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45. Seigo Fukushima, Akira Ueno, and Yukio Akahori: Studies on Benzochromones. VI.*1 Syntheses and Ring Isomerization of 2-Methyl-5-methoxy-6,7-benzochromone and 2-Methyl-5-methoxy-7,8-benzochromone.

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In the preceding paper,*1 the synthesis of 2-methyl-5,8-dimethoxy-6,7-benzochromone and the ring isomerization during the demethylation were described. The present paper deals with syntheses of 2-methyl-5-methoxy-6,7-benzochromone (Ⅷ) and 2-methyl-5-methoxy-7,8-benzochromone (Ⅳ) and the ring isomerization of the former compound.

2-Methyl-5-methoxy-6,7-benzochromone (Ⅷ) corresponds to a compound in which the furan ring of visnagin (X) is replaced by a benzenoid ring, and synthesis of Ⅷ has attracted considerable interest concerning its physiological activity and its behavior in the demethylation process, but an attempt[1] upon the synthesis was made without success.

Ethyl 2-(phenylacetyl)acetoacetate was converted to 2-acetyl-1,3-naphthalenediol (Ⅰ) by means of the modified method of Ogata, *et al.*,[2] and methylation of Ⅰ with dimethyl sulfate gave 2-acetyl-1,3-dimethoxynaphthalene (Ⅱ). Condensation of Ⅱ with ethyl acetate using sodium hydride led to a diketone (Ⅱ′), which showed deep red color with ferric chloride reagent but could not be obtained as a crystalline state. The crude product of Ⅱ′ was subjected to cyclization reaction in the presence of acetic anhydride and hydriodic acid, and there was obtained yellow plates, $C_{14}H_{10}O_3$, m.p. 188°, which showed stable green color with ferric chloride reagent. This compound was considered to have a structure of either 2-methyl-5-hydroxy-7,8-benzochromone (Ⅲ) or 2-methyl-5-hydroxy-6,7-benzochromone (Ⅸ). The ultraviolet spectrum of this chromone showed λ_{max}^{EtOH} mμ (log ε): 224 (4.67), 265 (4.51), 375 (3.36), and that of its methyl ether showed λ_{max}^{EtOH} mμ (log ε): 223 (4.57), 258 (4.56), 355 (3.44). They bear close relation to those of angular type benzochromone, as will be discussed in detail in another paper.[3] Thus this chromone can be formulated as 7,8-benzochromone (Ⅲ).

Methylation of Ⅲ with diazomethane or dimethyl sulfate gave 2-methyl-5-methoxy-7,8-benzochromone (Ⅳ), $C_{15}H_{12}O_3$, m.p. 193°, and alkali degradation of Ⅳ afforded 2-acetyl-3-methoxy-1-naphthol (Ⅴ), $C_{13}H_{12}O_3$, m.p. 116°, IR $\nu_{C=O}$: 1628 cm^{-1}.

Methylation of Ⅰ with equimolar dimethyl sulfate produced monomethyl ether (Ⅵ), $C_{13}H_{12}O_3$, m.p. 86~87°, IR $\nu_{C=O}$: 1642 cm^{-1}, which did not agree with the only possible isomer Ⅴ, and carbonyl frequency in infrared spectrum of Ⅵ is higher than that of Ⅴ by 14 cm^{-1}.

According to Hunsberger,[4] carbonyl frequency in infrared spectrum of 2-acetyl-3-naphthol is higher than those of 2-acetyl-1-naphthol and 1-acetyl-2-naphthol by 20 cm^{-1}, and this frequency shift is attributed to the weaker double bond character of the 2:3-double bond due to bond fixation.

It is therefore concluded that the structure of the said monomethyl ether is 1-methoxy-2-acetyl-3-naphthol (Ⅵ), and that Ⅴ has a structure of 2-acetyl-3-methoxy-1-naphthol.

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*1 Part Ⅴ: This Bulletin, **12**, 307 (1964).

