UDC 547.816.07

173. Seigo Fukushima: Studies on Benzochromones. II.*2 Synthesis of 2-Methyl-3-acetyl-5,6-dimethoxy-7,8-benzochromone.

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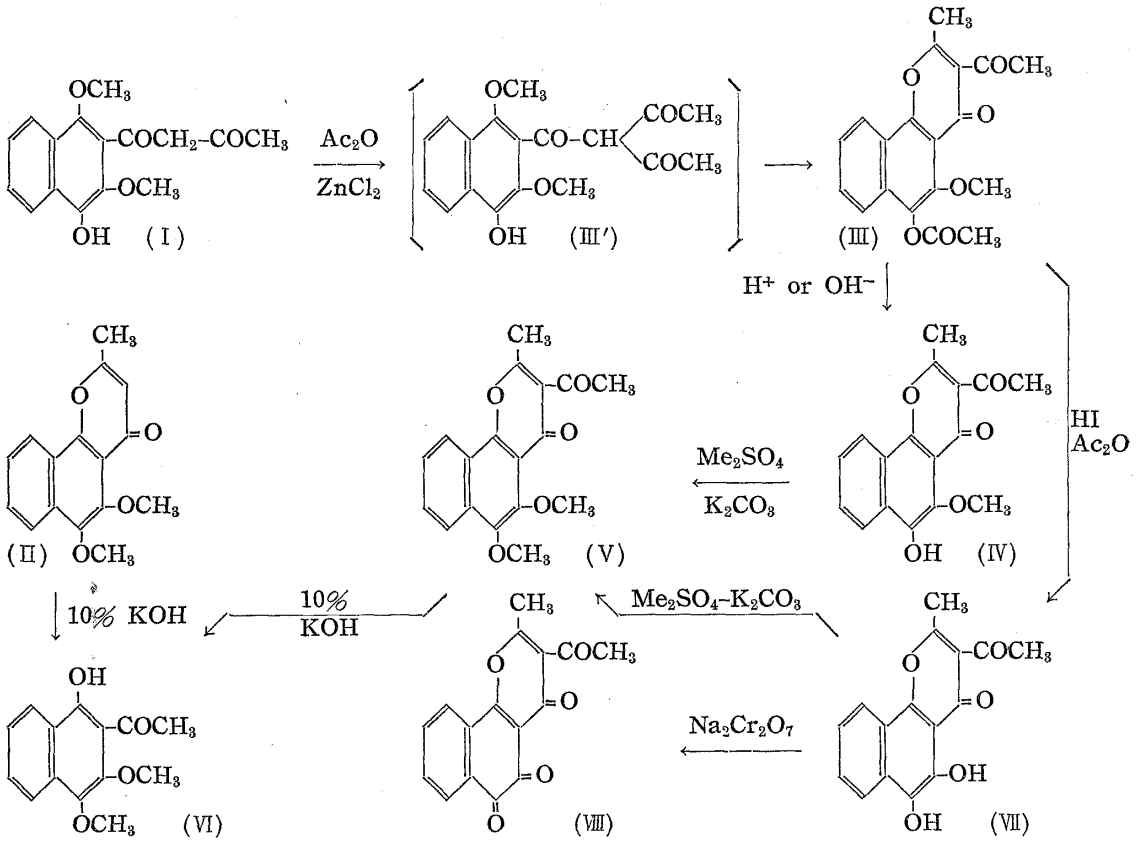
In the preceding paper,[*2] several methods for formation of 2-methyl-5,6-dimethoxy-7,8-benzochromone (II) were reported. The present paper deals with syntheses of 2-methyl-3-acetyl-5,6-dimethoxy-7,8-benzochromone (V) and related reactions.



Heating of the mixture of 1,3-dimethoxy-2-acetoacetyl-4-hydroxynaphthalene (I), zinc chloride, and acetic anhydride on a water bath for several minutes produced colorless needles (III), m.p. 158°, whose analytical values agreed with $C_{19}H_{16}O_6$. Infrared spectrum of this substance showed the absence of hydroxyl group and the presence of acetoxyl group. Assay of methoxyl group proved (III) had one methoxyl group. Hydrolysis of (III) with either alcoholic potassium hydroxide or sulfuric acid gave pale yellow needles (IV) of m.p. 217°, whose infrared spectrum exhibited the presence of a free hydroxyl group (3555 cm^{-1}). (IV) could easily be converted to a dimethyl ether (V) with dimethyl sulfate and potassium carbonate, and (V) exhibited an intensive red color with 5% sodium nitroferricyanide and 30% sodium hydroxide. This fact suggested the presence of a methyl ketone group.[1] Alkali degradation of (V) afforded yellow prisms (VI) of m.p. 51°, whose analytical values agreed with $C_{14}H_{14}O_4$ and the assay of methoxyl group proved the presence of two methoxyl groups. Infrared spectrum of (VI) showed the carbonyl absorption at 1616 cm^{-1} and

