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225. Shoji Shibata, Eisaku Morishita, and Yasuo Arima*1 : Metabolic Products of Fungi. XXV.*2 Synthesis of Rubrofusarin and Its Derivatives.*3

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Rubrofusarin, a metabolic product of *Fusarium culmorum* Sacc. and its methyl ethers were synthesized by the Claisen condensation of 2-acetylnaphthalene derivatives (XIII, XV and XVIII), which were prepared starting from α-resorcylic acid. The structures of rubrofusarin monomethyl ether A and nor-rubrofusarin diacetate were established spectrometrically and synthetically.

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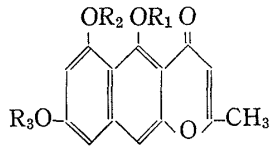
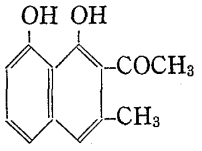
In 1937, Raistrick, *et al.*[1] isolated rubrofusarin, m.p. 210~211°, an orange red pigment from a plant pathogenic fungus, *Fusarium culmorum* (W.G. Smith) Sacc. The structure of this pigment was established as being 5,6-dihydroxy-8-methoxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-4-one (I) by Stout, *et al.*[2] by the X-ray crystallographical method, and at almost the same time by Tamura, *et al.*[3] by the chemical degradation.

Afterwards Roberts, *et al.*[4] proposed a structure (II) for rubrofusarin monomethyl ether A, m.p. 203~204°, which was prepared by methylation of rubrofusarin with diazomethane. This has been deduced by the anology of methylation of musizin (III) with diazomethane,[5] which contrary to usual expectation, methylates preferentially the hydrogen bonded hydroxyl adjacent to methylketone.

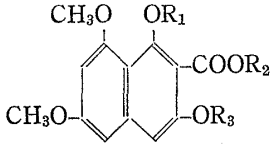


I : $R_1=R_2=H$, $R_3=CH_3$
II : $R_2=H$, $R_1=R_3=CH_3$



III

Chart 1.



IV : $R_1=R_3=H$, $R_2=C_2H_5$
V : $R_1=CH_3$, $R_2=C_2H_5$, $R_3=H$
VI : $R_1=R_3=CH_3$, $R_2=C_2H_5$
VII : $R_1=R_2=R_3=CH_3$

Chart 2.

In the present paper we report the synthesis of rubrofusarin and its methyl ethers. An attempt to condense ethyl 1,3-dihydroxy-6,8-dimethoxy-2-naphthoate (VI)[6] and its derivatives, V, VI and VII, with acetone by the Claisen reaction[7] was unsuccessful recovering the starting materials.

*1 Hongo, Bunkyo-ku, Tokyo (柴田承二, 森下顕策, 有馬康男).
*2 Part XXIV. J. Shoji, S. Shibata, U. Sankawa, H. Taguchi, Y. Shibanuma : This Bulletin, **13**, 1240(1965).
*3 Preliminary Report : S. Shibata, E. Morishita, Y. Arima : *Ibid.*, **11**, 821 (1963).

1) J.N. Ashley, B.C. Hobbs, H. Raistrick : Biochem. J., **31**, 385 (1937).
2) G.H. Stout, D.L. Dreyer, L.H. Jensen : Chem. & Ind.(London), 289(1961); Acta Cryst., **15**, 451(1962).
3) H. Tanaka, T. Tamura, Y. Ohne, N. Ogawa : Tetrahedron Letters, No. 4, 151 (1961); Agr. Biol. Chem., **27**, 48 (1963).
4) B.W. Bycroft, T.A. Dobson, J.C. Roberts : J. Chem. Soc., **1962**, 40.
5) C.J. Covell, F.E. King, J.W.W. Morgan : *Ibid.*, **1961**, 702.
6) A.J. Birch, F.W. Donovan : Austral. J. Chem., **8**, 529 (1955).
7) S. Wawzonek, H.A. Ready : J. Org. Chem., **17**, 1419 (1952).

The following process which involves 2-acetylnaphthalene as an intermediate for the synthesis of rubrofusarin has been studied. By the Arndt-Eistert reaction, 3,5-dimethoxybenzoic acid chloride (Ⅷ) was converted into 3,5-dimethoxyphenylacetic acid (X) whose chloride (Ⅺ) was reacted with ethyl acetoacetate by the Spassow[8] or Claisen condensation to afford ethyl 2-(3,5-dimethoxyphenylacetylacetoacetate (Ⅻ), which was characterized as the copper salt (m.p. 178~179°). On vacuum distillation,[9] Ⅻ was cyclized to afford 2-acetyl-6,8-dimethoxy-1,3-naphthalenediol (XIII), m.p. 193~194°, whereas by the action of polyphosphoric acid at 100°, for 5 min., Ⅻ or its copper salt yielded ethyl 3-hydroxy-6,8-dimethoxy-1-methyl-2-naphthoate (XIV), m.p. 130~131°.

