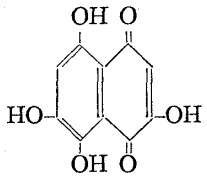
Chem. Pharm. Bull. 13(12)1472~1475(1965)

UDC 547.655.6.07

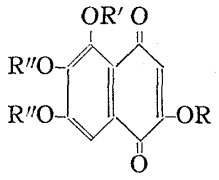
Shinsaku Natori*1 and Yuko Kumada*2 : Syntheses of 2,5,6,7-Tetramethoxy(hydroxy)- and 2,6,7,8-Tetramethoxy-1,4-naphthoquinone.

(*National Institute of Hygienic Sciences*[*1] *and Department of Chemistry, Tokyo Kyoiku University*[*2])

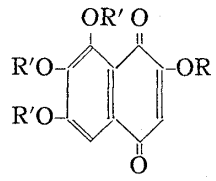
In the course of studies on the structure of mompain, which has now been elucidated as 2,5,7,8-tetrahydroxynaphthoquinone (I),[1] the two hitherto unknown isomers of tetrahydroxynaphthoquinone (II and III) became necessary for comparison. These compounds were synthesized essentially by the same method as the syntheses of 2,5,7-trihydroxy-(flaviolin) (IV) and 2,6,8-trihydroxy-1,4-naphthoquinone (V) by Roberts and his associates,[2,3] whose starting material, α-resorcylic acid, was replaced by gallic acid (VI) in the present case.



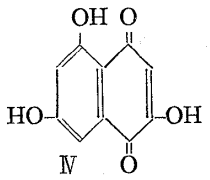
I



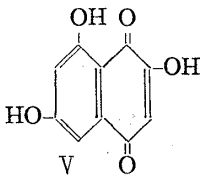
IIa : R=R′=R″=H
IIb : R=H, R′=R″=CH_3
IIc : R=R′=R″=CH_3
IId : R=R′=H, R″=CH_3



IIIa : R=R′=H
IIIb : R=H, R′=CH_3
IIIc : R=R′=CH_3

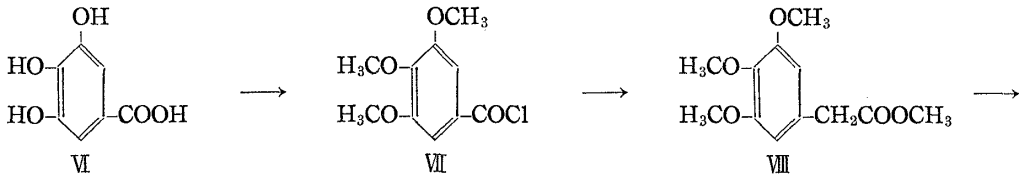


IV

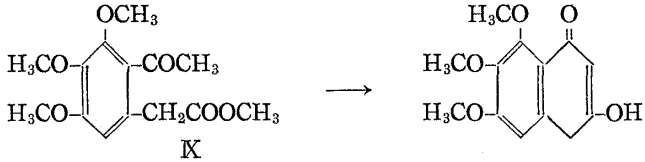


V

3,4,5-Trimethoxybenzoyl chloride (VII),[4] prepared from gallic acid, was homologated by the Arndt-Eistert reaction to methyl 3,4,5-trimethoxyphenylacetate (VIII). Acetylation of the ester with acetic anhydride and perchloric acid gave methyl 2-acetyl-3,4,5-trimethoxyphenylacetate (IX). Cyclization of this ester-ketone with base, followed by



