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172. Toshio Miyazaki, Susumu Mihashi, and Kinji Okabayashi :

Studies on the Constituents of *Boenninghausenia albiflora* MEISSNER var. *japonica* S. SUZUKI. II.[*1]

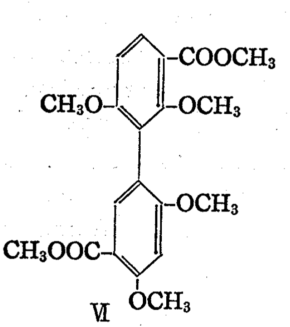
Structure of Matsukaze-lactone. (2).

(*Tokyo College of Pharmacy*[*2])

As described in the preceding paper,[*1] it was reported that the structure of matsukaze-lactone (I) was shown to be Ia, Ib, or Ic.[*3]

Owing to the fact that the majority of naturally occurring coumarins have been known to have an oxygen function at 7-position,[1] the formula (Ic) is most probable.

If the structure of matsukaze-lactone (I) is represented by Ic, the dimethyl ester (IIIb),[*1,*3] $C_{20}H_{22}O_8$, m.p. 161~163.5°, which was obtained by oxidative degradation of I with potassium permanganate followed by methylation should be the same compound as dimethyl 2,4′,6,6′-tetramethoxy-3,3′-biphenyldicarboxylate (VI). Therefore, the synthesis of VI was undertaken to compare it with the dimethyl ester (IIIb).

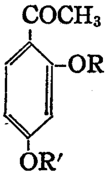


VI

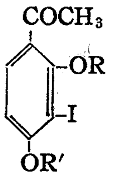
When resacetophenone (VIIa) was iodinated by the method of Shah, *et al.*,[2] it gave 3-iodoresacetophenone (VIIIa), which on methylation afforded its dimethyl ester (VIIIc).

Similarly, in order to obtained 5-iodo compounds, iodinations of VIIa and its 4-methyl ether (VIIb) with iodine and ammonia[2] were re-examined. But a poor yield of the desired compounds (IXa and IXb) was obtained, together with a large amount of 3-iodo compounds (VIIIa and VIIIb), respectively.

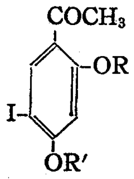
On the other hand, treatment of 2′,4′-dimethoxyacetophenone (VIIc) with iodine and nitric acid in glacial acetic acid at 15~16° gave only 5′-iodo-2′,4′-dimethoxyacetophenone (IXc) in 91% yield. The same product was also obtained in a good yield when VIIc was treated with iodine and iodic acid in methanol, but this reaction proceeded very slowly.



VIIa : R=R′=H
VIIb : R=H, R′=CH3
VIIc : R=R′=CH3



VIIIa : R=R′=H
VIIIb : R=H, R′=CH3
VIIIc : R=R′=CH3



IXa : R=R′=H
IXb : R=H, R′=CH3
IXc : R=R′=CH3

Attempted Ullmann reaction of VIIIc or IXc with copper powder was unsuccessful although many variations in the reaction conditions were employed. In these cases, the only detectable product was 2′,4′-dimethoxyacetophenone (VIIc), which was concluded to be formed by de-iodination of the starting materials.

[*1] Part I. (1) : This Bulletin, 12, 1232 (1964); This work was presented at the 83rd Annual Meeting of the Pharmaceutical Society of Japan, Nov., 1963, Tokyo.

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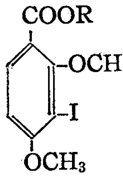
[*3] The formula numbering in this part continued the numbering of the Part I.[*1]

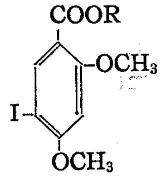
1) F.M. Dean : "Naturally Occurring Oxygen Ring Compounds," 176, 608 (1963), Butterworths, London; W.B. Whalley : "Recent Developments in the Chemistry of Natural Phenolic Compounds," Ed. by W.D. Ollis, 27 (1961), Pergamon Press, London.

