)		
XXII	220 (4.47)	240[b] (4.30)	258 (4.32)	265 (4.31)	306 (4.01)	320 (3.93)
	334 (3.95)					
XXIII	219 (4.55)	267～272 (4.24)		318 (3.99)	334[b] (3.84)	

a) These compounds were prepared according to the method of Menon and Venkataraman.[8]
b) Inflexion point.

8) B.K. Menon, K. Venkataraman : J. Chem. Soc., **1931**, 2591.

7,8-dimethoxy-5,6-benzochromone (XXIII) from XIII. XXI was converted into 2-methyl-3-acetyl-8-hydroxy-5,6-benzochromone (XXIV) by its hydrolysis with sulfuric acid, and methylation of XXIV with diazomethane gave 2-methyl-3-acetyl-8-methoxy-5,6-benzochromone (XXV).

The ultraviolet spectra of 2-methyl-5,6-benzochromones and 2-methyl-3-acetyl-5,6-benzochromones are shown in Figs. 1, 2, and 3, and Table I.

In the ultraviolet spectra of 2-methyl-5,6-benzochromones, three absorption bands are located at around 230, 260, and 305~340 mμ. There is no absorption in wave length region above than 360~380 mμ region, which was observed in the case[9] of 2-methyl-7,8-benzochromones and 2-methyl-6,7-benzochromones, except in the case of V, which showed very weak absorption at 367 mμ. This observation is in accordance with the observation of Schmid and Seiler[10] that a benzochromone, *i.e.* 2,8-dimethoxy-5,6-benzochromone produced from 2-naphthol, absorbs at a shorter wave lengths than benzochromone from 1-naphthol. Molecular extinction of the first K-band located at 230 mμ is larger than that of the second K-band at 260 mμ. The relative intensities of these two K-bands and absorption band in a longer wave length region are different from those of 2-methyl-7,8-benzochromones. Three absorption bands tend to show more or less the fine structure in each band, and this tendency is typical in the compounds (V) and (X) which free hydroxyl or methoxyl group was introduced at 7-position of 2-methyl-5,6-benzochromone. The relationship between the structure of 2-methyl-5,6-benzochromones and their spectra is similar to that observed in the case of 2-methyl-7,8-benzochromones as described in the preceding paper.[9] For example, IV and V absorb at a longer wave length than XIV, and the effect of free hydroxyl group at 7-position in 2-methyl-5,6-benzochromone corresponds to that at 5-position in 2-methyl-7,8-benzochromone on the point of formation of quinoid, which is *p*-form in this case. It seems difficult to assign correctly the bathochromic or hypsochromic shift of wave length in the spectra of 2-methyl-5,6-benzochromones because the relative intensities and the interval of peaks appearing in fine structure vary with the substituent groups and their position, and it is not clear whether this change is due to the shift of other associated absorption band or enhanced effect of absorption band.

The ultraviolet spectra of 2-methyl-3-acetyl-5,6-benzochromones are similar to those of 2-methyl-5,6-benzochromones. The two K-bands are located at 216 and 260 mμ, and the first K-band at 216 mμ shifts to a shorter wave length by 14 mμ from that of 2-methyl-5,6-benzochromones, and the fine structure in 2-methyl-3-acetyl-5,6-benzochromones is generally simpler than that of 2-methyl-5,6-benzochromones. Molecular extinction of the K-band in a shorter wave length is approximately two times larger than that of the K-band in a longer wave length, and differences of their relative intensities are larger than that of 2-methyl-5,6-benzochromones. These points might be useful for assigning the structure of 2-methyl-3-acetyl-5,6-benzochromones.

In the absorption band in loger a wave length region at 305~340 mμ, the spectral changes afforded by substituents on the aromatic ring are completely in accordance with the case of 2-methyl-5,6-benzochromones.

The above observations on the ultraviolet spectra are added to the observations on the ultraviolet spectra of 2-methylbenzochromones reported previously in this series.[9]

Experimental*3

1-Acetyl-2,3-naphthalenediol (I)——To a suspension of 2,3-diacetoxynaphthalene (7.8 g.) in chloro-

*3 All melting points are uncorrected.