VI → VII → VIII →



IX → IIb→IIa, IIc, IId

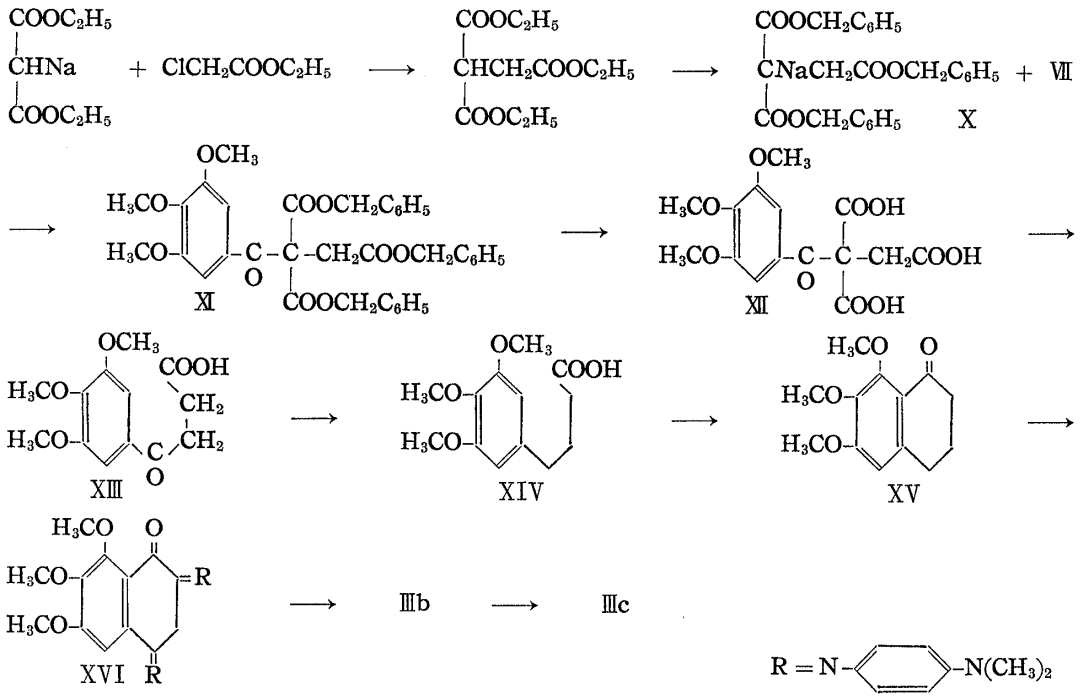
*1 Tamagawayoga, Setagaya-ku, Tokyo (名取信策).
*2 Present address : National Institute of Hygienic Sciences, Tokyo (熊田祐子).

1) S. Natori, Y. Kumada, H. Nishikawa : This Bulletin, **13**, 633 (1965).
2) J.E. Davies, F.E. King, J.C. Roberts : J. Chem. Soc., **1955**, 2782.
3) B.W. Bycroft, J.C. Roberts : *Ibid.*, **1962**, 2063.
4) J. Koo : J. Am. Chem. Soc., **75**, 720 (1953).

aereal oxidation, afforded 2-hydroxy-5,6,7-trimethoxy-1,4-naphthoquinone (IIb), m.p. 169~170°, which was methylated with diazomethane to give 2,5,6,7-tetramethoxy-1,4-naphthoquinone (IIc), m.p. 187~189°. Complete[3] and partial[5] demethylation of IIb by aluminum chloride afforded 2,5,6,7-tetrahydroxy-(IIa), m.p. 250~265° (decomp.), and 2,5-dihydroxy-6,7-dimethoxy-1,4-naphthoquinone (IId), m.p. 172~174°, respectively.

2,6,7,8-Tetramethoxy-1,4-naphthoquinone (IIIc) was synthesized in the following way. Benzyl sodio-1,1,2-ethanetricarboxylate (X)[6] was condensed with 3,4,5-trimethoxybenzoyl chloride (VII) and the crude keto-ester (XI) was submitted to catalytic debenzylation to afford keto-acid (XII). Decarboxylation of XII to XIII, followed by the Clemmensen reduction, yielded 3,4,5-trimethoxyphenylbutyric acid (XIV), which was cyclized with polyphosphoric acid to 6,7,8-trimethoxy-1-tetralone (XV). The tetralone was converted into a dianil (XVI) and hydrolysis of the anil, though rather in a poor yield[7], afforded 2-hydroxy-6,7,8-trimethoxy-1,4-naphthoquinone (IIIb), m.p. 177~178°. Methylation of IIIb with diazomethane gave 2,6,7,8-tetramethoxy-1,4-naphthoquinone (IIIc), m.p. 185~187°.

As shown in the previous communication,[1] four out of eight isomers of tetrahydroxy-1,4-naphthoquinone or their methyl ether have so far been recorded. The present work provides further two isomers to literatures.*3



Experimental*4

Methyl 3,4,5-Trimethoxyphenylacetate (VIII)——3,4,5-Trimethoxybenzoyl chloride,[4] $b.p_{20}$ 186°, was

*3 After the completion of this work, we learned that Thomson and his associates synthesized IIa, b, and d by their new synthetic method[7] (Prof. R. H. Thomson, University of Aberdeen, private communication).

*4 Melting points were determined on a Yanagimoto micro-melting point apparatus. Unless otherwise specified, infrared spectra were taken on a Koken Model 301 Infrared spectrophotometer in Nujol mull and ultraviolet spectra were measured in EtOH solution on a Hitachi EPS-2 Recording spectrophotometer.

