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227. Eisaku Morishita and Shoji Shibata*1 : Metabolic Products of Fungi. XXVII.*2 Synthesis of racemic Ustilaginoidin A and Its Related Compounds. (2).*3 Synthesis of racemic Ustilaginoidin A.

(*Faculty of Pharmaceutical Sciences, University of Tokyo*1)*)

Racemic ustilaginoidin A was synthesized by the oxidative coupling of nor-rubrofusarin dimethyl ether C (II) and rubrofusarin monomethyl ether A (III) using ferric chloride in dioxane as the reagent.

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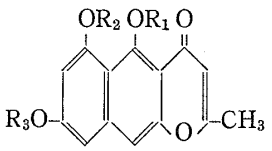
In the present paper, we report the synthesis of racemic ustilaginoidin A by the oxidative coupling of nor-rubrofusarin (I) whose synthesis was discussed in the previous paper.[1)]

As the direct oxidative coupling of nor-rubrofusarin was unsuccessful forming resinous substances, dimethyl ethers of nor-rubrofusarin having a free hydroxyl at the *ortho* or *para* position of $C_{(9)}$, nor-rubrofusarin dimethyl ether C (II) and rubrofusarin monomethyl ether A (III), were employed as the material for condensation.

Nor-rubrofusarin dimethyl ether C (II) was prepared starting from nor-rubrofusarin (I). Partial acetylation of (I) using acetic anhydride and sodium acetate at 65° for 40 min. yielded 7-monoacetate (IV) which was methylated with dimethyl sulfate to afford 5,6-dimethyl ether 7-acetate (Va). Deacetylation of Va with 10% H_2SO_4 gave nor-rubrofusarin dimethyl ether C (II), m.p. 276° (decomp.).



I : $R_1=R_2=R_3=H$
II : $R_1=R_2=CH_3$, $R_3=H$
III : $R_1=R_3=CH_3$, $R_2=H$
IV : $R_1=R_2=H$, $R_3=COCH_3$
Va : $R_1=R_2=CH_3$, $R_3=COCH_3$
Vb : $R_1=CH_3$, $R_2=H$, $R_3=COCH_3$
VI : $R_1=CH_3$, $R_2=R_3=H$

Chart 1.

Using diazomethane for methylation of 7-monoacetate (IV), Va and Vb, m.p. 204~205°, were afforded in the yield of 36.7% and 19%, respectively. The latter compound (Vb) gave nor-rubrofusarin 5-monomethyl ether (VI)[1)] on deacetylation.

The oxidative coupling of II and III were performed under the following conditions (Table I) :

Table I. Oxidative Coupling of II and III

Exp. No.	Oxidating reagents and conditions	Yield VII (%)	Recovering II (%)	Yield VIII (%)	Recovering III (%)
1	O_2 Stream in EtOH under UV illumination[2)]	—	—	0	0
2	$FeCl_3$ (1 moles) in 75% aq. dioxane	25	33	25	25
3	$FeCl_3$ (2 moles) in 75% aq. dioxane	32	trace	54~47	3.3
4	$FeCl_3$ (2 moles) in 75% aq. dioxane O_2 Stream under UV illumination	27	25	25	trace

*1 Hongo, Tokyo (森下顕策, 柴田承二).
*2 Part XXVI. E. Morishita, S. Shibata : This Bulletin, **15**, 1765 (1967).
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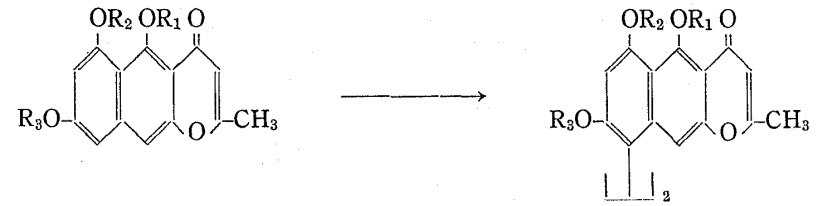
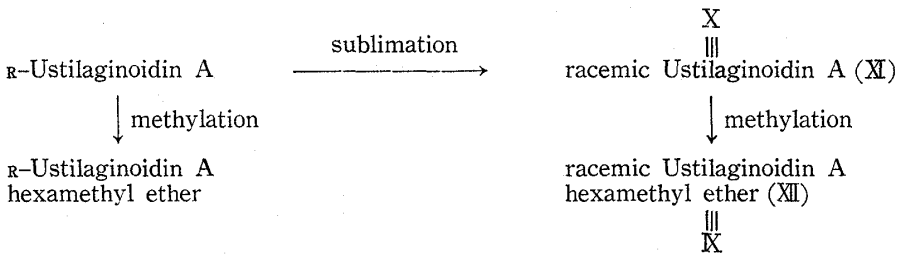