2) M.V. Shah, S. Sethna : J. Chem. Soc., 1959, 2676.

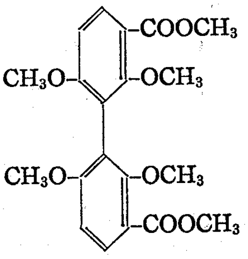
Then, VIIIc and IXc were respectively oxidized with sodium hypochlorite in methanol[3] to the corresponding acids (Xa and XIa), which were easily converted to their methyl esters (Xb and XIb).



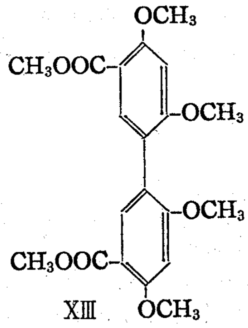
Xa : R=H
Xb : R=CH_3



XIa : R=H
XIb : R=CH_3



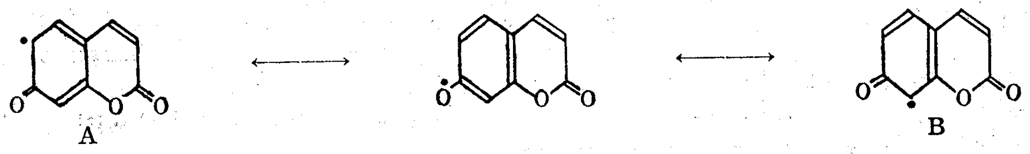
XII

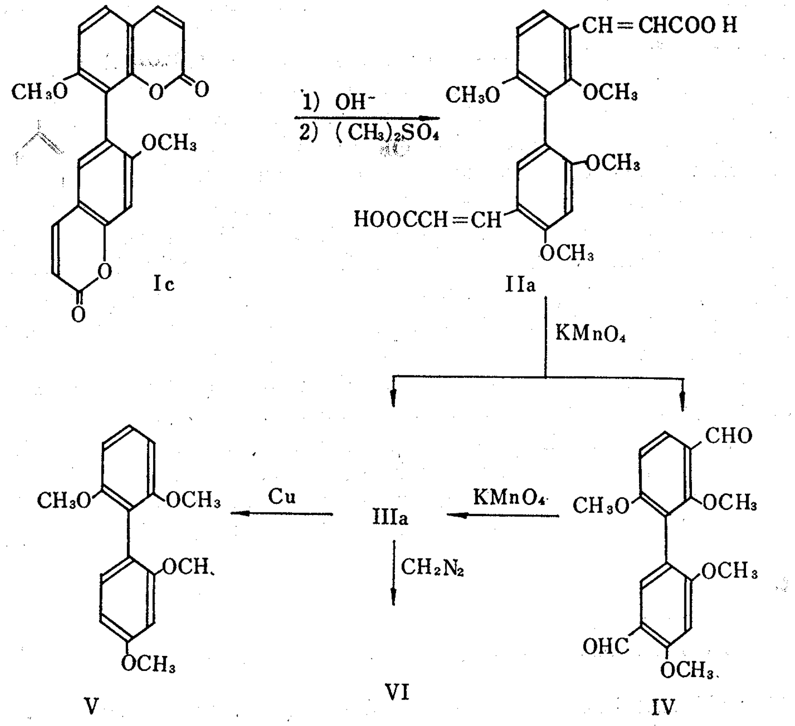


XIII

Respective heating of Xb and XIb with copper powder at 220° afforded dimethyl 2,2′,6,6′-tetramethoxy-3,3′-biphenyldicarboxylate (XII) and dimethyl 4,4′,6,6′-tetramethoxy-3,3′-biphenyldicarboxylate (XIII). Likewise, treatment of a mixture of Xb and XIb under the same condition gave three isomeric products, which were separated by repeated recrystallization. Two of them were identical with XII and XIII. The third product, $C_{20}H_{22}O_8$, m.p. 164~166°, was the unsymmetrical isomeride, dimethyl 2,4′,6,6′-tetramethoxy-3,3′-biphenyldicarboxylate (VI). It was found to be identical with the dimethyl ester (IIIb) derived from matsukaze-lactone (I) by a mixed fusion and comparison of infrared spectra.

