56. Osamu Tanaka and Chikara Kaneko: Metabolic Products of Fungi. VI.[1] The Structure of Skyrin. (2). Synthesis of Skyrin β,β'-Dimethyl Ether.

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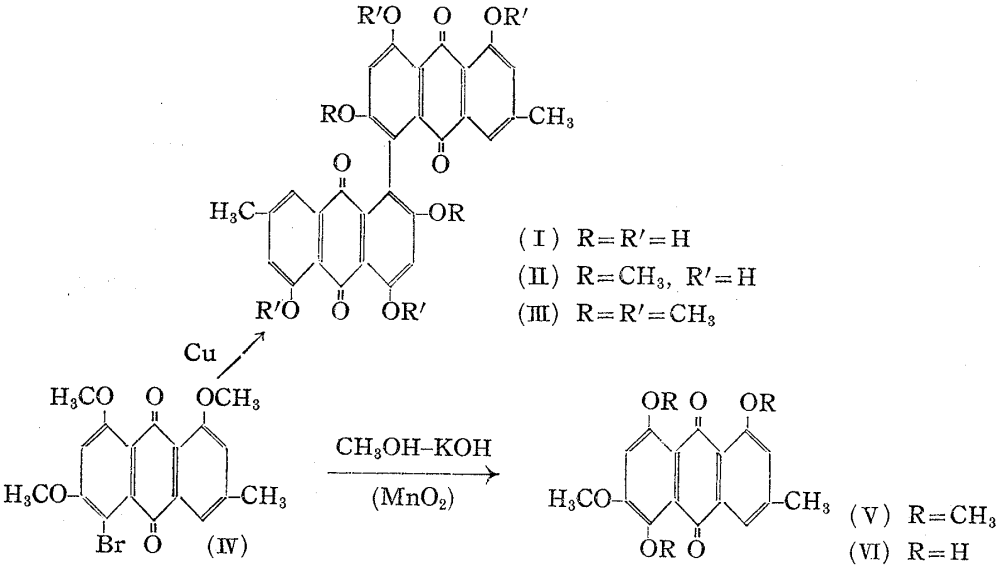
In the preceding paper,[1] the structure of skyrin, a coloring matter of *Penicillium islandicum* Sopp,[2] *Endothia parasitica* (Murr.) And. et And., and *Endothia fluens* Shear et Stevens[3] was proposed as being represented by the formula (I), 2,4,5,2′,4′,5′-hexahydroxy-7,7′-dimethylbianthraquinone-(1,1′).



The present report concerns chiefly with synthesis of dimethyl ether of skyrin.

Emodin trimethyl ether was brominated to give a monobromo derivative which was subjected to the Ullmann condensation to yield hexamethyl ether of diemodin. The condensation product afforded diemodin-β,β'-dimethyl ether (diphyscion) by boiling with HBr by which methoxyl in the α-position of bianthraquinone is demethylated.

The identity of the synthesized diemodin β,β'-dimethyl ether with skyrin β,β'-dimethyl ether, which does not melt below 360°, was established by a comparison of the infrared spectra and by a mixed fusion of their tetraethoxycarbonyl ether, m.p. 247~249°, by which they gave no melting point depression.

The position of bromine substituted in the trimethyl ether of emodin, at which the carbon-carbon linkage of the bianthraquinone forms by the Ullmann condensation, was proved by changing the bromine into methoxyl by the action of methanolic potash in the presence of MnO_2.[4] The methoxyl was demethylated with HBr and the occurrence of *p*-hydroxyls in the product (m.p. 244~246°) was shown by a fluorescence of the solution in acetic acid, and by the magnesium acetate reaction.

The possibility of the presence of the newly introduced hydroxyl in the 1-position (methyl in the 2-position) was ruled out by a comparison with erythroglaucin (1,4,5-trihydroxy-7-methoxy-2-methylanthraquinone[5]) which showed a quite different melting

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1) Part V. This Bulletin, **3**, 278 (1955).
2) B. H. Howard, H. Raistrick: Biochem. J., **56**, 56 (1954).
3) S. Shibata, T. Murakami, O. Tanaka, G. Chihara, M. Sumimoto: This Bulletin, **3**, 274 (1955).
4) O. H. Johnson, *et al.*: J. Am. Chem. Soc., **63**, 2867 (1941).
5) J. N. Ashley, H. Raistrick, T. Richard: Biochem. J., **33**, 1291 (1939); W. K. Anslow, H. Raistrick: *Ibid.*, **34**, 790 (1940); *Ibid.*, **35**, 1006 (1941).

point (m.p. 205~206°).