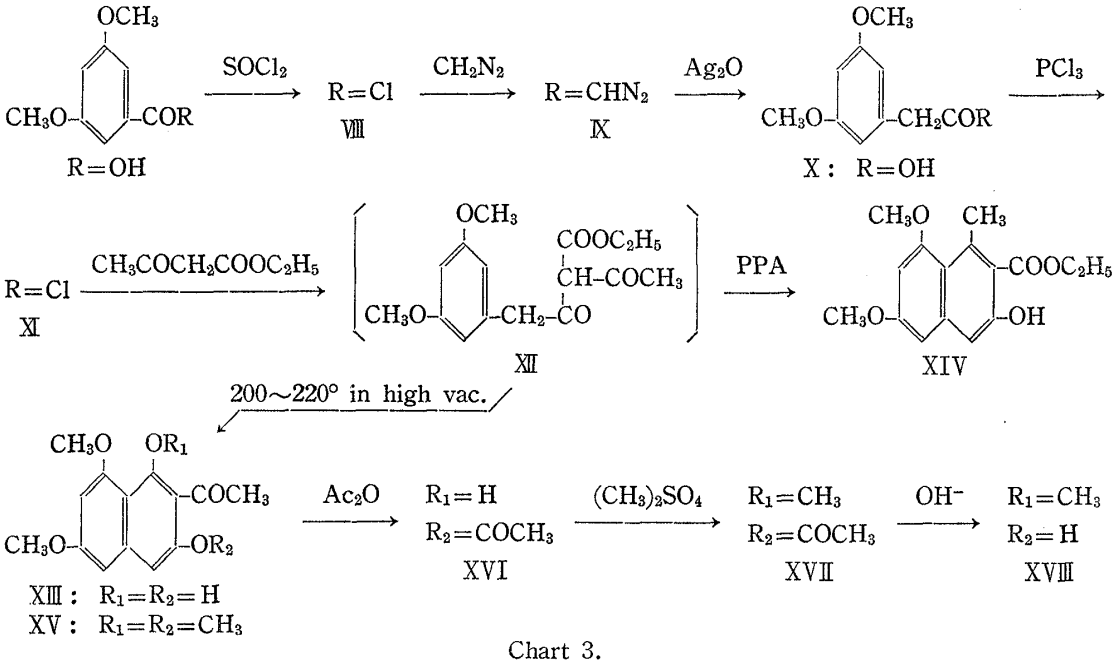


Chart 3.

The structures of XIII and XIV were proved by the ultraviolet (UV), infrared (IR) nuclear magnetic resonance (NMR) spectra whose data are given in the following table.

Table I.

	XIII	XIV
UV λ_{max}^{EtOH} mμ (log ε)	231(4.40), 278(4.66), 314(4.00), 326(3.98), 385(3.60)	245(4.64), 250(4.65), 295(3.67)
IR $\nu_{max}^{CHCl_3}$ cm^{-1}	3330(OH) 1645(C=O)	3260, 3560(OH) 1665, 1725(C=O)
NMR $\tau_{Me_4Si}^{CDCl_3}$: OH	−0.73(H), −2.80(H)	−0.55(H)
arom. H	3.46(H), 3.55(H, d, J=2 c.p.s.), 3.77(H, d, J=2 c.p.s.)	2.97(H), 3.44(H, d, J=2 c.p.s.), 3.62(H, d, J=2 c.p.s.)
-OCH$_2$CH$_3$		5.49(2H, q, J=5.6 c.p.s.)
arom. OCH$_3$	5.95(3H), 6.14(3H)	6.09(6H)
arom. CH$_3$		7.06(3H)
COCH$_3$	7.25(3H)	
-OCH$_2$CH$_3$		8.57(3H, t, J=5.6 c.p.s.)

Partial acetylation of XIII with acetic anhydride and anhydrous sodium acetate gave 3-acetoxy-2-acetyl-6,8-dimethoxy-1-naphthol (XVI) which was converted into XVIII on meth-

8) M. Viscontini, H. Köhler: Helv. Chim. Acta, **37**, 41 (1954).
9) F. H. Howell, D. A. H. Taylor: J. Chem. Soc., **1956**, 4252.

ylation, and XVIII by subsequent deacetylation. By the Claisen reaction, 2-acetyl-naphthalene derivatives (XIII), (XV) and (XVIII) with ethyl acetate afforded the corresponding 2-acetoacetylnaphthalene derivatives which were cyclized by the action of conc. HCl in methanol or HI in acetic anhydride to form XIX, XX, and XXI, respectively. The compound (XX) was proved to be identical with nor-rubrofusarin, m.p. 298~299° (decomp.) and XXI was identified as rubrofusarin dimethyl ether, m.p. 186~187°, by the comparison with the authentic specimens. By the comparison of the IR spectra and thin-layer chromatograms as well as by the mixed fusion, the product (XIX) was proved to be identical with rubrofusarin monomethyl ether B, m.p. 213°, which was yielded by the partial methylation of rubrofusarin (I) with dimethyl sulfate in acetone. This result showed the correctness of the structure of rubrofusarin monomethyl ether A (II) proposed by Roberts.[4]