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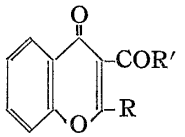
*2 Part I: This Bulletin, 8, 1028(1960).
1) F. Feigl: "Spot Tests in Organic Analysis," 223(1956).

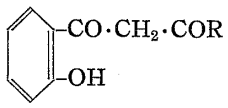
the substance was confirmed to be identical with the alkali degradation product of 2-methyl-5,6-dimethoxy-7,8-benzochromone(II) by admixture and infrared spectral determination. These facts indicate that (VI) must be 2-acetyl-3,4-demethoxy-1-naphthol and, consequently, the methyl ketone group of (V) cannot be other than in 3-position of the chromone ring. Therefore, (V) must be 2-methyl-3-acetyl-5,6-dimethoxy-7,8-benzochromone, and (IV) is 2-methyl-3-acetyl-5-methoxy-6-hydroxy-7,8-benzochromone and (III) is 2-methyl-3-acetyl-5-methoxy-6-acetoxy-7,8-benzochromone.

Demethylation of (III) with hydriodic acid and acetic anhydride gave 2-methyl-3-acetyl-5,6-dihydroxy-6,7-benzochromone (VII), which could be converted to the dimethyl ether (V) with dimethyl sulfate and was oxidized to a brick-red quinone (VIII). The color of (VIII) is consistent with its *ortho*-quinone structure.

Generally, 3-acyl-2-alkyl- or -aryl-chromones (IX : R=R' alkyl or aryl) are obtained by reaction of *o*-hydroxyacetophenone with the anhydride and sodium salt of an aliphatic or aromatic acid, and these chromones are similarly formed from 1,3-diketones[2] (X : R alkyl or aryl).



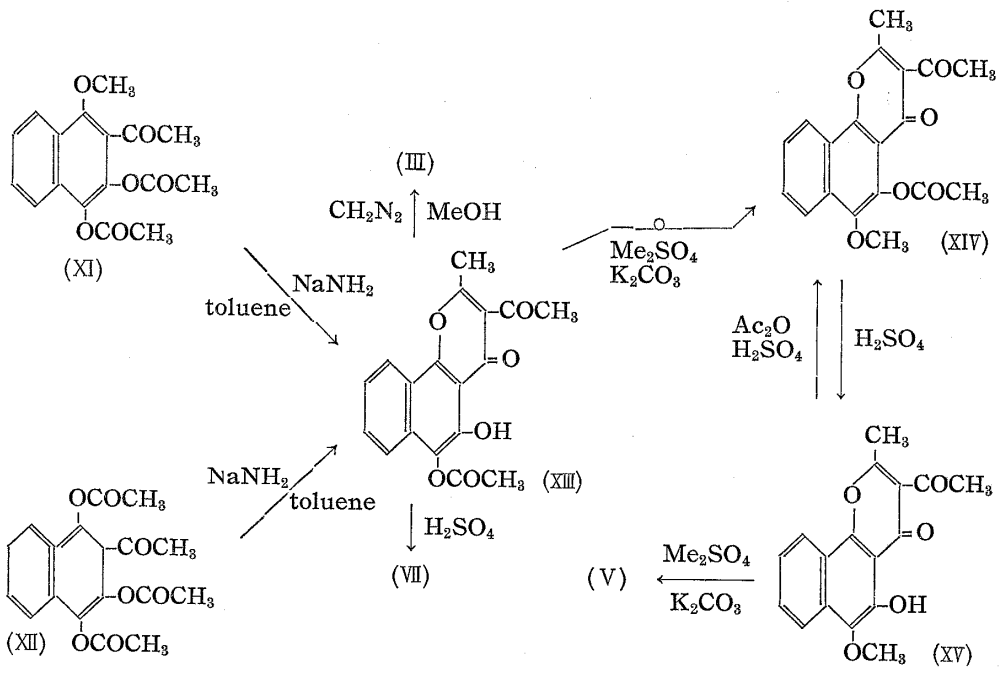
(IX)



(X)

It seems that zinc chloride has not been used as a catalyst, but the mechanism of this reaction might also involve hypothetical intermediate of a triacylmethane (III').