Thus the position at which bromine substitution occurs was unequivocally established to be the 8-position of emodin trimethyl ether (IV). Consequently, the synthesized skyrin β,β'-dimethyl ether was proved to be 2,2'-dimethoxy-4,5,4',5'-tetrahydroxy-7,7'-dimethylbianthraquinone-(1,1') (II). Thus the structure of skyrin (I) which was suggested in the preceding paper[1] was finally established.

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Experimental

Monobromoemodin Trimethyl Ether (8-Bromo-4,5,7-trimethoxy-2-methylanthraquinone) (IV) A mixture of emodin trimethyl ether, m.p. 224° (2.05 g.), HOAc (100 cc.), and NaOAc (1.8 g.) was added with Br_2 (1.05 g.), when red gelatinous precipitate separated out, changing to orange crystals during the reaction. After heating for 6 hrs. at 90~100°, the crystalline precipitate dissolved gradually to form an orange yellow solution. To the warm reaction mixture, hot water (450 cc.) was added and allowed to stand overnight. Yellow leaflets separated out were collected, washed with acetone (100 cc.), and dissolved in $CHCl_3$. The $CHCl_3$ solution was chromatographed on a column of activated alumina. The eluate was evaporated and the residue was crystallized successively from BuOH, toluene, and HOAc to yellow prisms, m.p. 232~234°. Yield: 0.8 g. *Anal.* Calcd. for $C_{18}H_{15}O_5Br$: C, 55.24; H, 3.83. Found: C, 55.13; H, 3.61.

Action of Methanolic Potash on Monobromoemodin Trimethyl Ether in the Presence of MnO_2 (Formation of 4,5,7,8-Tetramethoxy-2-methylanthraquinone (V))—A mixture of monobromoemodin trimethyl ether (450 mg.) and MnO_2 (500 mg.) in MeOH-KOH (150 cc.) was refluxed for 14 hrs. The reaction mixture was diluted with water and extracted with $CHCl_3$, and the solvent was evaporated.

The residue was dissolved again in $CHCl_3$ and the solution was passed through an alumina column. The eluates were fractionated* into several fractions. From the first eluate a small amount of emodin trimethyl ether was obtained and from the second one, its monobromo derivative was recovered unchanged. The third eluate was collected to give yellow needles, m.p. 185~186°, which were recrystallized from MeOH (yield: 100 mg.). It dissolves in AcOEt, benzene, acetone, and glacial HOAc. *Anal.* Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30; $4CH_3O$, 36.25. Found: C, 66.57; H, 5.31; CH_3O, 36.46.

4,5,8-Trihydroxy-7-methoxy-2-methylanthraquinone (VI)—The tetramethyl ether (V) (40 mg.) dissolved in glacial HOAc (2 cc.) was added with 48% HBr (1.5 cc.), and the solution was gently boiled in an oil bath. After boiling for 30 mins., red needles that separated were collected, washed, and recrystallized successively from glacial HOAc and benzene, m.p. 244~246°. It is insoluble in aq. Na_2CO_3 but dissolves in aq. NaOH to form a purple solution and the solution in HOAc shows a strong green fluorescence. The coloration given by $Mg(OAc)_2$ is similar to that of erythroglaucin. *Anal.* Calcd. for $C_{19}H_{18}O_6$: C, 64,00; H, 4.03; CH_3O, 10.33. Found: C, 64.02; H, 4.10; CH_3O, 9.93.

Action of Methanolic Potash on 4-Bromo-1,3-dimethoxyanthraquinone (Formation of Purpurin Trimethyl Ether)—4-Bromo-1,3-dimethoxyanthraquinone (Formula (I) in the preceding report[1]) (150 mg.) was refluxed in 10% MeOH-KOH for 3.5 hrs. The reaction mixture was cautiously acidified and extracted with $CHCl_3$. The $CHCl_3$ solution was chromatographed on alumina. From the first eluate yellow needles, m.p. 162~163°, were isolated, which were identified with xanthopurpurin dimethyl ether. Monomethyl ether of xanthopurpurin, m.p. 192~193°, was also obtained by treating the product with HBr. The second eluate gave a small amount of purpurin trimethyl ether which was identified by a mixed fusion. The conversion of bromine in the 4-position to methoxyl was accomplished in a better yield by the action of MeOH-KOH in the presence of MnO_2. Emodin trimethyl ether did not undergo any reaction with MnO_2 and MeOH-KOH.