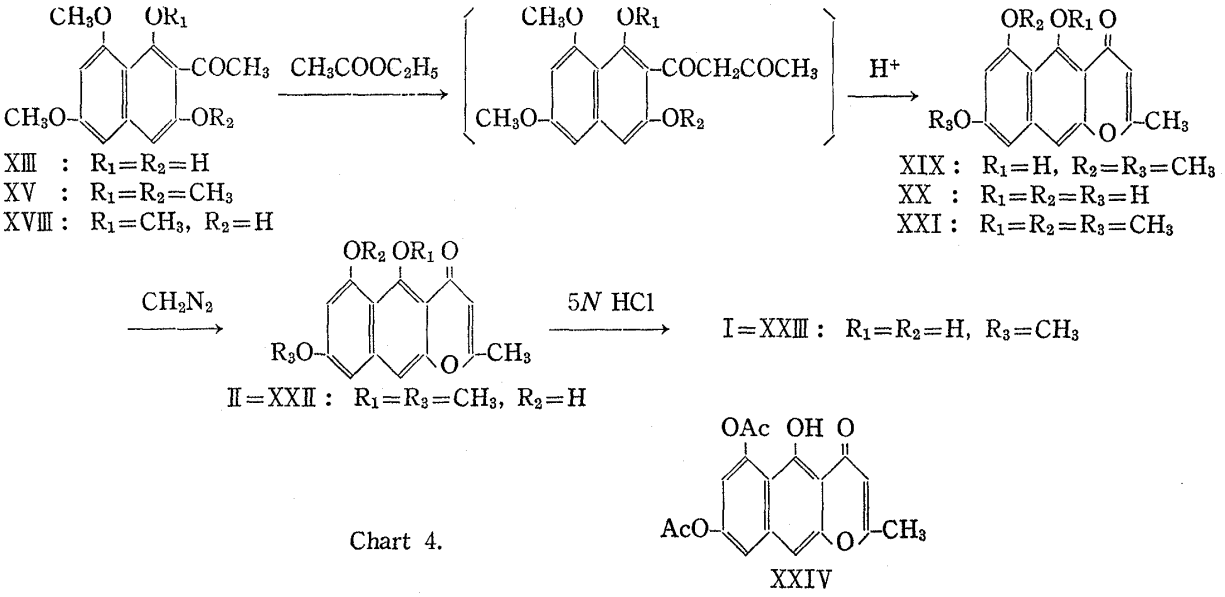


Chart 4.

An attempt for preparing rubrofusarin (I) by the partial methylation of nor-rubrofusarin (XX) was unsuccessful, but it has been performed by the partial demethylation of rubrofusarin monomethyl ether A (XXII) prepared from XX with 5 *N*-hydrochloric acid. Thus the final product, 5,6-dihydroxy-8-methoxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-4-one (XXIII), m.p. 210°, has been established to be identical with the naturally occurring rubrofusarin (I) by the mixed fusion and the comparison of IR spectra and thin-layer chromatograms.

The results of this study and the synthesis of hydroxynaphthopyrone derivatives of angular and linear types carried out by Fukushima, *et al.*[10] have shown that the Wessely-Moser rule[11] which was generally adopted to flavonoid, chromones, and xanthones has also been applied to the naphthopyrone. Thus naphthopyrones having a free hydroxyl at the 10 position is stable in angular type, and others are stabilized to form linear type. The structure of nor-rubrofusarin diacetate[1] which was remained ambiguous has now been established to be 6,8-diacetoxy-5-hydroxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-4-

10) K. Yamaguchi, S. Fukushima, H. Yamada : This Bulletin, **8**, 1028 (1960); S. Fukushima, A. Ueno, Y. Akahori : *Ibid.*, **12**, 307, 312 (1964).

11) F. Wessely, G. H. Moser : Monatsch., **56**, 97 (1930). K. M. Gallagher, A. C. Hughes, M. O'Donnell, E. M. Philbin, T. S. Wheeler : J. Chem. Soc., **1953**, 3770. T. R. Seshadri, *et al.* : Proc. Indian Acad. Sci., **35A**, 34, 82 (1952). S. M. Mukerjee, T. R. Seshadri : Chem. & Ind. (London), **1955**, 271. T. R. Seshadri : Tetrahedron, **6**, 169 (1959). D. M. Donnelly, E. M. Philbin, T. S. Wheeler : J. Chem. Soc., **1956**, 4409. E. M. Philbin, J. Swirski, T. S. Wheeler : *Ibid.*, **1956**, 4455.

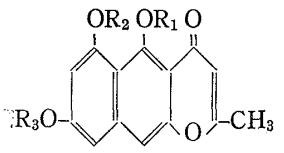
one (XXIV) by the comparison of chemical and spectroscopical properties with rubrofusarin monomethyl ethers A (XXII) and B (XIX). The result showed the presence of an enolic hydroxyl at $C_{(5)}$ which is strongly hydrogen bonded with the carbonyl of pyrone ring (Table II).

Table II.

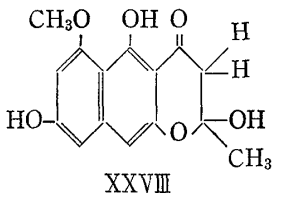
	XXIV	XXII	XIX
Fluorescence under UV	—	yellow	—
$FeCl_3$ in EtOH	dark green		dark green
5% NaOH	insoluble	soluble (orange red)	insoluble
IR $\nu_{max}^{CHCl_3}$ cm^{-1} (OH)		3770	
(C=O)	1775, 1650	1642	1655
NMR $\tau_{Me_4Si}^{CDCl_3}$ (OH)	−4.70	0.05	−4.95

6-Monomethyl ether of nor-rubrofusarin (XXV) had been suggested by Stodola[12] as the structure of fonsecin, m.p. 198° (decomp.), a pigment of *Aspergillus fonsecaeus*. At that time when we prepared the compound XIX, it was considered to be identical with monomethyl ether of fonsecin, m.p. 176°, but XIX showed remarkably different melting point (m.p. 213°).