When 1-methoxy-2-acetyl-3,4-diacetoxynaphthalene (XI) and equimolar sodium amide were heated in toluene at 160~180°, yellow needles (XIII) of m.p. 205° were obtained in a poor yield, and 1,3,4-triacetoxy-2-acetylnaphthalene (XII) also gave the same substance (XIII) by a similar procedure. Ethanol solution of (XIII) showed intensive blue-green color with ferric chloride reagent. Infrared spectrum of (XIII) exhibits a broad and weak hydroxyl band from 3400 to 2500 cm^{-1} which can be attributed to the presence of chelated hydroxyl group and a carbonyl band at 1764 cm^{-1} due to phenyl acetate.



2) W. Baker, *et al.* : J. Chem. Soc., **1933**, 1381; **1949**, 2142; **1950**, 2759; **1950**, 1294.

Treatment of (XIII) with cold sulfuric acid gave 2-methyl-3-acetyl-5,6-dihydroxy-7,8-benzochromone (VII). A suspension of (XIII) in benzene did not react with ether solution of diazomethane, but it began to react on addition of excess methanol[3] and afforded 2-methyl-3-acetyl-5-methoxy-6-acetoxy-7,8-benzochromone (III), though in a very poor yield.

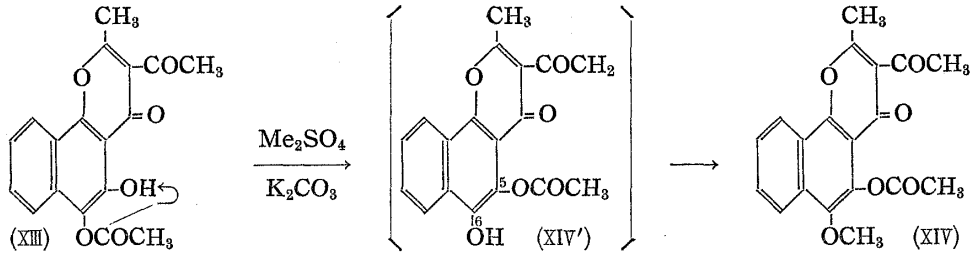
All of these facts apparently indicate that (XIII) is 2-methyl-3-acetyl-5-hydroxy-6-acetoxy-7,8-benzochromone, but methylation of (XIII) with dimethyl sulfate and potassium carbonate in acetone did not produce the expected 2-methyl-3-acetyl-5-methoxy-6-acetoxy-7,8-benzochromone (III). In its stead colorless microneedles of m.p. 156° (XIV) were produced whose analytical values agreed with $C_{19}H_{16}O_6$, and its melting point showed depression in admixture with 2-methyl-3-acetyl-5-methoxy-6-acetoxy-7,8-benzochromone (III). The infrared and ultraviolet spectra of (XIV) are very similar to those of (III).

Treatment of (XIV) with cold sulfuric acid gave yellow needles (XV) of m.p. 147°, $C_{17}H_{14}O_5$, ethanol solution of which showed intensive green color with ferric chloride reagent. Infrared spectrum of (XV) exhibits a broad and weak hydroxyl absorption band at 3400~2600 cm^{-1} due to the presence of chelated hydroxyl group. These facts suggest that the hydroxyl group of (XV) is in a position capable of forming a chelated ring system with carbonyl group. Acetylation with acetic anhydride and a trace of sulfuric acid converted (XV) back to (XIV).

Methylation*[3] of (XV) with dimethyl sulfate and potassium carbonate in acetone produced 2-methyl-3-acetyl-5,6-dimethoxy-7,8-benzochromone (V).

All of these facts indicate that (XV) is 2-methyl-3-acetyl-5-hydroxy-6-methoxy-7,8-benzochromone and (XIV) is 2-methyl-3-acetyl-5-acetoxy-6-methoxy-7,8-benzochromone. (XIV) corresponds to an isomer of (III) in which the positions of acetoxyl group and methoxyl group are in reverse.

