# The Synthesis of Benzofuroquinolines. III. Two Dihydroxybenzofuroquinolinones



Seiji Yamaguchi*, Yoshiteru Yoshimoto, Rikuko Murai, Fumihiko Masuda, Minoru Yamada, and Yoshiyuki Kawase

Department of Chemistry, Faculty of Science, Toyama University, Gofuku, Toyama 930, Japan

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Two dihydroxybenzofuroquinolinones, 3,9-dihydroxy-5*H*-benzofuro[3,2-*c*]quinolin-6-one (V) and 3,8-dihydroxy-6*H*-benzofuro[2,3-*b*]quinolin-11-one (VI), were obtained by the demethyl-cyclization of 3-(2,4-dimethoxyphenyl)-4-hydroxy-7-methoxy-1*H*-quinolin-2-one (IV). By the methylation with diazomethane, V gave a dimethylated compound (VII), while VI gave a trimethylated compound (VIII).

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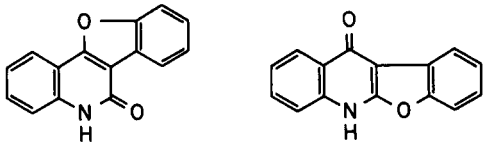
In the course of our studies of polycyclic heteroaromatic compounds, we studied the synthesis of benzofuroquinolines in order to investigate their chemical reactivities and also to test their activities as mutagens, carcinogens, and also as antitumor substances. In our previous paper [1], we reported the synthesis of two benzofuroquinolinones (I and II). In this paper, we will report the synthesis of 3,9-dihydroxy-5*H*-benzofuro[3,2-*c*]quinolin-6-one, which has an analogous structure to coumestrol. Coumestrol, 3,9-dihydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one, shows an estrogenic activity. Therefore, we expect V a similar activity.

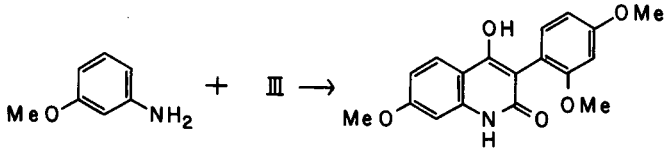
Chart 1



I II

Diethyl (2,4-dimethoxyphenyl)malonate (III) was prepared in three steps from 2,4-dimethoxyacetophenone, as shown below. Refluxing a mixture of *m*-methoxyaniline and the malonate (III) in diphenyl ether for 1 hour gave a condensed product IV in 94% yield. The $^1$H-nmr spectrum of IV showed a doublet signal (J = 10 Hz) at 7.9 ppm due to 5-H. It showed that the cyclization occurred at the *para* position of the methoxyl group to give IV.