Having doubt the Stodola's formula, we prepared an isomer of rubrofusarin, 5-monomethyl ether of nor-rubrofusarin (XXVII), m.p. 235~237° (decomp.), as a possible formula of fonsecin by the methylation of XXIV followed by the deacetylation with 10% H_2SO_4. Afterwards Stodola[13] amended the formula of fonsecin as being 6-methyl ether of hydrated nor-rubrofusarin (XXVIII) by the NMR spectral analysis.



XXV : $R_1=R_3=H$, $R_2=CH_3$
XIX : $R_1=H$, $R_2=R_3=CH_3$
XXVI : $R_1=CH_3$, $R_2=R_3=COCH_3$
XXVII : $R_1=CH_3$, $R_2=R_3=H$



XXVIII

Chart 5.

Experimental

Ethyl 1,3-Dihydroxy-6,8-dimethoxy-2-naphthoate (IV)[6] Derivatives——1) Diacetate : On acetylation with Ac_2O and pyridine, IV afforded diacetate. Colorless needles (from EtOH), m.p. 137~137.5°. Yield : 88%. *Anal.* Calcd. for $C_{19}H_{20}O_8$: C, 60.64; H, 5.32. Found : C, 60.88; H, 5.31. IR ν_{max}^{KBr} cm^{-1} : 1770, 1720 (C=O).

2) Dimethyl ether (VI) : On methylation with an excess of ethereal CH_2N_2 IV gave dimethyl ether. Colorless needles, m.p. 116~116.5°(from 60% EtOH). Yield : 91%. *Anal.* Calcd. for $C_{17}H_{20}O_6$: C, 63.75; H, 6.25. Found : C, 63.53; H, 6.29. IR ν_{max}^{KBr} cm^{-1} : 1730 (C=O).

3) Ethyl 3-hydroxy-1,6,8-trimethoxy-2-naphthoate (V) : A mixture of IV (0.7 g.), AcONa (12 ml.) and Ac_2O (0.1 g.) was allowed to stand overnight at room temperature to form 3-monoacetate which was recrystallized from EtOH to pale yellow needles, m.p. 123.5~124°. Yield : 0.72 g., 90%. *Anal.* Calcd. for $C_{17}H_{18}O_7$: C, 61.07; H, 5.39. Found : C, 61.29; H, 5.62. IR ν_{max}^{KBr} cm^{-1} : 1760, 1640 (C=O). Ethyl 3-acetoxy-1,6,8-trimethoxy-2-naphthoate, which was obtained by methylation of the above 3-monoacetate (0.8 g.) with ethereal CH_2N_2, was warmed with 5% $Ba(OH)_2$ solution (30 ml.) for 30 min. on a water bath. After

12) O.L. Galmarini, F.H. Stodola, K.B. Raper, D.I. Fennell : Nature, **195**, 502 (1962).
13) O.L. Galmarini, F.H. Stodola : J. Org. Chem., **30**, 112 (1965).

deacetylation, the solution was extracted with ether to remove dimethyl ether (Ⅳ). The aqueous layer was acidified with 5% H_2SO_4 and extracted with ether. The ether extract was shaken with 5% $NaHCO_3$ to remove a little amount of free acid (3-hydroxy-1,6,8-trimethyl-2-naphthoic acid). It is pale yellow needles, m.p. 172～173°(decomp.)(from MeOH). *Anal.* Calcd. for $C_{14}H_{14}O_6$: C, 60.43; H, 5.04. Found: C, 60.51; H, 5.13. IR ν_{max}^{KBr} cm^{-1}: 2930 (OH), 1700 (C=O). Its methyl ether was yielded as pale yellow needles, m.p. 98～99°(from 50% MeOH) by usual method using an ethereal CH_2N_2, *Anal.* Calcd. for $C_{15}H_{16}O_6$: C, 61.64, H, 5.48. Found: C, 61.73; H, 5.65. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1673 (C=O). The solvent was evaporated and the residue was recrystallized from 50% EtOH to pale yellow needles, m.p. 95～96°. Yield, 0.42 g., 58%. *Anal.* Calcd. for $C_{16}H_{18}O_6$: C, 62.75; H, 5.88. Found: C, 62.66; H, 5.84. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1670 (non-chelated C=O).

Methyl 1,3,6,8-Tetramethoxy-2-naphthoate (VII)——The compound (Ⅵ) suspended in 20% NaOH and EtOH was refluxed at 120～130° for 3 hr. in a sealed tube. After hydrolysis, the solution was acidified to separate precipitates which were recrystallized from MeOH to colorless needles, m.p. 161°(decomp.). Yield: 89%. *Anal.* Calcd. for $C_{15}H_{16}O_6$: C, 61.64; H, 5.48. Found: C, 61.42; H, 5.46. IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O).

Its methyl ester was obtained as colorless needles, m.p. 137～137.5°(from MeOH) by usual method using an ethereal CH_2N_2. Yield: 95%. *Anal.* Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.88. Found: C, 62.78; H, 5.88. IR ν_{max}^{KBr} cm^{-1}: 1735 (C=O).