9) S. Fukushima, Y. Akahori, A. Ueno: This Bulletin, **12**, 316 (1964).

10) H. Schmid, H. Seiler: Helv. Chim. Acta, **35**, 1990 (1952).

benzene (40 ml.), $AlCl_3$ (20 g.) was added slowly followed by 2,3-naphthalenediol (4.8 g.). The mixture was heated at 60° for 1.5 hr. and then poured into ice-water containing HCl. After removal of chlorobenzene by steam distillation, the residual solid was collected and extracted with benzene. The benzene extract was evaporated to dryness and the residue was recrystallized from EtOH–H_2O (1:2) to pale yellow needles (3 g., 25%), m.p. 96~97°.

1-Acetyl-2,3-dimethoxynaphthalene (II)——A mixture of I (2 g.), Me_2SO_4 (2 ml.), K_2CO_3 (6 g.), and acetone (30 ml.) was refluxed for 3 hr. After removal of K_2CO_3 by filtration, the filtrate was evaporated to a small volume and H_2O was added. The separated oil was extracted with ether, the ether extract was washed with H_2O, and dried over Na_2SO_4. Ether was evaporated and the residue was distilled under a reduced pressure to give a pale yellow oil (1.7 g., 80%), b.p_4 175°. *Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 71.86; H, 6.17. IR ν_{max}^{film} cm^{-1}: 1690 (C=O).

2-Methyl-8-hydroxy-5,6-benzochromone (III)——To a stirred suspension of NaH (0.5 g.) in dry ether (30 ml.), a mixture of II (1.3 g.) and AcOEt (5 g.) was aaded slowly at 0°. The mixture was stirred at 0° for 30 min., at room temperature for 1 hr., and then refluxed for 1 hr. After evaporation of ether, the viscous residue was heated on a boiling water bath for 1 hr., left to stand overnight at room temperature, and then poured into ice-water (200 g.) containing AcOH (8 ml.). The separated oil was extracted with ether, the ether extract was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue showed a deep red color with ethanolic $FeCl_3$, but could not be crystallized. This was mixed with Ac_2O (5 ml.) and HI (sp. gr. 1.7; 5 ml.) was added dropwise under cooling. The mixture was boiled for 2 hr. and then poured into a cold aq. solution of 2% $NaHSO_3$. The resulting precipitate was collected, washed with H_2O, and slurried with aq. 2% KOH. The slurry was filtered and the solid was washed with H_2O.

The filtrate was acidified, the separated precipitate was collected, washed with H_2O, and recrystallized from EtOH to pale brown needles (0.3 g.), m.p. 298°. *Anal.* Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.13; H, 4.63. IR ν_{max}^{KBr} cm^{-1}: 1640 (C=O).

The solid insoluble in aq. 2% KOH was recrystallized from EtOH to pale yellow plates (0.2 g.), m.p. 214°, which was found to be identical with IV on admixture and comparison of their IR spectra.

2-Methyl-8-methoxy-5,6-benzochromone (IV)——To a suspension of III (25 mg.) in MeOH (1 ml.), an ether solution of CH_2N_2 (prepared from 1 g. of N-methyl-N-nitrosourea) was added. After standing the mixture for 2 days, the solvent was evaporated together with excess CH_2N_2, and the residue was recrystallized from EtOH to pale yellow plates, m.p. 214°. *Anal.* Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.79; H, 5.08. IR ν_{max}^{KBr} cm^{-1}: 1650 (C=O).