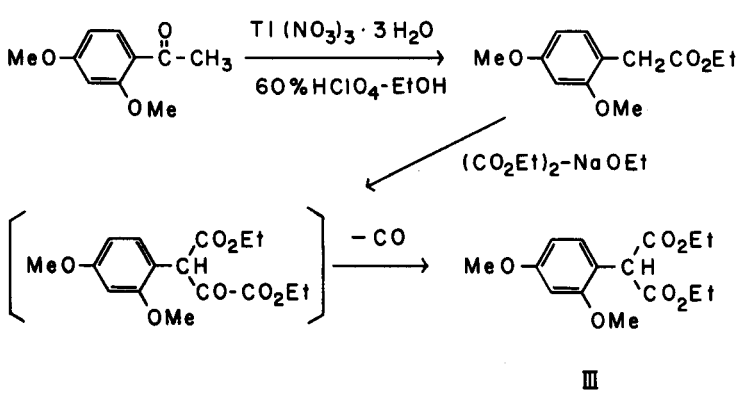
Chart 3



IV

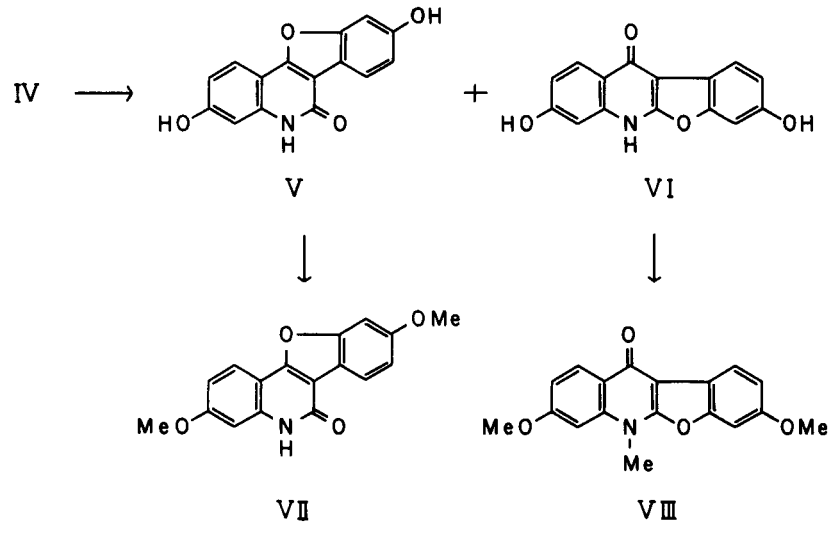
Demethyl-cyclization of IV with pyridine hydrochloride gave a mixture of two dihydroxybenzofuroquinolinones. The crystallization of the mixture from ethanol gave 3,9-dihydroxy-5*H*-benzofuro[3,2-*c*]quinolin-6-one (V), mp 358-360° dec; $\nu$ C=O 1665 cm$^{-1}$. The ethanol was removed from the filtrate. Then, the crystallization of the residue from aquous 60% ethanol gave 3,8-dihydroxy-6*H*-benzofuro[2,3-*b*]quinolin-11-one (VI), mp 396-400° dec; $\nu$ C=O 1640 cm$^{-1}$. Their carbonyl bands well corresponded to those of I and II, respectively. In the $^1$H-nmr spectra, V showed two doublets around 8.0 ppm due to 1-H and 7-H, while VI showed two doublets at 8.0 and 8.3 ppm due to 10-H and 1-H. Their uv spectra well corresponded to those

Chart 2



III

Chart IV



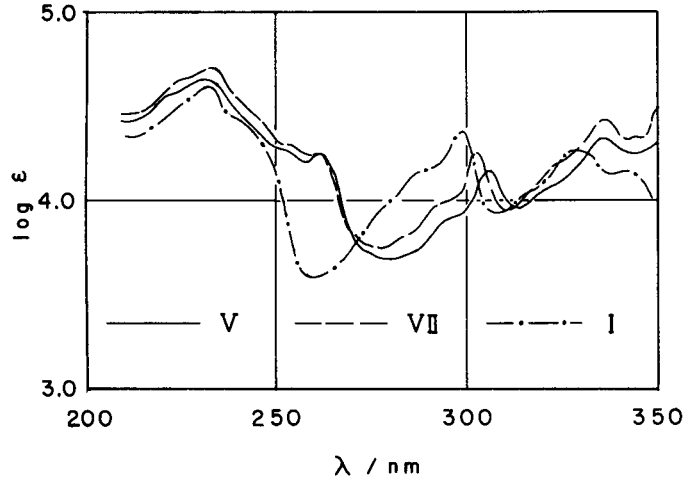




Figure 1. The uv spectra of 5*H*-benzofuro[3,2-*c*]quinolin-6-ones.