Attempted Preparations of 2-Acetoacetyl-3-hydroxy-1,6,8-trimethoxynaphthalene and Its Derivatives——The Claisen condensation of Ⅴ or Ⅵ with acetone was failed to react in the presence of NaH or Na, and also Ⅶ did not react by the method of Wawzonek.[7]

3,5-Dimethoxybenzoyl Chloride (VIII)——3,5-Dimethoxybenzoic acid (10 g.)[14] was refluxed with $SOCl_2$ (14 g.) for 1 hr. Evaporation of the excess $SOCl_2$ and the residue was distilled *in vacuo* to give a pale yellow oil, b.p_6 135°, Yield: 10 g. (91%), which was solidified under ice cooling to colorless needles, m.p. 30～32° (from ligroin). It was characterized as an amide, colorless needles, m.p. 141～142°(from EtOH).

3,5-Dimethoxybenzoyldiazomethane (IX)——A solution of Ⅷ (10 g.) in dry ether (30 ml.) was added dropwise to an ethereal CH_2N_2(prepared from 18 g. of of N-nitrosomethylurea) under ice cooling and vigorous stirring. After standing overnight, the solvent was removed under reduced pressure at room temperature, and finally at 30°. The crystalline yellow residue was recrystallized from benzene-light petroleum to pale yellow plate, m.p. 71～72°. Yield: 10 g. (91%). *Anal.* Calcd. for $C_{10}H_{10}O_3N$: C, 58.25; H, 4.85; N, 13.59. Found: C, 58.48; H, 4.92; N, 13.75. IR ν_{max}^{KBr} cm^{-1}: 2130, 2100 ($COCHN_2$).

3,5-Dimethoxyphenylacetic Acid (X)——To a mixture of freshly prepared Ag_2O (4 g.), Na_2CO_3 (4 g.) and sodium thiosulfate (10 g.) in water (140 ml.), the solution of Ⅸ (10 g.) in dioxane (40 ml.) was added slowly dropwise under vigorous stirring at 65～70°. After the addition was completed, stirring was continued for 30 min. at 70～80° and subsequent 30 min. at 80～90°. The solution was filtrated to remove Ag_2O, diluted with water and acidified with conc. HNO_3. The separated orange needles were collected and dissolved in ether from which acidic product was separated by shaking with 5% $NaHCO_3$ solution. The pale yellow needles which were separated on acidification were recrystallized from water using charcoal to colorless needles, m.p. 100～101°. Yield: 6 g. (63%). This product showed the almost same melting point with 3,5-dimethoxy phenylacetic acid (m.p. 99～100°) prepared by another synthetic method of F. Mauthner, *et al.*[15] IR ν_{max}^{KBr} cm^{-1}: 1710 (C=O).

3,5-Dimethoxyphenylacetyl Chloride (XI)——A solution of X (10 g.) and PCl_3 (3 ml.) in dried benzene (40 ml.) was refluxed for 1 hr. After filtration and evaporation *in vacuo*, a yellow syrupy oil (10 g., 92%), was obtained, which was employed for next step of reaction. It was characterized as an amide, colorless needles, m.p. 126～127°(from benzene). IR ν_{max}^{KBr} cm^{-1}: 3410, 3220 (NH_2), 1640 (C=O).

Ethyl 2-(3,5-Dimethoxyphenylacetyl) acetoacetate (XII)——1) By the Spassow reaction, Ⅻ was prepared from Ⅺ (10 g.), ethyl acetoacetate (7 g.), and Mg (1.3 g.) by the modified method of M. Viscontini, *et al.*[8] Ⅻ was obtained as an orange yellow oil, Yield: 1.3 g. (90.7%), which was confirmed as the copper salt, bluish white needles, m.p. 178～179°(from benzene). It gives a red $FeCl_3$ reaction. *Anal.* Calcd. for $C_{16}H_{19}O_6 \cdot \frac{1}{2}Cu$: C, 56.67; H, 5.61. Found: C, 56.86; H, 5.63. IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O).

2) By the Claisen reaction, a solution of ethyl acetoacetate (7.3 g.) in dry ether (30 ml.) was added dropwise under stirring and ice cooling into a suspension of NaH (1.4 g.) in dry ether (10 ml.). The reaction immediately took place under the evolution of hydrogen. After standing for 1 hr., a solution of Ⅺ (10 g.) in dry ether was added dropwise slowly into the above mixture at 0° under ice-cooling. Standing overnight, the reaction mixture was refluxed for 3 hr. and treated with 5% H_2SO_4 and ice by usual method. The ethereal layer was separated, shaken with 5% $NaHCO_3$ and washed with water to remove the unreacted free acid (X). The solvent and ethyl acetoacetate recovered were evaporated *in vacuo* to obtain orange yellow oil., Yield: 12 g. (76%).

