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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 attempt¹⁾ 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, C₁₄H₁₀O₃, 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 (X). The ultraviolet spectrum of this chromone showed $\lambda_{\max}^{\text{EtOH}}$ m μ (log ϵ): 224 (4.67), 265 (4.51), 375 (3.36), and that of its methyl ether showed $\lambda_{\max}^{\text{EtOH}}$ m μ (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), C₁₅H₁₂O₃, m.p. 193°, and alkali degradation of IV afforded 2-acetyl-3-methoxy-1-naphthol (V), C₁₃H₁₂O₃, m.p. 116°, IR $\nu_{\text{C=O}}$: 1628 cm⁻¹.

Methylation of I with equimolar dimethyl sulfate produced monomethyl ether (VI), C₁₃H₁₂O₃, m.p. 86~87°, IR $\nu_{\text{C=O}}$: 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.

*¹ Part V: This Bulletin, 12, 307 (1964).*² Oshika Shizuoka (福島清吾, 上野 明, 赤堀幸男).1) S. Wawzoneck, *et al.*: J. Org. Chem., 17, 1419 (1952).2) A. Ogata, *et al.*: Yakugaku Zasshi, 59, 105 (1939).

3) S. Fukushima, 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), $C_{16}H_{12}O_3$, 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, $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (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 occurring 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.), Ac₂O (10 ml.) and conc. H₂SO₄ (100 ml.). The resulting mixture was kept under occasional shaking for 24 hr. at 25°, and then poured into ice-H₂O (1.5 L.). The precipitate was collected, washed with H₂O and dried. Recrystallization from benzene or aq. EtOH gave yellow needles, m.p. 136°. Yield, 0.9 g. *Anal.* Calcd. for C₁₂H₁₀O₃: C, 71.28; H, 4.99. Found: C, 71.19; H, 5.17. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3360 (OH), 1620 (C=O).

2-Acetyl-1,3-dimethoxynaphthalene (II)—A mixture of I (3 g.), Me₂CO (50 ml.), K₂CO₃ (8.8 g.) and Me₂SO₄ (4.4 g.) was refluxed until it gave negative FeCl₃ reaction. The mixture was filtered, and the filtrate was concentrated to a small volume and H₂O was added. The separated oil was extracted with Et₂O and the Et₂O-extract was washed with H₂O, dried over anhyd. Na₂SO₄ 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 C₁₄H₁₄O₃: C, 73.02; H, 6.13. Found: C, 73.16; H, 6.13. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1700 (C=O).

2-Methyl-5-hydroxy-7,8-benzochromone (III)—To a stirred suspension of NaH (0.8 g.) in dry Et₂O (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 Et₂O, 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-H₂O (200 g.) containing AcOH (8 ml.). The separated viscous oil was washed with H₂O and extracted with Et₂O. On removal of Et₂O, a yellow viscous oil was obtained, which showed a deep red color with alcoholic FeCl₃ but could not be crystallized. This was mixed with Ac₂O (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% NaHSO₃. The separated crystals were collected, washed with H₂O and recrystallized twice from EtOH to give 0.7 g. of yellow plates, m.p. 188°. It showed a blue color with alcoholic FeCl₃. *Anal.* Calcd. for C₁₄H₁₀O₃: C, 74.33; H, 4.46. Found: C, 74.33; H, 4.71. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 Et₂O (20 ml.) was treated with an Et₂O solution of CH₂N₂ (prepared from 5 g. of N-methyl-N-nitrosourea) and the mixture was allowed to stand for 4 days at room temperature. An additional Et₂O solution of CH₂N₂ (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 CH₂N₂ and Et₂O was treated with a small amount of Et₂O. The insoluble material was collected and recrystallized from benzene to yield 0.3 g. of colorless prisms, m.p. 193°. *Anal.* Calcd. for C₁₅H₁₂O₃: C, 74.99; H, 5.05. Found: C, 74.72; H, 4.99. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1670 (C=O).

b) A mixture of III (0.9 g.), Me₂SO₄ (1 ml.), K₂CO₃ (3 g.) and Me₂CO (40 ml.) was refluxed for 8 hr. on a water bath, then Me₂SO₄ (0.5 ml.) and K₂CO₃ (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 H₂O were dissolved in CHCl₃. The CHCl₃-solution was passed through a column of Al₂O₃, the eluate was evaporated 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 of 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 H₂O 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 $\text{C}_{13}\text{H}_{12}\text{O}_3$: C, 72.21; H, 5.59. Found: C, 72.19; H, 5.81. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 $\text{C}_{13}\text{H}_{12}\text{O}_3$: C, 72.21; H, 5.59. Found: C, 72.49; H, 5.82. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 $\text{C}_{15}\text{H}_{14}\text{O}_4$: C, 69.75; H, 5.46. Found: C, 69.84; H, 5.52. IR $\nu_{\text{max}}^{\text{KBr}}$ 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. benzine gave 600 mg. of VIII as colorless prisms, m.p. 137°, which showed a negative test with alcoholic FeCl_3 . *Anal.* Calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_3$: C, 74.99; H, 5.03. Found: C, 74.62; H, 5.05. IR $\nu_{\text{max}}^{\text{KBr}}$ 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. benzine 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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