1,3-Dimethoxynaphthalene——This compound (4 g., 77%) was obtained as a pale yellow viscous oil, b.p_2 141~142°, by refluxing a mixture of 1,3-naphthalenediol (4.8 g.), Me_2SO_4 (6 ml.), K_2CO_3 (16 g.), and acetone (40 ml.) for 3 hr. The picrate crystallized from EtOH in brown-red needles, m.p. 141°.[11]

1-Acetyl-2,4-dimethoxynaphthalene (VI)——A mixture of 1,3-dimethoxynaphthalene (4 g.), Ac_2O (2.4 ml.), and I_2 (80 mg.) was heated at 100~110° for 3 hr., and then poured into cold H_2O. The separated solid was collected, washed with H_2O, and dried. Recrystallization of the product, once from ether and twice from EtOH–H_2O (7:3), gave colorless needles (3 g., 63%), m.p. 117~118°. *Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.00; H, 6.13. IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O).

1-Acetoacetyl-2,4-dimethoxynaphthalene (VII)——To a stirred suspension of NaH (0.35 g.) in dry ether (30 ml.), VI (0.6 g.) and then AcOEt (2.4 g.) were added with cooling. The mixture was refluxed for 2 hr. under stirring and the only ether was evaporated. The residual mixture was heated on a boiling water bath for 2 hr. with stirring, left to stand overnight at room temperature, and then poured into a mixture of AcOH (8 ml.), H_2O (100 ml.), and ice (100 g.). The separated solid was collected, washed with H_2O, and dried. Recrystallization from ether gave pale yellow prisms (0.5 g., 71%), m.p. 85°, whose ethanolic solution showed a deep red color with $FeCl_3$. *Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.61; H, 5.88.

1-Acetyl-4-methoxy-2-naphthol (VIII)——A solution of VI (2.8 g.) in benzene (100 ml.) was mixed with an ether-benzene solution of MgI_2,[5] prepared from I_2 (6 g.), Mg (1.2 g.), ether (40 ml.), and benzene (20 ml.), and the mixture was refluxed for 3 hr. When cooled, the mixture was treated with 0.5*N* HCl and then extracted with ether. The ether extract was washed with aq. 1% $NaHSO_3$ and H_2O, and dried over Na_2SO_4. Removal of the solvent and recrystallization of the residue from dil. EtOH gave colorless needles (2.3 g., 87%), m.p. 57°, whose ethanolic solution colored greenish brown with $FeCl_3$. *Anal.* Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.40; H, 5.78. IR ν_{max}^{KBr} cm^{-1}: 1628 (C=O).

1-Acetoacetyl-4-methoxy-2-naphthol (IX)——A solution of VIII (1.2 g.) in AcOEt (6 g.) was treated with a suspension of NaH (0.8 g.) in ether (20 ml.) by the same manner as described for III. The reaction mixture was poured into ice-water (200 g.) containing AcOH (10 ml.), the separated precipitate was collected, washed with H_2O, and ether. Recrystallization of the solid insoluble in ether, from EtOH gave

11) N. P. Buu-Hoï, D. Lavit: J. Org. Chem., **21**, 1022 (1956); R. Heck, S. Winstein: J. Am. Chem. Soc., **79**, 3105 (1957).

colorless prisms (0.6 g., 40%), m.p. 189°, whose ethanolic solution showed a greenish brown color with $FeCl_3$. *Anal.* Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.81; H, 5.64. IR ν_{max}^{KBr} cm^{-1}: 3300 (O-H), 1636 (C=O).

2-Methyl-7-methoxy-5,6-benzochromone (X)——a) A mixture of IX (1.2 g.), AcOH (10 ml.), and conc. HCl (1 drop) was boiled for 3 mim. and the mixture was diluted with H_2O (100 ml.). The separated solid was collected, washed with H_2O, and dried. Two recrystallizations from EtOH gave colorless needles (1 g., 90%), m.p. 206°. *Anal.* Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.75; H, 5.02. IR ν_{max}^{KBr} cm^{-1}: 1652 (C=O).

b) A solution of VII (1.7 g.) in benzene (60 ml.) was mixed with an ether solution of MgI_2 prepared from I_2 (3.1 g.), Mg (0.6 g.), and ether (25 ml.), and the mixture was refluxed for 3 hr. When cooled, the mixture was treated with 0.5*N* HCl and extracted with ether. The ether extract was washed with aq. 2% KOH and H_2O, and dried over Na_2SO_4. Removal of the solvent and recrystallization of the residue from EtOH gave colorless needles (0.2 g.), m.p. 206°.