Consequently, matsukaze-lactone (I) can be decidedly represented as 7,7′-dimethoxy-6,8′-bicoumarin (Ic), which is a new-type bicoumarin that have never been found in nature.





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[3] A. M. VanArendonk, M. E. Cupery: J. Am. Chem. Soc., 53, 3184 (1931).

The formation of Ic, as well as biflavonyls,[4] may involve the oxidative coupling of free radicals (*e.g.*, A and B) derived either from umbelliferon or closely related compound, association with O-methylation.

Matsukaze-lactone (Ie) and its degradation products are reasonably formulated as illustrated above:

Experimental*4

3′-Iodo-2′,4′-dimethoxyacetophenone (VIIIc)[2]——Colorless prismatic needles, m.p. 99~101° (reported, m.p. 101~102°). IR ν_{max}^{KBr} cm^{-1}: 1662 (carbonyl).

5′-Iodo-2′,4′-dimethoxyacetophenone (IXc)——a) To a stirred mixture of 2,4-dimethoxyacetophenone (VIIc) (900 mg., m.p. 35.5°) and iodine (635 mg.) in glacial AcOH (9 ml.) was added dropwise a solution of 63% HNO_3 (0.50 g.) in glacial AcOH (2 ml.) at 15~16°*5 for 1 hr., during which time fine needles were separated out. The reaction mixture was immediately poured into H_2O (100 ml.), and the precipitate was collected, washed with H_2O, dil. $Na_2S_2O_3$, and then H_2O, and dried. It was chromatographed on alumina with benzene to yield 1.39 g. of IXc, m.p. 145° (91.1%). Recrystallization from MeOH gave colorless fine needles, m.p. 145°, identical with IXc (m.p. 144.5~145.5°) obtained by the method of Shah, *et al.*[2] by a mixed fusion and comparison of IR spectra (in KBr). *Anal.* Calcd. for $C_{10}H_{11}O_3I$: C, 39.24; H, 3.62. Found: C, 39.55; H, 3.83. IR ν_{max}^{KBr} cm^{-1}: 1644 (carbonyl).

b) To a solution of VIIc (225 mg.) and iodine (254 mg.) in MeOH (8 ml.) was added a solution of I_2O_5 (42 mg.) in minimum quantity of H_2O and it was stirred at room temperature. After 6 hr., the reaction mixture was diluted with H_2O and the precipitate was purified by the same procedure as described in a). Yield, 346 mg., m.p. 145° (90.5%). This was identified with IXc by comparison of IR spectra (in KBr).

Attempted Ullmann Reactions of VIIIc and IXc——i) VIIIc (100 mg.) and Cu powder (100 mg.) were mixed thoroughly and heated in a salt bath at 240° for 30 min. After cooling, the reaction mixture was repeatedly extracted with boiling Me_2CO and the combined extracts were evaporated. The dark brown resinous residue was dissolved in $CHCl_3$ and the solution was passed through a column of alumina. From the $CHCl_3$ eluates, there was obtained a colorless oil (36.5 mg.), which solidified on standing as colorless crystals, m.p. 33.5°. The product was identified with VIIc by comparison of IR spectra (in KBr). The column was further eluted with $CHCl_3$ and $CHCl_3$-MeOH, but any other product was not found. By activation of Cu powder,[5] utilization of dimethylformamide as a solvent, or variations in reaction temperatures of 160 to 240°, the similar results were also obtained.

ii) Treatment of IXc (100 mg.) with Cu powder (200 mg.) by the same way as described for VIIIc, also gave VIIc, yield, 34 mg.