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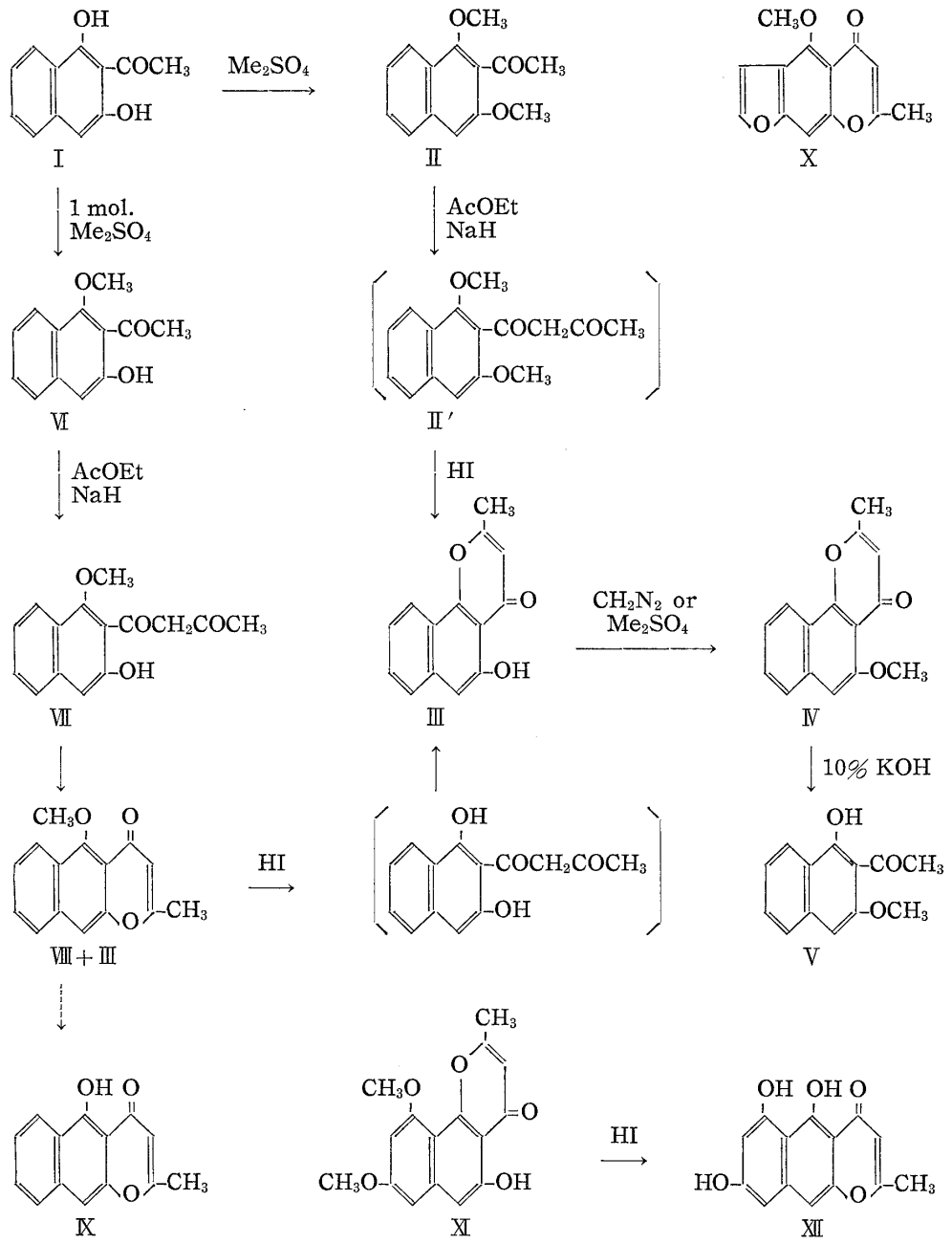
1) S. Wawzoneck, *et al.*: J. Org. Chem., **17**, 1419 (1952).
2) A. Ogata, *et al.*: Yakugaku Zasshi, **59**, 105 (1939).
3) S. Fukusima, Y. Akahori, A. Ueno: This Bulletin, **12**, 316 (1964).
4) I.M. Hunsberger: J. Am. Chem. Soc., **72**, 5626 (1950).



This observation affords another unambiguous evidence of the angular structure of III and IV.

Condensation of VI with ethyl acetate by the action of sodium hydride led to a crystalline diketone (VII), $C_{15}H_{14}O_4$, m.p. 117°. When the diketone (VII) in acetic acid with a few drops of hydrochloric acid was boiled for a few minutes, the main product was proved to be 2-methyl-5-methoxy-6,7-benzochromone (VIII), $C_{15}H_{12}O_3$, m.p. 137°, because of disagreement with the only possible isomer IV, and as a side product, a small amount of III was isolated from the alkali-soluble fraction.

Meanwhile, when the diketone (VII) in acetic acid with sodium acetate was heated for several hours, the main product was confirmed to be III, and VIII was also obtained, but in poor yield, from the alkali-insoluble fraction of the reaction products.

The ultraviolet spectrum of VIII, λ_{max}^{EtOH} mμ(log ε) : 218 (4.29), 248 (4.80), 293 (3.51), 304 (3.68), 316 (3.56), 366 (3.69), bears close relation to those of linear benzochromone.[3]

Demethylation of Ⅷ with hydriodic acid led to Ⅲ showing that the ring isomerization took place in this process.

These facts demonstrate that angular structures are more stable than linear structures in these benzochromones.

In this connection, it is very interesting to note that natural occuring benzochromone derivative, flavasperone (Ⅺ)[5] (angular type) undergoes ring isomerization to form nor-rubrofusarin (Ⅻ) (linear benzochromone) during demethylation with hydriodic acid.

