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

Structure of Matsukaze-lactone. (2).

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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} C₂₀H₂₂O₈, m.p. 161~163.5°, which was obtained by oxidative degradation of I with potassium permanganate followed by methylation*² 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).

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

Similarly, in order to obtain 5-iodo compounds, iodinations of VIIa and its 4-methyl ether (VIIb) with iodine and ammonia²⁾ were re-examined. But a poor yield of the desired compounds (Ka and Kb) was obtained, together with a large amount of

3-iodo compounds (VIIa 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 (Kc) 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'=CH₃VIIc : R=R'=CH₃

VIIa : R=R'=H

VIIb : R=H, R'=CH₃VIIc : R=R'=CH₃

Ka : R=R'=H

Kb : R=H, R'=CH₃Kc : R=R'=CH₃

Attempted Ullmann reaction of VIIc or Kc 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 methanol³⁾ to the corresponding acids (Xa and XIa), which were easily converted to their methyl esters (Xb and XIb).

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, C₂₀H₂₂O₈, 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.

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 $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1662 (carbonyl).

5'-Iodo-2',4'-dimethoxyacetophenone (IXc)—a) To a stirred mixture of 2,4-dimethoxyacetophenone (VIc) (900 mg., m.p. 35.5°) and iodine (635 mg.) in glacial AcOH (9 ml.) was added dropwise a solution of 63% HNO₃ (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 H₂O (100 ml.), and the precipitate was collected, washed with H₂O, dil. Na₂S₂O₃, and then H₂O, and dried. It was chromatographed on alumina with benzene to yield 1.39 g. of Kc, m.p. 145° (91.1%). Recrystallization from MeOH gave colorless fine needles, m.p. 145°, identical with Kc (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 C₁₀H₁₁O₃I: C, 39.24; H, 3.62. Found: C, 39.55; H, 3.83. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1644 (carbonyl).

b) To a solution of VIc (225 mg.) and iodine (254 mg.) in MeOH (8 ml.) was added a solution of I₂O₅ (42 mg.) in minimum quantity of H₂O and it was stirred at room temperature. After 6 hr., the reaction mixture was diluted with H₂O 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 Kc 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 Me₂CO and the combined extracts were evaporated. The dark brown resinous residue was dissolved in CHCl₃ and the solution was passed through a column of alumina. From the CHCl₃ 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 VIc by comparison of IR spectra (in KBr). The column was further eluted with CHCl₃ and CHCl₃-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 Kc (100 mg.) with Cu powder (200 mg.) by the same way as described for VIIIc, also gave VIc, yield, 34 mg.

3-Iodo-2,4-dimethoxybenzoic Acid (Xa)—To a mixture of VIc (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 H₂O, and then the excess hypochlorite was destroyed by addition of 2% NaHSO₃. Acidification with HCl gave a white precipitate, which was collected, washed with H₂O, and dried. The acid was recrystallized from Me₂CO 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 C₉H₉O₄I: C, 35.09; H, 2.95. Found: C, 34.96; H, 2.73. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1691, 1670 (carboxyl).

5-Iodo-2,4-dimethoxybenzoic Acid (XIa)—To a suspension of Kc (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 H₂O (150 ml.) and filtered. When the filtrate was treated with 2% NaHSO₃ 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 Me₂CO to colorless silky needles, m.p. 209.5~210.5° (decomp.). *Anal.* Calcd. for C₉H₉O₄I: C, 35.09; H, 2.95. Found: C, 35.00; H, 2.75. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1692, 1660 (carboxyl).

*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 H₂O and then 10% Na₂CO₃ to the residue, the precipitate was collected, washed with H₂O, and dried. The crystals thus obtained were dissolved in CHCl₃ 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 C₁₀H₁₁O₄I: C, 37.29; H, 3.44. Found: C, 37.45; H, 3.55. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 CHCl₃, 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 C₁₀H₁₁O₄I: C, 37.29; H, 3.44. Found: C, 37.28; H, 3.28. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 powder⁵⁾ (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 Me₂CO. Removal of Me₂CO 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 CHCl₃ afforded 56 mg. of XII (47.1%). Recrystallization from MeOH gave white prismatic needles, m.p. 138~139°. *Anal.* Calcd. for C₂₀H₂₂O₈: C, 61.53; H, 5.68. Found: C, 61.63; H, 5.26. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 powder⁵⁾ (400 mg.) was heated at 210~220° for 20 min. After cooling, the reaction mixture was extracted several times with warm CHCl₃. Evaporation of CHCl₃ 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 CHCl₃ afforded 91 mg. of XIII (74.7%). Recrystallization from MeOH gave colorless prisms, m.p. 208~208.5°. *Anal.* Calcd. for C₂₀H₂₂O₈: C, 61.53; H, 5.68. Found: C, 61.26; H, 5.89. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 powder⁵⁾ (1.20 g.). The mixture was heated at 210~220° for 15 min. After cooling, the reaction mixture was extracted with CHCl₃. Evaporation of CHCl₃ 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 C₂₀H₂₂O₈: 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).

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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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