Ⅱ : $R_1=R_2=CH_3$, $R_3=H$
Ⅲ : $R_1=R_3=CH_3$, $R_2=H$

Ⅵ : $R_1=R_2=CH_3$, $R_3=H$
Ⅶ : $R_1=R_3=CH_3$, $R_2=H$
Ⅸ : $R_1=R_2=R_3=CH_3$
Ⅹ : $R_1=R_2=R_3=H$

Chart 2.

The best yield of oxidative coupling was obtained when the monomer was treated with 2 moles of ferric chloride in boiling 75% aq. dioxane (Exp. No. 3). The ultraviolet (UV)-spectra of the oxidative coupling products, Ⅵ and Ⅶ, showed bathochromic shift in comparison with those of Ⅱ and Ⅲ, respectively. The NMR spectra in pyridine d-5 of Ⅵ and Ⅶ gave 2 aromatic protons at 7.39 and 6.93 p.p.m., and 7.61 and 7.23 p.p.m., respectively, while the signals corresponding to the aromatic proton of $C_{(9)}$ in Ⅱ and Ⅲ disappeared. These facts proved that the coupling took place at $C_{(9)}$ of the monomers. The compounds Ⅵ and Ⅶ were methylated with dimethyl sulfate to afford 5.5′,6.6′,8.8′-hexamethoxy-2.2′-dimethyl-9.9′-bi[4*H*-naphtho[2,3-*b*]pyran-4-one], m.p. 310° (decomp.), (Ⅸ), which was demethylated with hydroiodic acid to yield a dark red crystalline compound, 5.5′,6.6′,8.8′-hexahydroxy-2.2′-dimethyl-9.9′-bi[4*H*-naphtho[2,3-*b*]pyran-4-one], m.p.>320°, (Ⅹ). In comparison of the IR-spectra (KBr tablet) and thin-layer chromatograms, the product (Ⅹ) was proved to be identical with racemic ustilaginoidin A (Ⅺ) which was prepared from natural R-ustilaginoidin A, $[\alpha]_D-384°$ (dioxane), by sublimation in high vacuum. The identity of Ⅸ and racemic ustilaginoidin A hexamethyl ether (Ⅻ) prepared by the methylation of Ⅺ was also established by the comparison of IR-spectra (KBr tablet) and thin-layer chromatograms, whereas R-ustilaginoidin hexamethyl ether, m.p. 256°; $[\alpha]_D+89.5°$ (tetrahydrofurane), showed some different properties, such as in melting point, with the corresponding synthetic racemic compound (Ⅸ).



Experimental

8-Acetoxy-5,6-dihydroxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-5-one (Ⅳ)——A mixture of nor-rubrofusarin (Ⅰ) (1 g.), AcONa (0.6 g.), AcOH (12 ml.) and Ac_2O (70 ml.) was warmed at 65° on a water bath for 40 min. The reaction mixture was treated by the usual method and the product was chromatographed on silicic acid using the mixed solvent of $CHCl_3$-Me_2CO (9:1). The first orange yellow band was eluted and recrystallized from benzene to give orange red prisms, m.p. 228~229° (0.8 g., 69%). The starting material (Ⅰ) (19%) was recovered from the second band. On the other hand, a small amount of nor-rubrofusarin diacetate, m.p. 203~204°, was obtained from the mother liquor of recrystallization of the main product. *Anal.* Calcd. for $C_{16}H_{12}O_6$: C, 64.00; H, 4.00. Found : C, 64.07; H, 3.81. UV λ_{max}^{EtOH} mμ (log ε) : 218 (4.26), 269 (4.64), 350 (3.14), 412 (3.74). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3376 (OH), 1770, 1665 (C=O).