Experimental*3

2-Acetyl-1,3-naphthalenediol (I)——Ethyl 2-(phenylacetyl)acetoacetate, prepared from phenylacetyl chloride and ethyl acetoacetate by the method of Viscontini and Merckling,[6] was converted to the Cu-salt, and by the modified method of Ogata, *et al.*,[2] the Cu-salt was added at 0° to a mixture of AcOH (20 ml.), Ac_2O (10 ml.) and conc. H_2SO_4 (100 ml.). The resulting mixture was kept under occasional shaking for 24 hr. at 25°, and then poured into ice-H_2O (1.5 L.). The precipitate was collected, washed with H_2O and dried. Recrystallization from benzene or aq. EtOH gave yellow needles, m.p. 136°. Yield, 0.9 g. *Anal.* Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.19; H, 5.17. IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1620 (C=O).

2-Acetyl-1,3-dimethoxynaphthalene (II)——A mixture of I (3 g.), Me_2CO (50 ml.), K_2CO_3 (8.8 g.) and Me_2SO_4 (4.4 g.) was refluxed until it gave negative $FeCl_3$ reaction. The mixture was filtered, and the filtrate was concentrated to a small volume and H_2O was added. The separated oil was extracted with Et_2O and the Et_2O-extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated. The residue was distilled under reduced pressure to yield a pale yellow oil, $b.p_2$ 160~161°, which solidified on cooling. Two recrystallization from petr. ether gave colorless prisms, m.p. 55°. Yield, 2 g. *Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.16; H, 6.13. IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O).

2-Methyl-5-hydroxy-7,8-benzochromone (III)——To a stirred suspension of NaH (0.8 g.) in dry Et_2O (30 ml.), a mixture of Ⅱ (1.5 g.) and AcOEt (6 g.) was slowly added at 0°. The mixture was stirred at 0° for 30 min., then at room temperature for 1 hr., and was refluxed for 1 hr. on a water bath. After removal of Et_2O, the viscous residue was heated on a boiling water bath for 1 hr., left to stand overnight at room temperature and then added to an ice-H_2O (200 g.) containing AcOH (8 ml.). The separated viscous oil was washed with H_2O and extracted with Et_2O. On removal of Et_2O, a yellow viscous oil was obtained, which showed a deep red color with alcoholic $FeCl_3$ but could not be crystallized. This was mixed with Ac_2O (5 ml.), and HI (sp. gr. 1.7; 5 ml.) was slowly added under cooling. The mixture was boiled for 8 hr., then poured into a cold solution of 2% $NaHSO_3$. The separated crystals were collected, washed with H_2O and recrystallized twice from EtOH to give 0.7 g. of yellow plates, m.p. 188°. It showed a blue color with alcoholic $FeCl_3$. *Anal.* Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.33; H, 4.71. IR ν_{max}^{KBr} cm^{-1}: 1673 (C=O).

2-Methyl-5-methoxy-6,7-benzochromone (IV)——a) Ⅲ (0.5 g.) suspended in a mixture of MeOH (20 ml.) and Et_2O (20 ml.) was treated with an Et_2O solution of CH_2N_2 (prepared from 5 g. of N-methyl-N-nitrosourea) and the mixture was allowed to stand for 4 days at room temperature. An additional Et_2O solution of CH_2N_2 (prepared from 3 g. of N-methyl-N-nitrosourea) was then added to the reaction mixture, which was left to stand for 2 days at room temperature. The residue obtained by evaporation of excess of CH_2N_2 and Et_2O was treated with a small amount of Et_2O. The insoluble material was collected and recrystallized from benzene to yield 0.3 g. of colorless prisms, m.p. 193°. *Anal.* Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.05. Found: C, 74.72; H, 4.99. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O).

b) A mixture of Ⅲ (0.9 g.), Me_2SO_4 (1 ml.), K_2CO_3 (3 g.) and Me_2CO (40 ml.) was refluxed for 8 hr. on a water bath, then Me_2SO_4 (0.5 ml.) and K_2CO_3 (1 g.) were added. The mixture was refluxed for further 8 hr. and treated by the usual method. The brown crystals separated by addition of H_2O were dissolved in $CHCl_3$. The $CHCl_3$-solution was passed through a column of Al_2O_3, the eluate was evavorated to dryness, and the residue was recrystallized twice from 50% EtOH to form colorless prisms, m.p. 193°. Yield, 0.4 g. The two substances obtained by these methods a) and b) were proved to be identical with each others by admixture and agreement of their IR spectra.