In order to explain such a novel reaction as formation of (XIV) from (XIII) with dimethyl sulfate and potassium carbonate, it is necessary to assume that the acetyl migration from 6- to 5-position might occur prior to the methylation of hydroxyl group.



Such a facile migration of acetyl group has been observed in steroids,[4] but probably not in the aromatic system. Any attempt to prove such acetyl migration more directly, for example, by separation of an intermediate, 2-methyl-3-acetyl-5-acetoxy-6-hydroxy-7,8-benzochromone (XIV'), has not yet been successful.

Considering that the number of carbon in 1-methoxy-2-acetyl-3,4-diacetoxynaphthalene (XI), $C_{17}H_{16}O_6$, is one less than that in 2-methyl-3-acetyl-5-hydroxy-6-acetoxy-7,8-benzochromone (XIII), $C_{18}H_{14}O_6$, it is evident that complicated intermolecular rearrangement of acetyl group participates in the reaction from (XI) to (XIII).

The result of investigations on the mechanism of the reaction from (XII) to (XIII) will be reported later.

*[3] It took much longer to methylate (XV) than (IV). This fact is another support to the assumption that the hydroxyl group in (XV) is at 5-position.

3) A. Schönberg, *et al.*: J. Chem. Soc., **1946**, 746.

4) V. A. Petrow, *et al.*: *Ibid.*, **1943**, 135.

Experimental*4

2-Methyl-3-acetyl-5-methoxy-6-acetoxy-7,8-benzochromone (III)—a) A mixture of 1.0 g. of 1,3-dimethoxy-2-acetoacetyl-4-hydroxynaphthalene (I), 1 g. of $ZnCl_2$, and 15 cc. of Ac_2O was heated for 4 min. on a boiling water bath. Resulting red-brown solution was cooled and excess of water was added to afford somewhat resinous red-brown solid. The solid was collected, washed with water, a small amount of ice cold Et_2O, and Me_2CO, and recrystallized three times from hydr. Me_2CO to produce 0.22 g. (19%) of almost colorless needles, m.p. 158°. *Anal.* Calcd. for $C_{19}H_{16}O_6$: C, 67.05; H, 4.75; CH_3O, 9.12. Found: C, 66.79; H, 4.97; CH_3O, 9.28. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1768 (phenolic acetate) 1689, 1642 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 254 (4.57), 305 (3.84), 342 (3.53), 354 (3.53).

b) To a suspension of 0.5 g. of 2-methyl-3-acetyl-5-hydroxy-6-acetoxy-7,8-benzochromone (XIII) in 30 cc. of dehyd. benzene, an Et_2O solution of CH_2N_2, prepared from 1.5 g. of N-methyl-N-nitrosourea, and 20 cc. of MeOH were added. The mixture, after standing at room temperature for 4 hr., was evaporated in vacuum to a red-brown resinous oil, which was recrystallized twice from hydr. Me_2CO. Resulting yellow solid was purified over alumina in $CHCl_3$ and recrystallized twice from hydr. Me_2CO to afford 0.03 g. (6%) of (III), m.p. 156°.

2-Methyl-3-acetyl-5-methoxy-6-hydroxy-7,8-benzochromone (IV)—a) To a solution of 0.2 g. of (III) in 5 cc. of EtOH, 1 cc. of 30% KOH was added and the reaction mixture was warmed to 60° on a water bath. After cool, it was acidified with 10% HCl, diluted with H_2O, and the separated red-brown precipitate was collected. The solid was washed with H_2O, dried, and its $CHCl_3$ solution was purified with alumina. Recrystallization from EtOH gave 0.04 g. (23%) of pale yellow needles, m.p. 217°. Its dilute EtOH solution showed a red-brown color with $FeCl_3$. *Anal.* Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.72; CH_3O, 10.40. Found: C, 68.23; H, 5.15; CH_3O, 10.71. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3555 (free OH), 1688, 1643 (C=O).

b) To 0.1 g. of (III), 2.0 g. of ice-cold H_2SO_4 was added and the resulting intensive red solution was allowed to stand for 10 min. and poured into ice-water. Separated precipitate was recrystallized twice from EtOH to afford 0.06 g. (68%) of (IV).