2-Acetyl-6,8-Dimethoxy-1,3-naphthalenediol (XIII)——The above oil (Ⅻ) (12 g.) was distilled in a high vacuum (0.001～0.005 mm./Hg) to remove the volatile portion (b.p. 152～165°). The brown residue sublimed

14) Org. Syntheses, Coll. Vol. Ⅲ, 288 (1954).
15) F. Mauthner, *et al.*: J. prakt. Chem., **110**, 127 (1925).

at bath temp. 200~220°, for 2~3 hr. to form yellow crystals. The residue was extracted with $CHCl_3$ to obtain yellow solid. The yellow sublimate and solid obtained as above were chromatographed on silica gel column using $CHCl_3$ as the solvent. The bottom yellow band was eluted and recrystallized from benzene : MeOH (3:2) mixture to form pale yellow prisms, m.p. 193.5~194°, Yield : 920 mg. (18%). It dissolves in 5% NaOH and gives a dark green color with 1% $FeCl_3$ in EtOH and dark red color with Gibbs' reagent. *Anal.* Calcd. for $C_{14}H_{14}O_5$: C, 64.12; H, 5.34. Found : C, 64.19; H, 5.37.

1,3-Diacetoxy-2-acetyl-6,8-dimethoxynaphthalene——The compound (XIII) (0.1 g.) was acetylated with Ac_2O (3 ml.) and pyridine (0.5 ml.) on standing overnight at room temperature. On recrystallization from EtOH, colorless needles, m.p. 126~127°, were obtained. Yield : 100 mg. (76%). *Anal.* Calcd. for $C_{18}H_{18}O_7$: C, 62.23; H, 5.20. Found : C, 62.45; H, 5.17. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1770 (phenolic acetate C=O), 1700 (C=O).

2-Acetyl-1,3,6,8-tetramethoxynaphthalene (XV)——A mixture of XIII (1 g.), anhydr. K_2CO_3 (5 g.), Me_2SO_4 (2.5 ml.) and acetone (80 ml.) was refluxed for 5 hr. under vigorous stirring. The product on recrystallization from 60% MeOH gave colorless needles, m.p. 99~100.5°. Yield : 1 g. (90%). *Anal.* Calcd. for $C_{16}H_{18}O_5$: C, 66.21; H, 6.21. Found : C, 66.19 : H, 6.16. UV λ_{max}^{EtOH} mμ (log ε) : 233 (4.59), 240 (4.60), 300 (3.68). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1710 (C=O).

Methylation with diazomethane of XV gave no good result.

Ethyl 3-Hydroxy-6,8-dimethoxy-1-methyl-2-naphthoate (XIV)——A mixture of XII (4 g.) and PPA (prepared from phosphoric acid (5 ml.) and anhydr. P_2O_5 (5 g.)) was kept at 100° for 5 min. under stirring. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The extract was washed with 5% $NaHCO_3$ and water, dried, and chromatographed on silica gel column, using $CHCl_3$ as the solvent.

A yellow fluorescent band which was made visible under UV-illumination was eluted and recrystallized from petr. benzine (b.p. 70~80°) to form colorless needles, m.p. 130~131°. Yield : 2.2 g. (58.2%). *Anal.* Calcd. for $C_{16}H_{18}O_5$: C, 66.21; H, 6.21. Found : C, 66.49; H, 6.35. It gives no color reaction with $FeCl_3$ and a blue color with Gibbs' reagent. Moreover, a small amount of the free acid corresponding to XIV was obtained from the bicarbonate wahsings.

The Cu-salt of XII was treated with PPA as above described. Yield : 0.6 g. (56.5%).

3-Hydroxy-6,8-dimethoxy-1-methyl-2-naphthoic Acid——A solution of 0.5 g. of XIV in 15% NaOH (20 ml.) and EtOH (5 ml.) was refluxed for 1 hr. at 130~140° in a sealed tube and treated by usual method. Recrystallization of the product from (benzene : Me_2CO (7:3)) gave pale yellow needles, m.p. 202°(decomp.). Yield : 0.34 g. (84%). *Anal.* Calcd. for $C_{14}H_{14}O_5$: C, 64.12; H, 5.34. Found : C, 63.80; H, 5.39. IR ν_{max}^{KBr} cm^{-1} : 1658 (C=O).

3-Acetoxy-2-acetyl-1-hydroxy-6,8-dimethoxynaphthalene (XVI)——XIII (3 g.) was warmed for 1 hr. at 60° with Ac_2O (90 ml.) and AcONa (0.6 g.) and treated by usual method. The yellow product was chromatographed on silica gel column using $CHCl_3$ as the solvent. The starting material (XIII) was recovered from a yellow band at the bottom. Yield : 0.21 g. (7%). Then a pale yellow fluorescent band was eluted and recrystallized from MeOH to form pale yellow needles, m.p. 126~127°. Yield : 1.86 g. (53.6%). *Anal.* Calcd. for $C_{16}H_{16}O_6$: C, 63.16; H, 5.26. Found : C, 63.43; H, 5.32. IR $\nu_{max}^{CHCl_3}$: 3400 (OH), 1770, 1685, 1630 (C=O). Moreover, the diacetate of XIII was obtained from the blue fluorescent band immediately above the bottom one. Yield : 0.66 g.

2-Acetyl-3-hydroxy-1,6,8-trimethoxynaphthalene (XVIII)——A mixture of XVI (0.67 g.), K_2CO_3 (2.5 g.), Me_2SO_4 (1 ml.) and acetone (50 ml.) was refluxed for 1.5 hr. under stirring. After removal of K_2CO_3, acetone was evaporated *in vacuo*. Th residue (XVII) dissolved in MeOH (5 ml.) and 5% NaOH (10 ml.) was warmed for 15 min. on a water bath. After cooling, MeOH was evaporated and acidified with conc. HCl. The yellow solid separated was chromatographed on silica gel using $CHCl_3$ as the solvent. The yellow bottom band was eluted and recrystallized from MeOH to give orange yellow needles, m.p. 106~107°. Yield : 0.52 g. (85.5%). *Anal.* Calcd. for $C_{15}H_{16}O_5$: C, 65.22; H, 5.80. Found : C, 65.42; H, 5.64.