5) E. Hardegger, *et al.*: Helv. Chim. Acta, **47**, 2017 (1964).
6) R. E. Bowman: J. Chem. Soc., **1950**, 325.
7) H. A. Anderson, J. Smith, R. H. Thomson: *Ibid.*, **1965**, 2141.

derived to the corresponding diazoketone, m.p. 103~104°, by the known method,[8] yield, 70%. A suspension of silver oxide (freshly prepared from silver nitrate (5.10 g.) and NaOH (1.3 g.)) in dry MeOH (50 ml.) was added to a solution of the diazoketone (24.2 g.) in dry MeOH (700 ml.). After the vigorous evolution of nitrogen ceased, the mixture was heated for 2 hr. and filtered. Removal of MeOH and distillation of the residue gave methyl 3,4,5-trimethoxyphenylacetate (Ⅷ), $b.p_5$ 166~168°.*5 Yield, 17 g. (48.4%). Hydrolysis of the ester gave the corresponding acid, m.p. 119~120° (lit.,[8] m.p. 121°).*5

Methyl 2-Acetyl-3,4,5-trimethoxyphenylacetate (IX)——Aqueous perchloric acid (60%, 0.8 ml.) was added to a mixture of the ester (Ⅷ) (17 g.), acetic anhydride (20 g.), and acetic acid (40 g.), cooled by ice-water. After keeping the mixture at a room temperature for 20 hr., ice-water was added to decompose the excess of the anhydride. The brown oil was extracted with ether and the ethereal layer was washed with 5% $NaHCO_3$ soln. and then dried. Removal of ether gave reddish-brown oil (15.8 g.), which was proved to be a mixture of the starting material and the acetylated compound (Ⅸ)*5 by hydrolysis.

2-Acetyl-3,4,5-trimethoxyphenylacetic Acid——The oily mixture (1 g.) was hydrolyzed with MeOH-KOH. The crude hydrolyzate was treated with a small amount of ether and undissolved solid was crystallized from water to give 3,4,5-trimethoxyphenylacetic acid as colorless needles, m.p. 120.5~122°. The ether soluble portion was crystallized from water to afford 2-acetyl-3,4,5-trimethoxyphenylacetic acid as colorless needles, m.p. 102~103°.*5 IR cm^{-1}: 1639, 1742 ($CHCl_3$), 1662, 1700 (KBr). *Anal.* Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.33; H, 6.34.

2-Hydroxy-5,6,7-trimethoxy-1,4-naphthoquinone (IIb)——A solution of the mixture (5.3 g.) of the ester and the ester-ketone in dry EtOH (80 ml.) was added dropwise to a refluxing solution of NaOEt (prepared from 1 g. of Na and 120 ml. of EtOH). The solution was refluxed for 0.5 hr. and cooled. After a stream of dry air was passed through the solution for 4 hr., resultant red precipitates were collected and treated with N H_2SO_4. The yellow solid (2.15 g., 30.6% from Ⅷ) was crystallized from benzene to yellow needles, m.p. 169~170°. IR cm^{-1}: 866, 937, 1006, 1014, 1108, 1139, 1211, 1330, 1340, 1579, 1650, 3330. UV λ_{max}^{EtOH} mμ (log ε): 267, 307, 355 (4.33, 4.12, 3.56). *Anal.* Calcd. for $C_{13}H_{12}O_6$: C, 59.06; H, 4.58. Found: C, 58.92; H, 4.63.

2,5,6,7-Tetramethoxy-1,4-naphthoquinone (IIc)——A suspension of Ⅱb (130 mg.) in ether was treated with ethereal diazomethane. The bright yellow needles, separated, was recrystallized from benzene to give Ⅱc, m.p. 187~189°. IR cm^{-1}: 858, 1010, 1123, 1320, 1575, 1622, 1645, 1676. UV λ_{max}^{EtOH} mμ (log ε): 266.5, 301, 361 (4.33, 4.09, 3.47). *Anal.* Calcd. for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found; C, 60.41; H, 5.05.