2-Methyl-3-acetyl-5,6-dimethoxy-7,8-benzochromone (V)—a) A mixture of 0.2 g. of (IV), 0.2 g. of Me_2SO_4, 1.0 g. of K_2CO_3, and 10 cc. of Me_2CO was refluxed for 1 hr. on a water bath. After removal of K_2CO_3, Me_2CO was evaporated in vacuum to a small volume and 20 cc. of H_2O was added. Separated solid was recrystallized twice from hydr. EtOH to afford 0.15 g. (72%) of colorless needles, m.p. 151°. *Anal.* Calcd. for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16; CH_3O, 19.84. Found: C, 69.11; H, 4.95; CH_3O, 19.90.

b) A mixture of 0.2 g. of 2-methyl-3-acetyl-5,6-dihydroxy-7,8-benzochromone (VII), 0.3 g. of Me_2SO_4, 1.5 g. of K_2CO_3, and 20 cc. of Me_2CO was refluxed for 12 hr. on a water bath. Treatment of the reaction mixture as above gave 0.08 g. (36%) of (V).

c) A mixture of 0.1 g. of 2-methyl-3-acetyl-5-hydroxy-6-methoxy-7,8-benzochromone (XV), 0.1 g. of Me_2SO_4, 0.4 g. of K_2CO_3, and 5 cc. of Me_2CO was refluxed for 8 hr. on a water bath. After treating the reaction mixture as above, the substance was purified over alumina in $CHCl_3$ and recrystallized twice from hydr. EtOH to 0.03 g. (29%) of (V).

2-Acetyl-3,4-dimethoxy-1-naphthol (VI)—a) A mixture of 0.2 g. of (V) and 4 cc. of 10% KOH solution was boiled slightly for 30 min. in an oil bath, the resulting red-brown mixture was filtered, and the filtrate was acidified with 10% HCl. The separated yellow oil solidified on cooling and scratching, the yellow solid was treated with petr. ether (b.p. 40~60°), and insoluble substance was removed. Petr. ether was evaporated to dryness and the residue was recrystallized twice from MeOH to afford 0.05 g. of yellow prisms, m.p. 51°. *Anal.* Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73; CH_3O, 25.21. Found: C, 67.93; H, 5.35; CH_3O, 24.96. IR $\nu_{max}^{CHCl_3}$: 1616 cm^{-1} (C=O).

b) From a mixture of 0.2 g. of 2-methyl-5,6-dimethoxy-7,8-benzochromone*2 (II) and 4 cc. of 10% KOH solution, 0.06 g. of (V) was obtained by the same procedure as above.

2-Methyl-3-acetyl-5,6-dihydroxy-7,8-benzochromone (VII)—a) To a suspension of 0.2 g. of (III) in 3 cc. of ice-cold Ac_2O, 3 cc. of 70% HI was added cautiously with shaking after each addition, the mixture was kept for 10 min. at room temperature, and heated at 110~118° for 30 min. in an oil bath. After cool, the mixture was poured into crushed ice containing Na_2SO_3, the separated precipitate was collected, washed with H_2O, and dried. Two recrystallizations from EtOH gave 0.13 g. (78%) of yellow needles, m.p. 226°. *Anal.* Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.15; H, 4.58.

b) Intensive red solution of 0.1 g. of 2-methyl-3-acetyl-5-hydroxy-6-acetoxy-7,8-benzochromone (XIII) dissolved in 2.0 g. of ice-cold H_2SO_4 was kept at room temperature for 10 min. and poured into ice-water. Separated yellow solid was treated as above and 0.06 g. (63%) of (VII) was obtained.

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*4 In all cases two or three different methods of preparation of the same compound are reported. Admixture of samples produced no depression of m. p.

2-Methyl-3-acetyl-4*H*-naphtho[1,2-*b*]pyran-4,5,6-trione (VIII)—A mixture of 0.3 g. of (VII), 6 cc. of AcOH, 1.2 cc. of 30% H_2SO_4, and 2.4 cc. of 30% $Na_2Cr_2O_7$ solution was shaken vigorously for 30 min. Resulting solid was collected, washed with H_2O, and dried. Two recrystallizations from AcOH afforded 0.12 g. of brick-red prisms, m.p. 229° (decomp.). *Anal.* Calcd. for $C_{16}H_{10}O_5$: C, 68.08; H, 3.57. Found: C, 68.10; H, 3.78.