5-Hydroxy-6,8-dimethoxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-4-one (XIX) (Rubrofusarin Monomethyl Ether B)——A solution of XIII (1 g.) in dried AcOEt (2 ml.) was added dropwise to a suspension of NaH (0.8 g.) in dried AcOEt (1 ml.) at 0° under stirring. After 30 min. the ice bath was removed, and the mixture was kept under stirring at room temperature for 2 hr., and then refluxed for 30 min. Pouring the mixture into ice water and acidifying the aqueous layer with AcOH, orange precipitates were separated, which were failed to crystallize. Methanolic solution (10 ml.) of this product was added with one drop of conc. HCl, and refluxed for 5 min. After cooling, a brownish orange substance was separated, which was chromatographed on $CaHPO_4$ column using benzene as a solvent. The second yellow band from the bottom was eluted and recrystallized from EtOH to give orange yellow needles, m.p. 213°. Yield : 0.42 g. (38.7%). It is insoluble in 5% NaOH and gives a green color with $FeCl_3$ and blue color with Gibbs' reagent. *Anal.* Calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.89. Found : C, 67.08; H, 4.81. UV λ_{max}^{EtOH} mμ (log ε) : 225 (4.44), 275 (4.69), 322 (3.51), 395 (3.81). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1655 (C=O).

On methylation of this product with an ethereal diazomethane in a mixture of benzene and MeOH, rubrofusarin dimethyl ether (XXI) was obtained. Yield : 47.6%. It was identified with the dimethyl ether of natural rubrofusarin, m.p. 186~187°, by a mixed fusion (mixed m.p. 186~187°) and comparison of IR spectra (KBr) and thin-layer chromatograms.

Synthesis of Rubrofusarin Monomethyl Ether B by Partial Methylation of Natural Rubrofusarin——A mixture of I (0.1 g.), K_2CO_3 (0.5 g.), Me_2SO_4 (0.2 ml.) and acetone (10 ml.) was refluxed for 7 hr. under stirring and treated by usual method. The product obtained as above was chromatographed on silica gel using a mixture of benzene–acetone (4:1) as the solvent. The yellow bottom band was eluted and recrystallized from EtOH to give orange yellow needles, named rubrofusarin monomethyl ether B, m.p. 213°. Yield: 0.05 g. (47.5%). From the next yellow fluorescent band, Yield 0.05 g. (45.5%), rubrofusarin dimethyl ether, pale yellow needles, m.p. 186~187°, was obtained. *Anal.* Calcd. for $C_{16}H_{14}O_4$: C, 67.13; H, 4.89. Found: C, 66.89; H, 4.87. Rubrofusarin monomethyl ether B was proved to be identical with XIX by a mixed fusion (m.p. 213°), IR spectra (KBr) and thin-layer chromatogram.

5,6,8-Trimethoxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-4-one (XXI) (Rubrofusarin Dimethyl Ether)——A solution of 0.5 g. of XVIII in dried AcOEt (2 ml.) was added dropwise at 0° under stirring to a suspension of NaH (0.6 g.) in dried AcOEt (3 ml.) and the reaction mixture was treated in the same way, as described above (see XIX) to yield orange yellow solid. Yield: 0.43 g. (75%).

The product which was not able to crystallize was refluxed in a mixture of MeOH and conc. HCl for cyclization. A gray solids obtained were chromatographed on alumina column using a mixture of benzene: MeOH (3:2) as the solvent. The purified pale yellow solids recrystallized from 60% MeOH to give coloress needles, m.p. 186~187°. Yield: 0.175 g. (69%). *Anal.* Calcd. for $C_{17}H_{16}O_5$: C, 68.00; H, 5.37. Found: C, 68.28; H, 5.33. UV λ_{max}^{EtOH} mμ (log ε): 226 (4.47), 271 (4.67), 326 (3.53), 342 (3.62), 373 (3.79). IR ν_{max}^{KBr} cm^{-1}: 1650 (C=O).

This product was identified with the dimethyl ether of natural rubrofusarin, m.p. 186~187°, by a mixed fusion (mixed m.p. 186~187°) and comparison of IR spectra (KBr) and thin-layer chromatograms.