8-Acetoxy-5,6-dimethoxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-4-one (Va)——The compound (Ⅳ) (0.6 g.) was methylated by refluxing in Me_2CO (150 ml.) for 12 hr. with Me_2SO_4 (2.5 ml.) and K_2CO_3 (2.7 g.). After filtration and evaporation *in vacuo*, the residue was decomposed with ice water and extracted with $CHCl_3$. The extracts were purified by chromatography using benzene-acetone (9:1) as the solvent on silica gel.

The second yellow fluorescent band gave *the methyl ether* as pale yellow needles, m.p. 226~227° (from MeOH) (0.4 g., 61.2%). *Anal.* Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.88. Found: C, 66.03; H, 4.99. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1762, 1655 (C=O).

8-Acetoxy-6-hydroxy-5-methoxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-4-one (Vb)——The compound (IV) (0.1 g.) dissolved in benzene was methylated with an ethereal CH_2N_2 [prepared from N-nitrosomethylurea (1 g.)]. After standing overnight, the solvent was removed *in vacuo*. The product was chromatographed on silica gel using benzene-acetone (4:1) as the solvent. This first blue fluorescent band was eluted and crystallized form EtOH to give yellow needles (Vb), m.p. 204~205° (0.02 g., 19%), and from the second band, the compound (Va) (0.4 g., 36.7%) was separated. This product (Vb) is soluble in 5% NaOH showing an orange red color and a light blue color with Gibbs' reagent. *Anal.* Calcd. for $C_{17}H_{14}O_6 \cdot \frac{1}{2}H_2O$: C, 63.16; H, 4.64. Found: C, 63.34; H, 4.86. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (OH), 1766, 1650 (C=O). Hydrolysis of Vb with 10% H_2SO_4 in EtOH produced orange yellow needles (from EtOH), m.p. 235~237° (decomp.); identical with norrubrofusarin 5-monomethyl ether (VI).[1]

8-Hydroxy-5,6-dimethoxy-2-methyl-4*H*-naphtho[2,3-*b*]pyran-4-one (II) (Rubrofusarin Monomethyl Ether C)——Va (1.05 g.) dissolved in EtOH (155 ml.) was refluxed for 30 min. on a steam bath with 10% H_2SO_4 (75 ml.). After removal of the solvent *in vacuo*, the separated yellow product was recrystallized from 75% dioxane to obtain yellow needles, m.p. 275° (decomp.) (0.8 g., 87.5%). *Anal.* Calcd. for $C_{16}H_{14}O_5$ (dried over 150° *in vacuo* for 6 hr.): C, 67.13; H, 4.89. Found: C, 66.93; H, 4.81. UV λ_{max}^{EtOH} mμ (log ε): 225 (4.47), 247 (4.33), 273 (4.63), 382 (3.78). IR ν_{max}^{KBr} cm^{-1}: 3400, 3200 (OH), 1645 (C=O). NMR $\delta_{Me_4Si}^{pyridine\text{-}d_5}$: 7.35 (H, s), 7.02 (H, d, J=2.5 c.p.s.), 6.75 (H, d, J=2.5 c.p.s.), 5.93 (H, s) [arom. H]; 4.10 (3H, s), 3.86 (3H, s) [$OC\underline{H}_3$]; 2.11 (3H, s) [$C\underline{H}_3$].