1,3,4-Triacetoxy-2-acetylnaphthalene (XII)—A mixture of 1.0 g. of 2-acetyl-3,4-diacetoxy-1-naphthol,*2 30 mg. of AcONa, and 20 cc. of Ac_2O was heated for about 4 min. on a water bath. The solid that separated on addition of H_2O was recrystallized twice from EtOH to produce 0.7 g. (62%) of almost colorless prisms, m.p. 135°. *Anal.* Calcd. for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68. Found: C, 62.23; H, 4.93. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1777 (phenolic acetate C=O), 1697 (C=O).

2-Methyl-3-acetyl-5-hydroxy-6-acetoxy-7,8-benzochromone (XIII)—a) A mixture of 0.894 g. of 1-methoxy-2-acetyl-3,4-diacetoxynaphthalene,*2 0.109 g. of powdered $NaNH_2$, and 9 cc. of dehyd. toluene was heated in an oil bath at 160~180° for about 10 min., forming dark brown precipitate. After cool, 20 cc. of H_2O was added and the toluene layer was separated. Aqueous layer was washed several times with Et_2O and Et_2O washings were added to the toluene layer. From the toluene-Et_2O layer, yellow needles separated in several hours and collected needles were recrystallized twice from EtOH to afford 0.143 g. (16%) of yellow needles, m.p. 205° (measured in a bath which was previously heated to 180°). Dilute EtOH solution of it showed an intense blue-green color with $FeCl_3$. *Anal.* Calcd. for $C_{18}H_{14}O_6$: C, 66.25; H, 4.32. Found: C, 65.91; H, 4.18. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400~2500 (chelated OH), 1764 (phenolic acetate, C=O), 1688, 1670 (C=O).

b) A mixture of 4.48 g. of (XII), 0.51 g. of powdered $NaNH_2$, and 36 cc. of dehyd. toluene was heated in an oil bath at 160~180° for about 10 min. to separate brown crystalline precipitate with vigorous foaming. After cooling for several min.*5 with running water, the precipitate was collected, washed several times with a small amount of Et_2O, and dissolved in H_2O. After insoluble yellow substance was removed, deep red solution was acidified with 10% HCl to produce a yellow-brown precipitate. The precipitate was collected, washed thoroughly with H_2O, and dried. Recrystallizations twice from EtOH produced yellow needles (XIII), m.p. 205°. The small amount of insoluble yellow substance also produced yellow needles (XIII), m.p. 205°, by recrystallization from EtOH. Overall yield, 1.27 g. (30%).

From toluene-Et_2O layer, yellow needles that separated in several hours were collected and recrystallized several times from EtOH to produce 0.83 g. of yellow needles, m.p. 182°. They were proved to be identical with 2-acetyl-3,4-diacetoxy-1-naphthol*2 by admixture and infrared spectral determination.

2-Methyl-3-acetyl-5-acetoxy-6-methoxy-7,8-benzochromone (XIV)—a) A mixture of 1.0 g. of (XIII), 1.0 g. of Me_2SO_4, 4.0 g. of K_2CO_3, and 40 cc. of Me_2CO was refluxed for 6 hr. on a water bath. After removal of K_2CO_3 the sotution was evaporated in vacuum to a small volume and 60 cc. of H_2O was added. Separated red-brown, somewhat resinous substance was collected, washed with H_2O and a small amount of ice-cold EtOH, and recrystallized several times from hydr. Me_2CO to afford 0.23 g. (22%) of colorless microneedles, m.p. 156°. *Anal.* Calcd. for $C_{19}H_{16}O_6$: C, 67.05; H, 4.75; CH_3O, 9.12. Found: C, 67.05; H, 5.11; CH_3O, 9.01. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (phenolic acetate, C=O), 1689, 1642 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 254 (4.54), 305 (3.83), 342 (3.63), 354 (3.62).

b) To an ice-cold solution of 0.1 g. of 2-methyl-3-acetyl-5-hydroxy-6-methoxy-7,8-benzochromone (XV) in 5 cc. of Ac_2O, one drop of H_2SO_4 was added, the mixture was allowed to stand for 20 min. at room temperature, and poured into ice-water. Separated solid was recrystallized twice from hydr. EtOH to give 0.06 g. (53%) of (XIV).