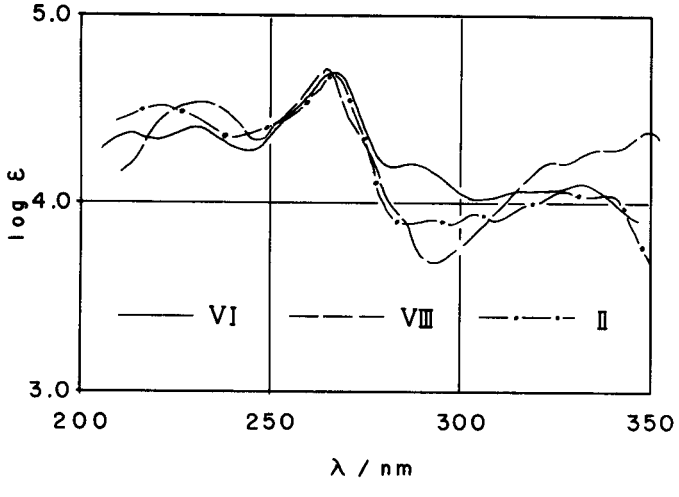



Figure 2. The uv spectra of 6*H*-benzofuro[2,3-*b*]quinolin-11-ones.

of I and II, respectively.

The methylation of V with diazomethane in methanol-ether gave a dimethylated compound, 3,9-dimethoxy-5*H*-benzofuro[3,2-*c*]quinolin-6-one (VII), which showed two *O*-methyl signals in the $^1$H-nmr spectrum. But, the methylation of VI by the same procedure gave a trimethylated compound, 3,8-dimethoxy-6-methyl-6*H*-benzofuro[2,3-*b*]-quinolin-11-one (VIII), which showed two *O*-methyl signals and one *N*-methyl signal in the $^1$H-nmr spectrum.

The carbonyl bands in the ir spectra showed that V and VII had a 2(1*H*)-quinolinone of an amide type and VI and VIII had a 4(1*H*)-quinolinone of a cross-conjugated ketone type.

## EXPERIMENTAL

All melting points were measured in a salt bath, and all melting points and all boiling points are uncorrected. The ir spectra were taken on a Hitachi EPI-S2 spectrophotometer as potassium bromide disk; UV spectra were taken on a Hitachi 220A spectrophotometer in ethanolic solution. Mass spectra were recorded on a JEOL LMS-OISG-2 mass spectrometer. The $^1$H-nmr spectra were recorded on a JEOL JNM-MH-60 nmr spectrometer. Some uv data are summarized in Figures 1 and 2.

Diethyl (2,4-Dimethoxyphenyl)malonate (III).

To an ethanolic solution of sodium ethoxide prepared from ethanol (20 ml) and sodium metal (0.90 g, 39 mmole), diethyl oxalate (5.7 g, 39 mmole) was added, and then ethyl (2,4-dimethoxyphenyl)acetate (4.3 g, 19 mmole) (bp 143-153°/4 mm Hg) prepared from 2,4-dimethoxyacetophenone by the McKillop's procedure [2] was added with stirring. The mixture was stirred for 30 minutes at room temperature. After the removal of the ethanol from the mixture, the residue was treated with water and benzene. The benzene layer was extracted with 5% sodium hydroxide solution. The alkaline layer was combined with the aquous layer separated from the reaction mixture, and acidified with 50% hydrochloric acid. The separated oil was extracted with benzene. The benzene layer was washed with sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate. After the removal of the benzene the residual oil was

carefully heated around 175° under reduced pressure (17 mm Hg) for 5 hours. After the thermal decarbonylation, the residual oil was distilled to give diethyl (2,4-dimethoxyphenyl)malonate (III), bp 169-178° (3 mm Hg), mp 59-61.5°; ir: 1750, 1730 $cm^{-1}$.

3-(2,4-Dimethoxyphenyl)-4-hydroxy-7-methoxy-1*H*-quinolin-2-one (IV).