5,6,8-Trihydroxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-4-one (XX) (Nor-rubrofusarin)——A solution of XV (0.5 g.) in dried AcOEt (2 ml.) was added dropwise at 0° under stirring to a suspension of NaH (0.25 g.) in dried AcOEt (5 ml.). The reaction mixture was treated in the same way as described for XIX to yield the pale brown amorphous solids. Yield: 0.4 g. (70%). This was cyclized by refluxing for 8 hr. in a mixture of Ac_2O (12 ml.) and HI (sp. gr. 1.7; 20 ml.). The reaction mixture was poured into a cold solution of 3% $NaHSO_3$. The separated solids were collected, washed with water and then chromatographed on silicic acid (Mallinckrodt) column using benzene–acetone (4:1) mixture as the solvent. An orange red band was eluted and recrystallized from 75% dioxane to give orange red needles, m.p. 298~299° (decomp.). Yield.: 0.2 g. (44%). This product was identified with nor-rubrofusarin, which was obtained by the demethylation of natural rubrofusarin, by the comparison of IR spectra (KBr) and thin-layer chromatograms. *Anal.* Calcd. for $C_{14}H_{10}O_5$: C, 65.12; H, 3.87. Found: C, 64.95; H, 3.86. UV λ_{max}^{EtOH} mμ (log ε): 225 (4.43), 278 (4.65), 329 (3.43), 415 (3.73). IR ν_{max}^{KBr} cm^{-1}: 1645 (C=O).

6-Hydroxy-5,8-dimethoxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-4-one (XXII) (Rubrofusarin Monomethyl Ether A)——XX (0.15 g.) dissolved in a mixture of benzene and tetrahydrofuran (15 ml.: 5 ml.) was treated with an excess of ethereal diazomethane and kept at room temperature for 4 hr. The reaction mixture was filtrated to remove the purple precipitates and the filtrate was evaporated *in vacuo*. The residue was chromatographed on $CaHPO_4$ column using benzene as the solvent. The blue fluorescent bottom band was eluted and recrystallized from MeOH to give pale yellow needles, m.p. 203~204°. Yield: 0.05 g. (31%). This product was identified with rubrofusarin monomethyl ether A (II) by a mixed fusion (the mixed m.p. 203~204°), IR spectra and thin-layer chromatograms as the comparison. *Anal.* Calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.89. Found: C, 67.37; H, 4.94. IR $\lambda_{max}^{CHCl_3}$ cm^{-1}: 3370 (OH), 1642 (C=O).

5,6-Dihydroxy-8-methoxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-4-one (XXIII) (Rubrofusarin)——To a solvent of XXII (0.1 g.) in dioxane (4 ml.) 5*N* HCl (3 ml.) was added and the mixture was refluxed for 1 hr., when the color turned into dark red. On addition of water orange red solids were separated. Red crystals obtained by sublimation of the product *in vacuo* at 200° were recrystallized from benzene to form orange red needles, m.p. 210°. Yield: 0.05 g. (52.6%). This product was identified with natural rubrofusarin by a mixed fusion (the mixed m.p. 210°) and comparison of IR spectra and thin-layer chromatograms. *Anal.* Calcd. for $C_{15}H_{12}O_5$: C, 66.18; H, 4.41. Found: C, 66.15; H, 4.40. UV λ_{max}^{EtOH} mμ (log ε): 224 (4.41), 277 (4.66), 325 (3.51), 340 (3.34), 410 (3.74). IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O).

6,8-Diacetoxy-5-hydroxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-4-one (XXIV) (Nor-rubrofusarin Diacetate)——On acetylation with pyridine (0.5 ml.) and Ac_2O (5 ml.), standing overnight at room temperature, nor-rubrofusarin (0.2 g.) afforded diacetate (XXIV) which had been obtained by H. Raistrick, *et al.*[1] (1937) while its structure was remained unestablished. Pale yellow needles (from AcOH), m.p. 203~204°. Yield: 0.2 g. (76%). *Anal.* Calcd. for $C_{18}H_{14}O_7$: C, 63.16; H, 4.09. Found: C, 63.04; H, 4.22. UV λ_{max}^{EtOH} mμ (log ε): 253 (4.65), 267 (4.69), 299 (3.45), 313 (3.52), 326 (3.27), 385 (3.68).

6,8-Diacetoxy-5-methoxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-4-one (XXVI)——The mixture of XXIV (0.1 g.), Me_2SO_4 (4 ml.), K_2CO_3 (0.8 g.), and acetone (15 ml.) was refluxed for 4 hr. After treatment by usual method, product was purified by chromatography on silica gel column using a mixture of benzene and acetone (4:1). From the bottom blue fluorescent band colorless needles, m.p. 156~157° (from MeOH) were isolated. Yield: 0.09 g. (86.9%). *Anal.* Calcd. for $C_{19}H_{16}O_7$: C, 64.02; H, 4.50. Found: C, 64.07; H, 4.57. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1660 (C=O).

6,8-Dihydroxy-5-methoxy-2-methyl-4*H*-naptho[2,3-*b*]pyran-4-one (XXVII) (Nor-rubrofusarin 5-Monomethyl Ether)——XXVI (0.1 g.) dissolved in MeOH (10 ml.) and 10% H_2SO_4 (10 ml.) was refluxed for 3 hr. on a water bath. After cooling, the resulting solid was collected, washed with H_2O and dried. It was chromatographed on silica gel column using a mixture of benzene–acetone (4:1). The bottom orange yellow fluorescent band was eluted and recrystallized from EtOH to give orange yellow needles, m.p. 235~237° (decomp.). Yield: 0.05 g. (65.3%). *Anal.* Calcd. for $C_{15}H_{12}O_5$: C, 66.18; H, 4.41. Found: C, 66.18; H, 4.43. UV λ_{max}^{EtOH} mμ (log ε): 226 (4.43), 277 (4.68), 333 (3.43), 350 (3.43), 396 (3.69). IR ν_{max}^{KBr} cm^{-1}: 1630~1640 (C=O).

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