2-Acetyl-3-methoxy-1-naphthol (V)——A mixture or Ⅵ (200 mg.) and 10% KOH (4 ml.) was boiled for 1 hr. The resulting orange solution was filtered, cooled and then acidified with 10% HCl. The separated crystals were collected, washed with H_2O and recrystallized twice from aq. EtOH to give yellow

*3 All melting points are uncorrected.

5) B. W. Bycroft, *et al.*: J. Chem. Soc., **1962**, 40.
6) M. Viscontini, N. Merckling: Helv. Chim. Acta, **35**, 2280 (1952).

needles, m.p. 116°. Yield, 100 mg. It showed a green color with alcoholic $FeCl_3$. *Anal.* Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found : C, 72.19; H, 5.81. IR ν_{max}^{KBr} cm^{-1} : 1628 (C=O).

1-Methoxy-2-acetyl-3-naphthol (VI)——A mixture of I (3 g.), Me_2SO_4 (2 g.), K_2CO_3 (4 g.), and Me_2CO (30 ml.) was refluxed for 6 hr. on a water bath and filtered. The filtrate was evaporated to a small volume under reduced pressure, and H_2O (150 ml.) was added. The separated crystals were extracted with Et_2O and Et_2O extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to dryness. Two recrystallization of the residue from MeOH gave yellow prisms, m.p. 86~87°. Yield, 1.6 g. Its EtOH-solution showed a green color with $FeCl_3$. *Anal.* Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found : 72.49; H, 5.82. IR ν_{max}^{KBr} cm^{-1} : 1642 (C=O).

2-Acetoacetyl-3-methoxy-1-naphthol (VII)——To a stirred suspension of NaH (2.7 g.) in dry Et_2O (50 ml.), a mixture of VI (4 g.), AcOEt (20 g.) and dry Et_2O (10 ml.) was slowly added at 0° and the reaction mixture was treated in the same manner as described above. Yellow crystals were separated when the reaction mixture was poured into a mixture of ice (400 g.) and AcOH (30 ml.). Two recrystallization from Et_2O gave 2.4 g. of yellow prisms. m.p. 117°. *Anal.* Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found : C, 69.84; H, 5.52. IR ν_{max}^{KBr} cm^{-1} : 3450 (OH), 1670 (C=O).

2-Methyl-5-methoxy-6,7-benzochromone (VIII)——a) A mixture of VII (1.2 g.), AcOH (6 ml.) and conc. HCl (1 drop) was boiled for 3 min. and H_2O (30 ml.) was then added. After cooling the mixture, the separated crystals were collected, washed with H_2O and dried. Yield, 1.1 g. Two recrystallization from Me_2CO-petr. benzin gave 600 mg. of VIII as colorless prisms, m.p. 137°, which showed a negative test with alcoholic $FeCl_3$. *Anal.* Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found : C, 74.62; H, 5.05. IR ν_{max}^{KBr} cm^{-1} : 1658 (C=O). The mother liquor of the recrystallization was evaporated to dryness and the residue was dissolved in Et_2O. The Et_2O-solution was shaken with 5% KOH and the aq. layer was acidified with 10% HCl, and the separated crystals were recrystallized from EtOH to give 8 mg. of yellow needles, m.p. 188°, which was identified with III.

b) A mixture of VII (1.2 g.), AcONa (4 g.) and AcOH (20 ml.) was boiled for 6 hr. and cooled. H_2O was added to the reaction mixture, and the separated crystals were collected, washed with H_2O and dried. Yield, 1 g. Two recrystallization from EtOH yielded 0.5 g. of III as yellow needles, m.p. 188°. The mother liquor was evaporated to dryness and the residue dissolved in Et_2O was shaken with 5% KOH to remove phenolic compound, then washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was recrystallized twice from Me_2CO-petr. benzin to yield 200 mg. of VIII as colorless needles, m.p. 137°. Both III and VIII, obtained by these methods were proved to be identical with their authentic samples by the mixed fusion and comparison of their IR spectra.

Action of Hydriodic Acid on 2-Methyl-5-methoxy-6,7-benzochromone (VIII)——To a cold mixture of VIII (200 mg.) and Ac_2O (3 ml.), HI (sp. gr. 1.7; 3 ml.) was added dropwise and the reaction mixture was boiled for 30 min., then poured into ice-H_2O containing a small amount of $NaHSO_3$. The separated crystals were collected, washed with H_2O and recrystallized twice from EtOH to give 135 mg. of III as yellow needles, m.p. 188°, which was identified with an authentic sample of III on an admixture and by comparison of the IR spectra.

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Summary

2-Methyl-5-methoxy-6,7-benzochromone (VIII), and 2-methyl-5-methoxy-7,8-benzochromone (IV) were synthesized from 2-acetylnaphthalene-1,3-diol (I), and it was found that VIII underwent irreversible ring isomerization to form 2-methyl-5-hydroxy-7,8-benzochromone (III) during demethylation with hydriodic acid.

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