2,5,6,7-Tetrahydroxy-1,4-naphthoquinone (IIa)——2-Hydroxy-5,6,7-trimethoxynaphthoquinone (Ⅱb) (90 mg.) was added to a melt of $AlCl_3$ (1.6 g.) and NaCl (0.3 g.) and heated. The mixture was treated with 6N HCl (20 ml.) and extracted with ether. Removal of ether gave a dark orange solid (60 mg.), which was sublimed at 150° under 6 mm. Hg to yield the desired compound as red crystals, m.p. 250~265° (decomp.). IR cm^{-1}: 865, 1075, 1220, 1312, 1585, 1608, 1643, 3280, 3440. UV λ_{max}^{EtOH} mμ (log ε): 273.5, 317, 428 (4.11, 3.85, 3.54). *Anal.* Calcd. for $C_{10}H_6O_6$: C, 54.05; H, 2.72. Found: 53.65; H, 3.13.

2,5-Dihydroxy-6,7-dimethoxy-1,4-naphthoquinone (IId)——A solution of Ⅱb (90 mg.) in nitrobenzene (20 ml.) was stirred with $AlCl_3$ (6.0 g.) in nitrobenzene (50 ml.) for 2.5 hr.[5] The reaction mixture was poured on a mixture of ice and conc. HCl (60 ml.). The aqueous layer was separated, washed with ether, and heated with conc. HCl (120 ml.) at 50~55° for 2 hr. After cooling the solution was extracted with ether. Removal of ether and purification by chromatography over $CaHPO_4$ and by sublimation at 105° under 8 mm. Hg gave orange needles of m.p. 172~174°. *Anal.* Calcd. for $C_{12}H_{10}O_6$: C, 57.60; H, 4.03. Found: C, 57.80; H, 4.02. UV λ_{max}^{EtOH} mμ (log ε): 261, 315, 415 (4.25, 4.07, 3.66). IR cm^{-1}: 930, 1020, 1125, 1324, 1358, 1586, 1614, 1650, 3260 (br), 3580.

Benzyl 1-(3,4,5-Trimethoxybenzoyl)-1,1,2-ethanetricarboxylate (XI)——Benzene solution of 3,4,5-trimethoxybenzoyl chloride (Ⅶ) (48 g.) was added to the benzene solution of benzyl sodio-1,1,2-tricarboxylate (Ⅹ).[6] The mixture was refluxed for 0.5 hr., cooled, and poured into ice-water (400 ml. containing a few drops of conc. H_2SO_4). The organic layer was separated and aqueous layer was extracted with benzene. Combined benzene solution was washed with water and dried with $MgSO_4$. Benzene was removed under the reduced pressure and the residue was kept at 166° under 2~3 mm. Hg to remove water, benzyl alcohol and benzyl chloride. The product was a very viscous yellow-brown oil (129.3 g., 98%).

4-Oxo-3,4,5-trimethoxyphenylbutyric Acid (XIII)——The above oil (120.8 g.) in a mixture of EtOH (75 ml.) and EtOAc (75 ml.) was hydrogenolyzed in the presence of palladised carbon (10%, 2 g.). Whenever absorption became slow, the catalyst was filtered off and fresh palladised $SrCO_3$ (10%, 13 g.) was added and hydrogenation continued. When the hydrogenation was completed (13.3 L. of H_2 was taken up), the

*5 Note Added in Proof: After the submission of this manuscript, we learned that A. Kamal, *et al.* (Tetrahedron, **21**, 1411 (1965)) established the structure of curvulic acid and curvin, metabolites of *Curvularia siddiqui* sp. novo, as 2-acetyl-3,5-dihydroxy-4-methoxyphenylacetic acid and the ethyl ester, respectively, and Ⅷ, $b.p_{0.5}$ 148°, the corresponding acid, m.p. 120°, Ⅸ, m.p. 62°, $b.p_{0.1}$ 178~180°, and the corresponding acid, m.p. 102°, were prepared as the derivatives.

8) K.H. Slotta, J. Müller: Z. physiol. Chem., Hoppe-Seyler's, **238**, 14 (1936).

catalyst was removed by filtration and removal of the solvent left brown oil, to which 2*N* NaOH (300 ml.) was added and refluxed for 45 min. After cooling, benzyl alcohol was separated off, and the aqueous layer was acidified with conc. HCl. The precipitates were repeatedly crystallized from EtOH–H_2O to colorless needles (36 g.), m.p. 107~109°. Since thin-layer chromatography of the crystal proved to be a mixture of two compounds, an ethanol solution of the mixture was treated with aqueous semicarbazide acetate to form the semicarbazone of 4-oxo-3,4,5-trimethoxyphenylbutyric acid as red crystals (31.7 g.), m.p. 184~187°. From the mother liquor 3,4,5-trimethoxybenzoic acid (9.2 g.) was recovered. The semicarbazone was hydrolyzed with 2*N* HCl for 1/2 hr. to give the keto-acid (XIII) (21 g., 38.6%), which was crystallized from benzene-petr. ether to colorless needles, m.p. 117~118°. IR cm^{-1} : 830, 996, 1124, 1162, 1320, 1585, 1689, 1702. *Anal.* Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found : C, 58.41; H, 6.10.