A mixture of *m*-methoxyaniline (1.0 g, 8.1 mmoles), diethyl malonate III (2.1 g, 7.1 mmoles), and diphenyl ether (5.0 g) was refluxed for 1.5 hours. The cooled reaction mixture was then treated with ether and 5% sodium hydroxide solution. The ether layer was extracted with 5% sodium hydroxide solution. The combined alkaline layer was acidified with 50% hydrochloric acid. The white precipitates formed were collected and recrystallized from acetic acid to give IV (2.2 g, 94%) as pale brown fine needles; mp 302-304°; ir: 1650 $cm^{-1}$; $^1$H-nmr (DMSO-$d_6$): 3.8 (3H, s), 3.9 (6H, s), 6.5-7.0 (4H, m), 7.1 (1H, d, J = 10 Hz), 7.9 ppm (1H, d, J = 10 Hz); ms: m/e 327 ($M^+$), 310 ($M^+$-OH), 296 ($M^+$-$OCH_3$).

*Anal.* Calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.24; N, 4.28. Found: C, 65.96; H, 5.20; N, 4.01.

Demethyl-cyclization of IV.

A mixture of IV (3.6 g, 11 mmoles) and pyridine hydrochloride (30 g) (bp 218°) was vigorously refluxed for 1.5 hours. The cooled reaction mixture was treated with water and the resulting precipitates were collected. The precipitates were crystallized from ethanol to give V (1.4 g, 47%), mp 358-360° dec; ir: 3500-3000 (broad), 1665 $cm^{-1}$; $^1$H-nmr (DMSO-$d_6$): 6.9-7.2 (3H, m), 7.2 (1H, d, J = 2 Hz), 8.0 ppm (2H, d, J = 10 Hz); ms: m/e 267 ($M^+$).

*Anal.* Calcd. for $C_{15}H_9NO_4$: C, 67.41; H, 3.39; N, 5.24. Found: C, 67.26; H, 3.49; N, 5.35.

The ethanol was removed from the filtrate. The crystallization of the residue from aquous 60% ethanol gave VI (0.55 g, 19%), mp 396-400° dec; ir: 3500-3000 (broad), 1640 $cm^{-1}$; $^1$H-nmr (DMSO-$d_6$): 7.0-7.3 (4H, m), 8.0 (1H, d, J = 9 Hz), 8.3 ppm (1H, d, J = 9 Hz); ms: m/e 267 ($M^+$). In the elemental analysis, good agreement between the found values and the calculated values was not obtained, because the crystals of VI were so hygroscopic as to take up water rapidly during weighing.

Methylation of V and VI.

To a solution of V or VI in methanol, ether containing excess diazomethane was added. The mixture was allowed to stand in a refrigerator overnight. The ether and the excess diazomethane were removed and the residue was recrystallized from acetic acid or ethanol to give VII or VIII.

Compound VII had mp 301-303° (recrystallized from acetic acid); ir: 1675 $cm^{-1}$; $^1$H-nmr (DMSO-$d_6$): 3.9 (6H, s), 7.1-7.3 (3H, m), 7.5 (1H, d, J = 2 Hz), 8.1 ppm (2H, d, J = 9 Hz); ms: m/e 295 ($M^+$), 280 ($M^+$-$CH_3$).

*Anal.* Calcd. for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.44; N, 4.74. Found: C, 68.94; H, 4.45; N, 4.96.

Compound VIII had mp 206.5-208.5° (recrystallized from ethanol); ir: 1635 $cm^{-1}$; $^1$H-nmr (DMSO-$d_6$): 3.9 (3H, s), 4.0 (3H, s), 4.3 (3H, s), 7.0-7.5 (4H, m), 8.0 (1H, d, J = 9 Hz), 8.3 ppm (1H, d, J = 10 Hz); ms: 309 ($M^+$), 294 ($M^+$-$CH_3$).

*Anal.* Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.15; H, 5.07; N, 4.40.

## REFERENCES AND NOTES

[1] Y. Kawase, S. Yamaguchi, M. Morita, and T. Uesugi, *Bull. Chem. Soc. Japan*, **53**, 1057 (1980).

[2] A. McKillop, B. R. Swann, and E. C. Taylor, *J. Am. Chem. Soc.*, **95**, 3340 (1973).