Acidification of the aq. 2% KOH washings with AcOH gave recovered VII (1 g.).

The substances obtained by these two methods were proved to be identical with each other by a mixed fusion and comparison of their IR spectra.

2-Methyl-7-hydroxy-5,6-benzochromone (V)——To a suspension of X (0.7 g.) in benzene (20 ml.), an ether solution of MgI_2, prepared from I_2 (1.5 g.) and Mg (0.3 g.) in ether (10 ml.), was added. The mixture was refluxed for 3 min. and the solvent was evaporated under a reduced pressure below 130°. The resulting red solid was heated at 160~165° for 1.5 hr. and cooled. After pulverization, the reaction product was decomposed with dil. H_2SO_4. The precipitate formed was collected, washed with H_2O, aq. dil. $NaHSO_3$, and H_2O, and slurried with aq. 2% KOH, the slurry was filtered, and X (0.1 g.) was recovered. The portion soluble in 2% KOH was acidified with AcOH, the separated solid was collected, washed with H_2O, and dried. Two recrystallizations from EtOH gave colorless needles (0.5 g., 76%), m.p. 301°. *Anal.* Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.23; H, 4.50. IR ν_{max}^{KBr} cm^{-1}: 3100~2400 (O-H), 1643 (C=O).

3-Methoxy-1,2-naphthalenediol (XI)——3-Methoxy-1,2-naphthoquinone, m.p. 185°, prepared from 3-methoxy-2-naphthol (1.7 g.) and $NO(SO_3K)_2$ (6.5 g.) by the method of Teuber and Götz,[6] was suspended in H_2O (60 ml.). To this suspension, $Na_2S_2O_4$ (2 g.) was added and the mixture was shaken for several minutes. After decolorization, the suspended crystals were collected, washed with H_2O, and dried. Three crystallizations from CCl_4 gave colorless needles (1.5 g., 80%), m.p. 136°. *Anal.* Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.42; H, 5.24. IR ν_{max}^{KBr} cm^{-1}: 3540, 3400 (O-H), 1645, 1610 (m., C=C).

1,2,3-Trimethoxynaphthalene (XII)——A mixture of XI (6 g.), Me_2SO_4 (6.4 ml.), acetone (120 ml.), and K_2CO_3 (17 g.) was refluxed for 3 hr. with stirring, and then filtered. The filtrate was evaporated to a small volume and the residue was dissolved in ether. The ether solution was washed with aq. 2% KOH and H_2O, and dried over Na_2SO_4. After evaporation of the solvent, the residue was distilled under a reduced pressure to give a pale yellow viscous oil (5 g., 95%), $b.p_2$ 146°. *Anal.* Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.39; H, 6.46. IR ν_{max}^{film} cm^{-1}: 2930 (C-H).

1-Acetyl-3,4-dimethoxy-2-naphthol (XIII)——A mixture of XII (5 g.), Ac_2O (3 ml.), and I_2 (100 mg.) was heated at 145~150° for 3 hr., and then poured into ice-water. The separated oil was extracted with ether, the ether extract was washed with aq. dil. $NaHSO_3$ and H_2O, and dried over Na_2SO_4. After evaporation of the solvent, the residue was distilled to give a pale yellow viscous oil (3 g.), $b.p_2$ 160~170°, which could not be obtained in a pure state by redistillation. IR ν_{max}^{film} cm^{-1}: 2930 (C-H), 1685 (C=O).