3-Iodo-2,4-dimethoxybenzoic Acid (Xa)——To a mixture of VIIIc (306 mg.) in MeOH (4.5 ml.) and 20% NaOH (1 ml.) was added a NaClO solution (4.0 g.)*6 and it was stirred at room temperature. After 2.5 hr., the reaction was completed by warming to 60° for 15 min. The reaction mixture was diluted with H_2O, and then the excess hypochlorite was destroyed by addition of 2% $NaHSO_3$. Acidification with HCl gave a white precipitate, which was collected, washed with H_2O, and dried. The acid was recrystallized from Me_2CO to afford 287 mg. of colorless needles, m.p. 173.5~186° (93.1%). Further recrystallization from dil. MeOH gave an analytical sample of Xa as colorless silky needles, m.p. 184~186°. *Anal.* Calcd. for $C_9H_9O_4I$: C, 35.09; H, 2.95. Found: C, 34.96; H, 2.73. IR ν_{max}^{KBr} cm^{-1}: 1691, 1670 (carboxyl).

5-Iodo-2,4-dimethoxybenzoic Acid (XIa)——To a suspension of IXc (918 mg.) in a mixture of MeOH (13.5 ml.) and 20% NaOH (3 ml.) added dropwise two-thirds portion of a NaClO solution (12.0 g.)*6 with stirring at room temperature for 10 min. As the reaction proceeded, starting materials disappeared, and Na salt of an acid formed was precipitated. The remaining one-third portion of NaClO solution was further added, and the temperature was kept at 50° for 10 min. The reaction mixture was dissolved in H_2O (150 ml.) and filtered. When the filtrate was treated with 2% $NaHSO_3$ and HCl in the same procedure as described above, the nearly pure product as a white powder, m.p. 206~207°, was obtained. Yield, 897 mg. (97.1%). It was recrystallized from Me_2CO to colorless silky needles, m.p. 209.5~210.5° (decomp.). *Anal.* Calcd. for $C_9H_9O_4I$: C, 35.09; H, 2.95. Found: C, 35.00; H, 2.75. IR ν_{max}^{KBr} cm^{-1}: 1692, 1660 (carboxyl).

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*4 All melting points are uncorrected.

*5 The reaction must be carried out cautiously to keep the temperature at 15~16°, otherwise the yield of IXc decreased.

*6 Prepared by passing chlorine into a cold NaOH solution (Org. Syntheses, Coll. Vol. 2, 429 (1943)).

4) W. Baker, A.C.M. Finch, W.D. Ollis, K.W. Robinson: J. Chem. Soc., **1963**, 1485.

5) Org. Syntheses, Coll. Vol. 3, 339 (1955).

Methyl 3-Iodo-2,4-dimethoxybenzoate (Xb)——The above acid (Xa) (1.00 g.) was refluxed with 5% HCl–MeOH (9.0 ml.) for 30 min. The solvent was removed, and after addition of H_2O and then 10% Na_2CO_3 to the residue, the precipitate was collected, washed with H_2O, and dried. The crystals thus obtained were dissolved in $CHCl_3$ and the solution was passed through a column of alumina to yield Xb (958 mg.), m.p. 61~73° (91.4%). Recrystallization from MeOH gave colorless pillars, m.p. 74~76°. *Anal.* Calcd. for $C_{10}H_{11}O_4I$: C, 37.29; H, 3.44. Found: C, 37.45; H, 3.55. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1690 (ester carbonyl).

Methyl 5-Iodo-2,4-dimethoxybenzoate (XIb)——The acid (Ⅺa) (300 mg.) was refluxed with 5% HCl–MeOH (3.0 ml.) for 30 min. The reaction mixture was treated in the same way as described above. After chromatography with $CHCl_3$, Ⅺb, m.p. 122~123°, was obtained (300 mg., 96.0%). Recrystallization from MeOH gave colorless prismatic needles, m.p. 123~123.5°. *Anal.* Calcd. for $C_{10}H_{11}O_4I$: C, 37.29; H, 3.44. Found: C, 37.28; H, 3.28. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1692 (ester carbonyl).