8.8′-Dihydroxy-5.5′,6.6′-tetramethoxy-2.2′-dimethyl-9.9′-bi[4*H*-naphtho[2,3-*b*]pyran-4-one] (VII)——Exp. No. 2: To a hot solution of II (0.3 g., 0.001 mole) in 75% dioxane (40 ml.), $FeCl_3 \cdot 6H_2O$ (0.3 g., 0.001 mole) dissolved in H_2O was added dropwise for 10 min. under refluxing. Immediately after the addition of reagent, the reaction mixture was poured into ice water (120 ml.). The separated solid was extracted with $CHCl_3$ repeatedly and the extracts were washed with H_2O and dried. After concentration, it was chromatographed on $CaHPO_4$ using mixed solvents of benzene-acetone (4:1) and (2:1). From the fluorescent band, the starting material (II) (0.1 g., 33%) was recovered unchanged, and the next band gave yellow prisms (from 75% dioxane), m.p. >320° (0.07 g., 25%). $[\alpha]_D^{31}$ 0° (pyridine, c=0.15/100 ml.). It is soluble in 5% NaOH giving a red color and insoluble in usual organic solvents. *Anal.* Calcd. for $C_{32}H_{26}O_{10}$ (dried over at 180°): C, 67.37; H, 4.56. Found: C, 67.20; H, 4.40. UV λ_{max}^{EtOH} mμ (log ε); 227 (4.71), 249 (4.65), 265 (4.72), 288 (4.95). IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O). NMR $\delta_{Me_4Si}^{pyridine\text{-}d_5}$: 7.39 (H, s), 6.93 (H, s), 6.04 (H, s) [arom-H]; 4.16 (3H, s), 4.10 (3H, s) [$OC\underline{H}_3$]; 1.92 (3H, s) [$C\underline{H}_3$].

Exp. No. 3: With $FeCl_3 \cdot 6H_2O$ (0.4 g., 0.0015 mole), II (0.2 g., 0.0007 mole) dissolved in 75% dioxane (40 ml.) was treated in the same manner as described above. VII was produced in a yield of 0.06 g. (32%); II was not recovered.

Exp. No. 4: The solution of II (0.2 g., 0.0007 mole) in 75% dioxane (40 ml.) was reacted with $FeCl_3 \cdot 6H_2O$ (0.4 g., 0.0015 mole) under O_2-stream and irradiation of a mercury arc lamp. The yield of VII was 0.05 g. (27%), and II (0.05 g., 25%) was recovered.

6.6′-Dihydroxy-5.5′,8.8′-tetramethoxy-2.2′-dimethyl-9.9′-bi[4*H*-naphtho[2,3-*b*]pyran-4-one] (VIII)——Exp. No. 1: VIII was not yielded by boiling solution of III (0.05 g.) in EtOH (10 ml.) under UV-illumination and O_2-stream.

Exp. No. 2: To a refluxed solution of III (0.2 g., 0.0007 mole) in 75% dioxane (20 ml.), $FeCl_3 \cdot 6H_2O$ (0.2 g., 0.0007 mole) in H_2O (5 ml.) was gradually dropped for 10 min. and then ice water was added to the reaction mixture. The reaction mixture was extracted with $CHCl_3$, and after evaporation, the residue was purified by chromatography on silica gel using benzene-acetone (4:1) as the solvent. From the first yellow fluorescent band, the starting material (III) (0.05 g., 25%) was recovered and the second pale yellow band was eluted and recrystallized from 75% dioxane to give orange yellow needles, m.p. 320° (decomp.), in a yield of 0.05 g. (25%). It is soluble in 5% NaOH to give a red solution but insoluble in usual organic solvents. $[\alpha]_D^{31}$ 0° (dioxane, c=0.14/100 ml.). *Anal.* Calcd. for $C_{32}H_{26}O_{10} \cdot \frac{1}{2}C_4H_8O_2$: C, 66.45; H, 4.89. Found: C, 66.50, 66.59; H, 4.92, 4.74. UV λ_{max}^{EtOH} mμ (log ε): 228 (4.54), 268 (4.67), 289 (4.76), 334 (3.60), 4.05 (3.87). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (OH), 1648 (C=O). NMR $\delta_{Me_4Si}^{pyridine\text{-}d_5}$: 7.61 (H, s), 7.23 (H, s), 6.00 (H, s) [arom.-H]; 4.26 (3H, s), 3.74 (3H, s) [$OC\underline{H}_3$]; 1.95 (3H, s) [$C\underline{H}_3$].