This product (2.8 g.) was dissolved in benzene (100 ml.) and the solution was mixed with an ether solution of MgI_2 prepared from Mg (1.2 g.), I_2 (6 g.), and ether (40 ml.). The mixture was refluxed for 3 hr., cooled, and then poured into a mixture of ice and 0.5*N* HCl. The separated oil was extracted with ether, the ether extract was washed with H_2O, and then shaken with aq. 2% KOH. The aqueous layer was acidified, extracted with ether, the ether extract was washed with H_2O, and dried over Na_2SO_4. After removal of the solvent, the residue was distilled under a reduced pressure to give a faintly reddish viscous oil (1.5 g.), $b.p_2$ 171~172°, which showed a dark violet color with $FeCl_3$ in EtOH solution. *Anal.* Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.00; H, 5.62. IR ν_{max}^{film} cm^{-1}: 3450 (O-H), 2935 (C-H), 1670 (weak).

The portion insoluble in aq. 2% KOH gave a small amount of pale yellow viscous oil, which was identified as XII by the IR spectrum.

2-Methyl-7,8-dimethoxy-5,6-benzochromone (XIV)——a) A mixture of XIII (1 g.) and AcOEt (5 g.) was treated with NaH (0.7 g.) in ether (20 ml.) by the same method as described for III.

The product was a yellow viscous oil and could not be purified. The crude product (0.8 g.) was dissolved in AcOH (10 ml.) and conc. HCl (1 drop) was added. After boiling for 3 min., the mixture was poured into H_2O and the separated oil was extracted with ether. The ether extract was washed with aq. 2% KOH and H_2O, and dried over Na_2SO_4. Removal of the solvent and recrystallization of the

residue from EtOH-H_2O (1:1) gave colorless plates (0.2 g.), m.p. 119°. *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.20; H, 5.32. IR ν_{max}^{KBr} cm^{-1}: 2930 (C-H), 1657 (C=O).

b) To a cold solution of XVIII (0.6 g.) in AcCl (10 ml.), 70% $HClO_4$ (8 drop) was added slowly under cooling. The solution colored a deep red and crystals separated out. After standing at room temperature for 3 days, the mixture was poured on ice (50 g.) and the separated solid was extracted with ether. The ether extract was washed with dil. Na_2CO_3 solution and H_2O, and dried over Na_2SO_4. Removal of the solvent and recrystallization of the residue from EtOH-H_2O (1:1) gave colorless plates (0.4 g., 72%), m.p. 119°, which was identified with the product obtained by the above method (a), by a mixed fusion and comparison of their IR spectra.

3,4-Dimethoxy-2-naphthamide (XV)——A mixture of 3,4-dimethoxy-2-naphthoic acid (22 g.), $SOCl_2$ (25 ml.), and dry ether (30 ml.) was refluxed for 3 hr., and excess $SOCl_2$ was distilled off together with ether under a reduced pressure. The residue was dissolved in benzene (25 ml.) and $(NH_4)_2CO_3$ (20 g.) was added to the solution with stirring under cooling. After standing at room temperature under stirring for 2 hr., the mixture was heated on a boiling water bath to evaporate $(NH_4)_2CO_3$ and benzene. The residue was treated with H_2O and then extracted with ether. The ether extract was washed with dil. $KHCO_3$ solution and H_2O, and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from MeOH containing H_2O to colorless needles (10 g., 48%), m.p. 110°. *Anal.* Calcd. for $C_{13}H_{13}O_3N$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.60; H, 5.67; N, 6.33. IR ν_{max}^{KBr} cm^{-1}: 3500, 3400 (N-H), 2930 (C-H), 1672, 1645 (C=O).

3-Amino-1,2-dimethoxynaphthalene (XVI)——A solution of XV (9.2 g.) in MeOH (40 ml.) was added in one portion to a stirred solution of NaOCl, prepared from NaOH (11 g.), H_2O (70 ml.), ice (40 g.), and Cl_2 (generated from 28 g. of $KMnO_4$ and 20 ml. of conc. HCl). The mixture was warmed slowly with stirring and the temperature was kept at 70° for 1 hr. Then a solution of KOH (16 g.) in H_2O (16 ml.) was added to the mixture, the temperature of the mixture was rised to 80°, and maintained at 80° for 1 hr. under stirring. When cooled, the mixture was extracted with ether and the ether extract was shaken with *N* HCl. The HCl layer was washed with ether, basified with dil. NH_4OH, and the separated oil was extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness. Recrystallization of the residue from petr. benzin (b.p. 70~80°) gave colorless prisms (6 g., 75%), m.p. 76°. *Anal.* Calcd. for $C_{12}H_{13}O_2N$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.66; H, 6.37; N, 6.83. IR ν_{max}^{KBr} cm^{-1}: 3500, 3400 (N-H), 2930 (C-H), 1626 (v. s.).