Dimethyl 2,2′,6,6′-Tetramethoxy-3,3′-biphenyldicarboxylate (XII)——The above ester (Xb) (200 mg.) and freshly prepared activated Cu powder[5)] (400 mg.) were mixed thoroughly and heated in an oil bath at 200~235° for 30 min. After cooling, the reaction mixture was repeatedly extracted with boiling Me_2CO. Removal of Me_2CO gave a dark brown oily residue (108 mg.), which crystallized on treatment with a small amount of MeOH. The crystalline product was chromatographed on alumina. After a trace of an oily substance had been eluted with benzene, elution with $CHCl_3$ afforded 56 mg. of Ⅻ (47.1%). Recrystallization from MeOH gave white prismatic needles, m.p. 138~139°. *Anal.* Calcd. for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68. Found: C, 61.63; H, 5.26. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1717, 1692 (ester carbonyl).

Dimethyl 4,4′,6,6′-Tetramethoxy-3,3′-biphenyldicarboxylate (XIII)——A mixture of Ⅺb (200 mg.) and activated Cu powder[5)] (400 mg.) was heated at 210~220° for 20 min. After cooling, the reaction mixture was extracted several times with warm $CHCl_3$. Evaporation of $CHCl_3$ gave brownish crystals, which were chromatographed on alumina. After a trace of an oily substance had been eluted with benzene, successive elution with benzene and $CHCl_3$ afforded 91 mg. of ⅩⅢ (74.7%). Recrystallization from MeOH gave colorless prisms, m.p. 208~208.5°. *Anal.* Calcd. for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68. Found: C, 61.26; H, 5.89. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1726, 1691 (ester carbonyl).

Dimethyl 2,4′,6,6′-Tetramethoxy-3,3′-biphenyldicarboxylate (VI)——Xb (300 mg.) and Ⅺb (300 mg.) were finely pulverized and thoroughly mixed with activated Cu powder[5)] (1.20 g.). The mixture was heated at 210~220° for 15 min. After cooling, the reaction mixture was extracted with $CHCl_3$. Evaporation of $CHCl_3$ gave a brown oily residue (363 mg.) which solidified on standing. The residual solid was slightly boiled with MeOH (6 ml.). The MeOH-insoluble part (57 mg.) was filtered while warm, washed with MeOH (2 ml.), and recrystallized from MeOH as colorless prisms, m.p. 208~208.5°, identical with ⅩⅢ by comparison of IR spectra (in KBr). The MeOH-soluble part and the MeOH washing were combined and allowed to stand overnight. The prismatic crystals separated out were collected and washed with MeOH. The combined mother liquor and washings were concentrated to a small volume (about 5 ml.) and the same crystals were further obtained. Repeated recrystallization of them (123 mg., m.p. 160~162°) from MeOH afforded 50 mg. of Ⅵ, colorless prisms, m.p. 164~166°, which were identified with Ⅲb derived from matsukaze-lactone by a mixed fusion and comparison of IR spectra (in KBr). *Anal.* Calcd. for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68. Found: C, 61.25; H, 5.72. Concentration of the mother liquor separated from Ⅵ gave a crystals, which was repeatedly recrystallized from dil. MeOH to a small amount of Ⅻ, m.p. 138~139°, identical with the samples obtained above by comparison of IR spectra (in KBr).

The authors express their gratitude to Dr. Y. Murayama, the Dean of the College, and Prof. S. Niinobe of this College for encouragements throughout the course of this work. Thanks are also to Mrs. Y. Baba and Miss Y. Gusokujima for elemental analyses.

Summary

A mixed Ullmann reaction of methyl 3-iodo-(Xb) and 5-iodo-2,4-dimethoxybenzoate (Ⅺb) gave dimethyl 2,4′,6,6′-tetramethoxy-3,3′-biphenyldicarboxylate (Ⅵ), m.p. 164~166°. It was proved to be identical with an ester (Ⅲb) which was derived from matsukaze-lactone (I). Consequently, matsukaze-lactone was represented by formula (Ic), 7,7′-dimethoxy-6,8′-bicoumarin and its biogenesis undoubtedly involves oxidative coupling.

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