Exp. No. 3: In a yield of 0.07~0.08 g. (47~54%), VIII was obtained from III (0.15 g., 0.0005 mole) by treatment with $FeCl_3 \cdot 6H_2O$ (0.3 g., 0.001 mole) in 75% dioxane solution (20 ml.) in the same manner as described above.

Exp. No. 4: The reaction of III (0.2 g., 0.0007 mole) in 75% dioxane (20 ml.) and $FeCl_3 \cdot 6H_2O$ (0.4 g., 0.0015 mole) under UV-illumination and O_2-stream by the same method as described above gave VIII (0.05 g., 25%), and III was not recovered.

5.5′,6.6′,8.8′-Hexamethoxy-2.2′-dimethyl-9.9′-bi[4*H*-naphtho[2,3-*b*]pyran-4-one] (IX) (racemic Ustilaginoidin A Hexamethyl Ether)——1) VII (0.05 g.) was methylated by refluxing in acetone (20 ml.) with Me_2SO_4 (0.15 ml.) and K_2CO_3 (0.5 g.) for 5 hr. After treatment by the usual way, the product was purified by chromatography on silica gel using benzene-acetone (4:1) as the solvent to obtain pale yellow needles (from

EtOH), m.p. 310° (decomp.) (0.05 g., 95%), identical with racemic ustilaginoidin A hexamethyl ether. *Anal.* Calcd. for $C_{34}H_{30}O_{10}$: C, 68.23; H, 5.02. Found: C, 68.27; H, 4.94. UV λ_{max}^{EtOH} mμ (log ε): 228 (4.76), 263 (4.82), 289 (4.97), 332 (3.82), 393 (4.11). IR ν_{max}^{KBr} cm^{-1}: 1655 (C=O). NMR $\tau_{Me_4Si}^{CDCl_3}$: 3.20 (H, s), 3.25 (H, s), 4.12 (H, s) [arom. H]; 5.89 (3H, s), 5.97 (3H, s), 6.21 (3H, s) [OCH_3]; 7.84 (3H, s) [CH_3].

2) Methylation of Ⅷ (0.1 g.) with Me_2SO_4 (0.2 ml.) and K_2CO_3 (1 g.) in Me_2CO (40 ml.) by the same way as described above gave Ⅸ (0.1 g., 95%). *Anal.* Calcd. for $C_{34}H_{30}O_{10}$: C, 68.23; H, 5.02. Found: C, 68.09; H, 5.08.

5.5′,6.6′,8.8′-Hexahydroxy-2.2′-dimethyl-9.9′-bi[4*H*-naphtho[2,3-*b*]pyran-4-one] (Ⅹ) (**racemic Ustilaginoidin A**)——A mixture of Ⅸ (0.06 g.) in HI (sp. gr. 1.7; 7 ml.) and Ac_2O (1.5 ml.) was heated at 110~120° for 5 hr. After cooling, the reaction mixture was poured into ice water and the separated orange red precipitates were collected and then washed with 5% $NaHSO_3$ and water. Purification by chromatography on silicic acid using benzene–acetone (4:1) as the solvent and recrystallization from dioxane afforded red prisms, m.p. >320° (0.015 g., 29%), which was identified by the IR spectra and TLC with racemic ustilaginoidin A prepared from natural R-ustilaginoidin A by sublimation in high vacuum. *Anal.* Calcd. for $C_{28}H_{18}O_{10}$: C, 65.37; H, 3.50. Found: C, 65.08; H, 3.65. UV λ_{max}^{EtOH} mμ (log ε): 226 (4.65), 289 (4.79), 333 (3.89), 348 (3.83), 422 (3.98). IR ν_{max}^{KBr} cm^{-1}: 3370 (OH), 1655 (C=O).

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