3,4-Dimethoxy-2-naphthol (XVII)——XVI (5 g.) was dissolved in dil. H_2SO_4 (250 ml. of H_2O and 5 ml. of conc. H_2SO_4) by warming. To this solution, 2*N* $NaNO_2$ (12.5 ml.) was added slowly with cooling to below 5°. This diazotized solution was slowly added to a boiling solution of conc. H_2SO_4 (7.5 ml.) in H_2O (500 ml.). When cooled, the reaction mixture was extracted with ether, the ether extract was washed with H_2O, and shaken with *N* KOH. The KOH layer was acidified with AcOH and then extracted with ether. The ether extract was washed with dil. $NaHCO_3$ solution and H_2O, and dried over Na_2SO_4. Removal of the solvent and distillation of the residue under a reduced pressure gave a faintly reddish viscous oil (1.2 g., 22%), b.p_2 141°. This product showed a negative test with $FeCl_3$ and an intense blue color with phosphomolybdic acid and NH_4OH in EtOH solution. *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.62; H, 6.03.

3-(3,4-Dimethoxy-2-naphthoyloxy)crotonic Acid (XVIII)——To a refluxing solution of XVII (1 g.) in MeCOEt (20 ml.) containing K_2CO_3 (5 g.), a solution of ethyl 3-chlorocrotonate (1.5 g.) in MeCOEt (10 ml.) was added dropwise with stirring over a period of 3 hr. The mixture was refluxed with stirring for 8 hr. and then filtered to remove an inorganic substance. The filtrate was evaporated under a reduced pressure, the residue was boiled with 2*N* NaOH (30 ml.) and MeOH (50 ml.) for 2 hr., and MeOH was distilled off under a reduced pressure. The residual solution was acidified with *N* HCl and the separated solid was extracted with ether. The ether extract was shaken with dil. $NaHCO_3$ and dil. Na_2CO_3 solution. The portion soluble in dil. Na_2CO_3 solution was acidified, the separated solid was collected, washed with H_2O, and dried. Recrystallization from EtOH-H_2O (1:1) gave colorless needles (1 g., 71%), m.p. 124°. This compound was insoluble in aq. dil. $NaHCO_3$ and soluble in aq. dil Na_2CO_3. *Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.90; H, 5.59. IR ν_{max}^{KBr} cm^{-1}: 3200~2400 (O-H), 2930 (C-H), 1865 (C=O).

2-Methyl-7,8-dihydroxy-5,6-benzochromone (XIX)——A solution of XIV (0.3 g.) in benzene (5 ml.) was mixed with an ether solution of MgI_2, prepared from I_2 (2 g.) and Mg (0.4 g.) in ether (10 ml.), and the mixture was evaporated to dryness under a reduced pressure below 130°, and the residue was heated for 2 hr. in an oil bath (160~165°). When cooled, the residue was pulverized and decomposed with a mixture of dil. HCl and ice. The resulting precipitate was extracted with a large amount of ether. The ether extract was washed with 1% $NaHSO_3$, dil. $NaHCO_3$ and H_2O, and dried over Na_2SO_4. Removal of the solvent and two recrystallizations of the residue from EtOH gave colorless needles, m.p. 285° (decomp.), which colored a pale yellow by drying. An ethanolic solution of this product colored greenish brown, immediately changing to yellow, with $FeCl_3$. *Anal.* Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.43; H, 4.14. IR ν_{max}^{KBr} cm^{-1}: 3400 (O-H), 1644 (weak).