3,4,5-Trimethoxyphenylbutyric Acid (XIV)——The keto-acid (XIII) (10.7 g.) in toluene (50 ml.) was added to a mixture of amalgamated zinc (prepared from Zn (80 g.), water (120 ml.), mercuric chloride (4 g.) and 10% HCl (8 ml.)) and conc. HCl (50 ml.). The mixture was refluxed for 11 hr. under the addition of several portions of conc. HCl (50 ml.), cooled, and extracted with ether. Removal of the solvent gave crystalline solids (6.5 g.), which was used without further purification. Recrystallization from ligroin gave 3,4,5-trimethoxyphenylbutyric acid as colorless needles, m.p. 83~85°. IR cm^{-1} : 802, 1002, 1127, 1589, 1698. *Anal.* Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found : C, 61.40; H, 7.04.

6,7,8-Trimethoxy-1-tetralone (XV)——The crude acid (6.4 g.) and polyphosphoric acid (50.0 g.) were shaken occasionally at 80° for 45 min. The red-brown syrup was poured into ice-water and extracted with ether. The organic layer was washed with water, 5% $NaHCO_3$, and dried. Removal of ether gave a crystalline solid (5 g., 84.1%). Recrystallization from lygroin-ether gave 6,7,8-trimethoxy-1-tetralone as colorless needles (1.25 g.), m.p. 126~128°. IR cm^{-1} : 842, 1015, 1107, 1143, 1252, 1271, 1330, 1591, 1602, 1665. *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found : C, 66.19; H, 6.53.

Dianil (XVI)——To a mixture of the tetralone (XV) (1.2 g.) and *p*-nitroso-N,N-dimethylaniline hydrochloride (3.2 g.) in EtOH (25 ml.) was gradually added 10% solution of NaOH (8 ml.). After slight warming, NaCl was filtered off and the filtrate was kept at a room temperature for 2 days. Filtration gave the dianil (1.30 g., 51.1%) as dark green needles, m.p. 193~195°. *Anal.* Calcd. for $C_{29}H_{20}O_4N_4$: N, 11.20. Found : N, 11.17.

2-Hydroxy-6,7,8-trimethoxy-1,4-naphthoquinone (IIIb)——The dianil (1.15 g.) was stirred with 2*N* H_2SO_4 (35 ml.) at 80° for 1.5 hr. The mixture was extracted with ether and the extract was washed with water and 5% $NaHCO_3$. The alkaline solution was acidified and extracted with ether. Removal of ether afforded red-yellow solid (180 mg.). Crystallization from benzene-hexane yielded 2-hydroxy-6,7,8-trimethoxy-1,4-naphthoquinone as orange needles, m.p. 177~178°. IR cm^{-1} : 856, 989, 1182, 1353, 1570, 1651, 3305. UV λ_{max}^{EtOH} mμ (log ε) : 268.5, 305, 354 (4.38, 4.21, 3.54). *Anal.* Calcd. for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found : C, 58.79; H, 4.43.

2,6,7,8-Tetramethoxy-1,4-naphthoquinone (IIIc)——Methylation of IIIb (80 mg.) with diazomethane in ether, followed by chromatography through a column of alumina (neutral, grade III) and crystallization from benzene-hexane, afforded IIIc as yellow needles, m.p. 185~187° (55 mg., 65.3%). IR cm^{-1} : 858, 1012, 1141, 1237, 1352, 1574, 1618, 1649, 1677. UV λ_{max}^{EtOH} mμ (log ε) : 269, 299, 359 (4.35, 4.17, 3.49). *Anal.* Calcd. for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found : C, 60.18; H, 5.45.

The authors' thanks are due to Dr. Oba and Miss Koyama of this Institute for the measurement of IR spectra and to members of Central Analytical Laboratory, Faculty of Pharmaceutical Sciences, University of Toyko, for carrying out elemental analyses.

Summary

2,5,6,7-Tetramethoxy(hydroxy)- and 2,6,7,8-tetramethoxynaphthoquinones were synthesized, starting from gallic acid.

(Received June 16, 1965)