2,4,5,2',4',5'-Hexamethoxy-7,7'-dimethylbianthraquinone-(1,1') (III)—A mixture of 8-bromo-

* Uniformity of each fraction of eluates was determined by paper chromaography using a mixture of acetone and water (1 : 5) as a developing solvent. Rf values: Emodin trimethyl ether, 0.0; 8-bromoemodin trimethyl ether, 0.36~0.38; 4,5,7,8-tetramethoxy-2-methylanthraquinone: 0.60~0.62.

4,5,7-trimethoxy-2-methylanthraquinone (=8-bromoemodin trimethyl ether) (IV) (650 mg.), active Cu-bronze (800 mg.), and naphthalene (1.8 g.) was refluxed for 2.5 hrs. in an oil bath (bath temp. 225°). The cooled mixture was extracted with warm EtOH and acetone to remove naphthalene and the dried residue was extracted with $CHCl_3$. The concentrated $CHCl_3$ solution was chromatographed using acetone-$CHCl_3$ mixture (1:1) as a developing solvent. To the orange yellow eluate a small amount of EtOH was added and the mixture was concentrated to separate yellow crystals (300 mg.), which were collected, washed with warm EtOH, and crystallized from aq. HOAc to give orange yellow microneedles, m.p. about 350°(decomp.). The properties agree with those of hexamethylskyrin.[3] *Anal.* Calcd. for $C_{36}H_{30}O_{10}$: C, 69.45; H, 4.82. Found: C, 69.20, 69,19; H, 4.70, 4.56,

2,2′-Dimethoxy-4,5,4′,5′-tetrahydroxy-7,7′-dimethylbianthraquinone-(1,1′) (II) (β,β′-Dimethylskyrin (V: R=CH_3 in the preceding paper[1])—2,4,5,2′,4′,5′-Hexamethoxy-7,7′-dimethylbianthraquinone-(1,1′) (150 mg.) was boiled in a mixture of 48% HBr and glacial HOAc (1:1). During the reaction, orange red crystals separated out. After boiling for 1.5 hrs. the crystals were collected, washed successively with water, glacial HOAc, and warm acetone, then crystallized from nitrobenzene or nitrobenzene containing BuOH. The product, orange red microcrystals, does not melt below 360°(darkens from 321°) and gives a stable red solution with conc. H_2SO_4. On reduction with alkaline $Na_2S_2O_4$, it quantitatively affords physcion.

The properties and the infrared spectrum of this compound agree with that of β,β′-dimethylskyrin. *Anal.* Calcd. for $C_{32}H_{22}O_{10}$: C, 67.84; H, 3.89. Found: C, 68.09; H, 3.90.

On treatment with $ClCO_2Et$ in pyridine, 2,2′-dimethoxy-4,5,4′,5′-tetrahydroxy-7,7′-dimethylbianthraquinone-(1,1′) gives yellow needles, m.p. 247~249°. It gives no melting point depression by admixture with β,β′-dimethylskyrin tetraethoxycarbonyl ether (m.p. 247~249°). *Anal.* Calcd. for $C_{44}H_{38}O_{18}$: C, 61.83; H, 4.45. Found: C, 62.08; H, 4.62.

Summary

Skyrin β,β′-dimethyl ether was synthesized by the Ullmann condensation of 8-bromoemodin trimethyl ether followed by a partial demethylation. The structure of skyrin, therefore, was unequivocally established as 2,4,5,2′,4′,5′-hexahydroxy-7,7′-dimethylbianthraquinone-(1,1′).

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57. Shoji Shibata, Michio Takido, and Terumi Nakajima: Metabolic Products of Fungi. VII*. Paper Chromatography of the Coloring Matters of *Penicillium islandicum* Sopp.

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Howard and Raistrick[1~3] isolated several coloring matters from some strains of *Penicillium islandicum* Sopp. Of these pigments, chrysophanol[2] is well known as it is widely distributed in higher plants though it has been isolated for the first time from fungi.

A deep red compound which was named islandicin[1] was shown to be 1,4,5-trihydroxy-2-methylanthraquinone, and another orange red pigment named skyrin[3] has also been found in the mycelium of Endothia spp., whose structure has recently been established by us as shown in the preceding reports.[5~7] No decisive evidences have yet been obtained for the chemical structures of the remainder of the pigments of *Penicillium islandicum*, termed flavoskyrin[3], rubroskyrin, iridoskyrin, and erythroskyrin[4],

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1) B. H. Howard, H. Raistrick: Biochem. J., **44**, 227 (1949).
2) B. H. Howard, H. Raistrick: *Ibid.*, **46**, 49 (1950).
3) B. H. Howard, H. Raistrick: *Ibid.*, **56**, 56 (1954).
4) B. H. Howard, H. Raistrick: *Ibid.*, **57**, 213 (1954).