2-Methyl-3-acetyl-5-hydroxy-6-methoxy-7,8-benzochromone (XV)—Intensive red solution of 0.2 g. of (XIV) dissolved in 4.0 g. of ice-cold H_2SO_4 was allowed to stand for 10 min. at room temperature and poured into ice-water. Separated yellow precipitate was collected, washed with H_2O, and dried. Two recrystallizations from EtOH afforded 0.12 g. (68%) of yellow needles, m.p. 147°. *Anal.* Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.72; CH_3O, 10.40. Found: C, 68.61; H, 5.22; CH_3O, 10.46. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400~2600 (chelated OH), 1688, 1661 (C=O).

The author wishes to express his deep gratitude to Prof. Emeritus E. Ochiai and Prof. T. Okamoto of the University of Tokyo, and Dr. K. Yamaguchi, for their kind and helpful guidance, and to Dr. T. Kariyone, Director of this Institute, for his encouragement. He is also grateful to Mr. T. Oba for the infrared spectral determination, Mr. H. Yamada for his technical co-operation, and to Mr. T. Nakajima and Miss S. Nakamura, all of this Institute, for elementary analyses.

*5 If the mixture is cooled completely, 2-acetyl-3,4-diacetoxy-1-naphthol*2 begins to separate and disturbs further refining.

Summary

1,3-Dimethoxy-2-acetoacetyl-4-hydroxynaphthalene (I) was converted to 2-methyl-3-acetyl-5-methoxy-6-acetoxy-7,8-benzochromone (III) with zinc chloride and acetic anhydride. (III) was hydrolysed to 2-methyl-3-acetyl-5-methoxy-6-hydroxy-7,8-benzochromone (IV), then methylated to 2-methyl-3-acetyl-5,6-dimethoxy-7,8-benzochromone (V). Either 1-methoxy-2-acetyl-3,4-diacetoxynaphthalene (XI) or 1,3,4-triacetoxy-2-acetylnaphthalene (XII) was converted to 2-methyl-3-acetyl-5-hydroxy-6-acetoxy-7,8-benzochromone (XIII) by heating either at 160~180° with equimolar sodium amide in toluene. Methylation of (XIII) with diazomethane in the presence of excess of methanol produced the expected methyl ether, 2-methyl-3-acetyl-5-methoxy-6-acetoxy-7,8-benzochromone (III), but methylation of (XIII) with dimethyl sulfate and potassium carbonate in acetone unexpectedly afforded 2-methyl-3-acetyl-5-acetoxy-6-methoxy-7,8-benzochromone (XIV) which is an isomer of (III).

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174. **Takahiro Yabuuchi**: Studies on Thiophene Derivatives. VI.*1 Syntheses of 3-Amino-1,1-di(2-thienyl)-1-alkanols and -1-alkenes.

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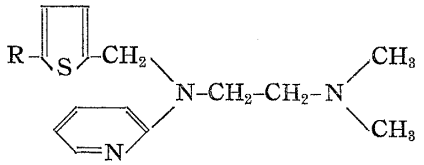
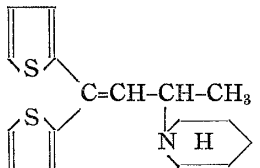
Some compounds are known to become more active on nervous system and, at the same time, with less untoward side-effect, by introduction of halogen atom into the structure of the compound. For example, Chlorothen (A), in which chlorine was introduced into 5-position of thiophene ring of N,N-dimethyl-N'-(2-pyridyl)-N-(2-thenyl)ethylenediamine (Methapyrilene) (B), has more potent antihistamine effect than (B) compound without too much side-effects.

In the preceding paper,[1,2] the author reported on antitussive activity of 3-piperidino-1,1-di(2-thienyl)-1-butene (C) and its optical isomers, and it was found that this compound shows more potent antitussive action than codeine, morphine, or Methadone.



(A) R=Cl (B) R=H



(C)

Therefore, an attempt was made to synthesize 3-piperidino-1,1-di(5-chloro-2-thienyl)-1-alkenes (D), which have chlorine in 5-position of the thiophene ring in (C). Their benzene analogs were also synthesized to compare their pharmacological action with (D).

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*1 This report constitutes a part of a series entitled "Studies on Thiophene Derivatives" by Ryuichi Kimura. Part V: This Bulletin, 8, 169(1960).

*2 Yoshida-konoe-cho, Sakyo-ku, Kyoto (藪内隆弘).

1) R. Kimura, T. Yabuuchi: This Bulletin, **7**, 171(1959).

2) *Idem*: *Ibid.*, **7**, 175(1959).