2-Methyl-7,8-diacetoxy-5,6-benzochromone (XX)——a) A mixture of XIX (50 mg.), Ac_2O (2 ml.), and pyridine (1 drop) was left to stand overnight and poured into ice-water. The separated precipitate was collected, washed with H_2O, and dried. Two recrystallizations from MeOH gave colorless needles, m.p. 214°. *Anal.* Calcd. for $C_{18}H_{14}O_6$: C, 66.25; H, 4.32. Found: C, 66.30; H, 4.25. IR ν_{max}^{KBr} cm^{-1}: 1780 (O-C=O), 1654 (C=O).

b) To a solution of III (200 mg.) in H_2O (30 ml.) containing KOH (0.3 g.) and pyridine (6 ml.), a solution of $K_2S_2O_8$ (0.3 g.) in H_2O (6 ml.) was added dropwise at 0° with stirring. After standing overnight in a refrigerator, the mixture was acidified with dil. HCl to Congo-Red, filtered to remove the resulting precipitate, and the filtrate was shaken with ether. The aqueous layer was heated with conc. HCl (1 ml.) on a boiling water bath for 10 min., cooled, and extracted with ether. The ether extract was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was suspended in Ac_2O (1 ml.) and pyridine (1 drop) was added. After standing overnight at room temperature, the mixture was poured into ice-water, the separated precipitate was collected, washed with H_2O, and dried. Recrystallization from MeOH gave colorless needles, m.p. 214°.

c) V (200 mg.) was oxidized with $K_2S_2O_8$ (0.3 g.) by the same method as in (b). The product was acetylated and recrystallization from MeOH gave colorless needles, m.p. 214°.

The substances obtained by these three methods were proved to be identical with each other by mixed fusion and comparison of their IR spectra.

2-Methyl-3-acetyl-8-acetoxy-5,6-benzochromone (XXI)——A mixture of I (0.5 g.), Ac_2O (3 ml.), and AcONa (1 g.) was heated in an oil bath (maintained at 180°) for 8 hr. When cooled, the mixture was poured into ice-water, the separated solid was collected, washed with H_2O, and dried. Two recrystallizations from EtOH gave yellow needles (0.5 g., 65%), m.p. 173°. *Anal.* Calcd. for $C_{18}H_{14}O_5$: C, 69.67; H, 4.55. Found: C, 69.49; H, 4.48. IR ν_{max}^{KBr} cm^{-1}: 1770 (O-C=O), 1690, 1642 (C=O).

2-Methyl-3-acetyl-8-hydroxy-5,6-benzochromone (XXIV)——A solution of XXI (0.3 g.) dissolved in conc. H_2SO_4 (2 ml.) was left to stand for 5 min. at room temperature and then poured into ice-water. The separated solid was collected, washed with H_2O, and dried. Two recrystallizations from EtOH-H_2O (1:1) gave colorless needles (0.2 g., 56%), m.p. 207°. *Anal.* Calcd. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.54; H, 4.46. IR ν_{max}^{KBr} cm^{-1}: 3400, 3200 (O-H), 1690 (C=O).

2-Methyl-3-acetyl-8-methoxy-5,6-benzochromone (XXV)——To a suspension of XXIV (100 mg.) in MeOH (1 ml.), an ether solution (20 ml.) of CH_2N_2 (prepared from 2 g. of N-methyl-N-nitrosourea) was added. After standing at room temperature for 1 day, the mixture was evaporated to remove excess of CH_2N_2 and ether, and the residue was recrystallized from HtOH to colorless needles, m.p. 209°. *Anal.* Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.64; H, 5.05. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O), 1637.

2-Methyl-3-acetyl-7-methoxy-5,6-benzochromone (XXII)——A mixture of VIII (100 mg.), Ac_2O (1 ml.), and AcONa (0.5 g.) was heated in an oil bath (180°) for 8 hr. When cooled, the mixture was poured into ice-water and the separated oil was extracted with ether. The ether extract was washed with dil. $NaHCO_3$ solution and H_2O, and dried over Na_2SO_4. Removal of the solvent and recrystallization of the residue from MeOH gave colorless needles (50 mg.), m.p. 171°. *Anal.* Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.10; H, 4.96. IR ν_{max}^{KBr} cm^{-1}: 1690, 1680 (C=O).

2-Methyl-3-acetyl-7,8-dimethoxy-5,6-benzochromone (XXIII)——A mixture of XIII (200 mg.), Ac_2O (2 ml.), and AcONa (0.7 g.) was heated in an oil bath (180°) for 8 hr. When cooled, the mixture was poured into cold H_2O and the separated oil was extracted with ether. The ether extract was washed with dil. $NaHCO_3$ solution and H_2O, and dried over Na_2SO_4. Removal of the solvent gave a pale yellow oil, IR ν_{max}^{film} cm^{-1}: 2935 (C-H), 1770 (O-C=O), 1685 (C=O), which could not be crystallized and was assumed to be 1-acetyl-2-acetoxy-3,4-dimethoxynaphthalene. This product was heated with Ac_2O (2 ml.) and AcONa (0.7 g.) in an oil bath (185~200°) for 8 hr. and then treated in the same manner as above. When the product was treated with a small amount of cold MeOH, crystals separated out and recrystallization of which from EtOH-H_2O (1:1) gave pale yellow needles (30 mg.), m.p. 134°. *Anal.* Calcd. for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 68.86; H, 5.12. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O), 1635.

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Summary

Syntheses of hydroxyl derivatives of 2-methyl-5,6-benzochromone were investigated, and following benzochromone derivatives were obtained together with related

compounds, and physical and chemical properties of these chromones were characterized: 2-Methyl-8-methoxy-5, 6-benzochromone (Ⅳ), 2-methyl-7-methoxy-5,6-benzochromone (X), 2-methyl-7,8-dimethoxy-5,6-benzochromone (XIV), 2-methyl-3-acetyl-8-methoxy-5,6-benzochromone (XXV), 2-methyl-3-acetyl-7-methoxy-5,6-benzochromone (XXII), and 2-methyl-3-acetyl-7,8-dimethoxy-5,6-benzochromone (XXIII).

Hydroxylation of 2-methyl-8-hydroxy-5,6-benzochromone (Ⅲ) or 2-methyl-7-hydroxy-5,6-benzochromone (V) gave 2-methyl-7,8-dihydroxy-5,6-benzochromone (XX) from both.

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22. Hidetaka Yuki, Fumihiko Sano, Shin-ichi Takama, and Seikichi Suzuki: Studies on Antiviral Agents. I. Relationship between Chemical Reactivity of Sulfhydryl Reagents and Their Inactivating Activity of Adenovirus Type 5.

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For a number of viral diseases, only three antiviral chemotherapeutic agents are available at present; iodouracil deoxyriboside (IUDR)[1,2] for herpes simplex virus, N,N′-anhydrobis(2-hydroxyethyl)biguanide (ABOB)[3] for influenza virus, and N-methyl isatine β-thiosemicarbazone[4,5] for pox viruses. As viral diseases are increasing in frequency and virulency, various kinds of works have been carried out hoping an appearance of effective agent.

Several workers reported that sulfhydryl reagents could inactivate the various viruses, suggesting one of the directions towards the investigation of the antiviral agents. As typical sulfhydryl reagents, *p*-chloromercuribenzoic acid (PCMB) and other organo-mercuric compounds have mostly been studied, and it was found that these reagents inactivate streptococcal bacteriophage,[6] enteroviruses[7] and many others.[8,9]

Buckland[10] reported that PCMB inactivated hemagglutinating activity of various viruses, and Allison and co-workers[9] found that PCMB and iodoacetamide could reduce the virus infectivity of the thirty-six viruses including adenovirus type 5.

Considerable part of human respiratory and eye diseases is caused by adenoviruses, but little work has been known on the study of chemotherapeutic agents against these viruses.

In order to approach towards the investigation of the antiviral agents, a relationship between chemical reactivities of sulfhydryl reagents and their inactivating activities against adenovirus type 5 was examined. These results are reported below.

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