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Hydrogenolysis of a Quinonoid Oxygen of Alkoxynaphthoquinones

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During the course of our experiments on the structural determination of hydroxytanshinone[1] (I), catalytic hydrogenation of I was carried out in an acidic condition to afford two substances. One was a known orange pigment cryptotanshinone[2] (II), which was formed by hydrogenolytic removal of benzylic hydroxy group followed by autoxidation of the corresponding hydroquinone. The other was a colorless compound which was also slowly autoxidized to cryptotanshinone (II), but the structure remained undecided.

In order to determine the structure of this unusual reaction product, the hydrogenation product was isolated as a stable acetate. After prolonged hydrogenation of hydroxytanshinone (I) in the presence of palladium charcoal and acid, the reaction product was immediately acetylated to afford a monoacetate (IV). Acetate (IV) was also obtained from tanshinone-II[3] (VI) under the same conditions of reaction and time. Although quinones are usually reduced to the corresponding hydroquinones by catalytic hydrogenations and smoothly re-oxidized in the air into the original quinones, physical and chemical properties of acetate (IV) showed that, besides benzylic hydroxy group of hydroxytanshinone (I), one of the quinonoid oxygen atoms was also removed during the course of hydrogenation reaction. The position of the removed oxygen atom was first deduced from the NMR spectrum. The NMR spectrum of monoacetate (IV) is quite similar to that of cryptotanshinone (II), and shows the presence of *gem*-dimethyl group (δ 1.32, s), a methyl group (δ 1.30, d, $J=6$ Hz) attached to a methine group (δ 3.75, m), a methylene (δ 4.25, 4.82, dq, $J=10$, 9 and 6 Hz) bonded to an oxygen atom and two aromatic protons (C_9-H and C_{10}-H; δ 7.35, d, $J=9$ Hz and δ 7.70, brd, $J=9$ Hz, respectively). However, there are differences between the two spectra; whereas aromatic protons (C_9-H and C_{10}-H) of cryptotanshinone appear at δ 7.50 and δ 7.68 as sharp AB-quartet, one component (δ 7.70) of the corresponding AB-quartet of acetate (IV) is broadened by a long-range coupling[4] with epi-proton C_4-H (δ 7.12, br s). This type of long-range coupling was also found in the spectrum of a synthetic compound[5] (VII), in which the signal of C_{10}-H (δ 7.95, brd, $J=9$ Hz) is broadened by a long-range coupling with C_4-H (δ 6.80, brd, $J=2$ Hz). Benzylic protons of acetate (IV) appear at a higher field (δ 2.98, br t) than that (δ 3.24, br t) of diacetyldihydrotanshinone-II[3] (VIII), in which benzylic

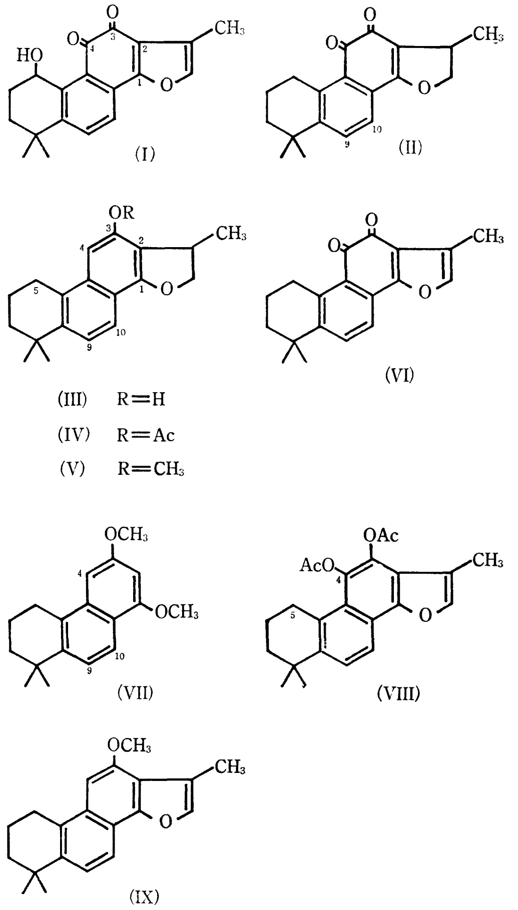

Fig. 1

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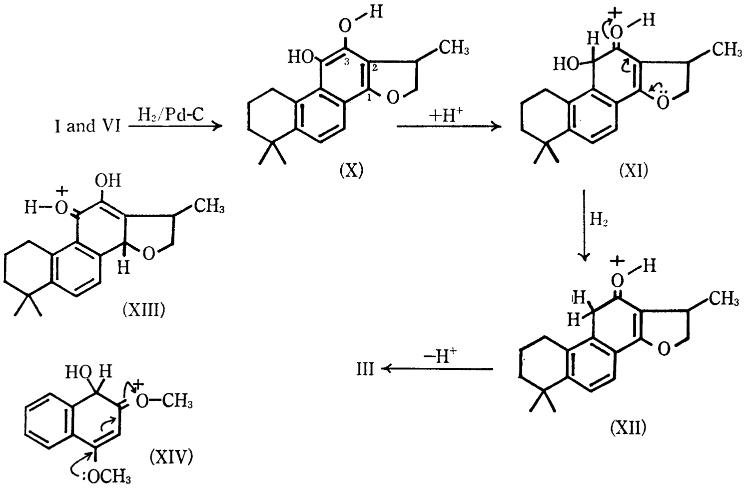

Fig. 2

protons (C_5-2H) are shifted to a low field by the deshielding effect of C_4-acetoxyl group. From these NMR properties, the position of the removed oxygen atom was assigned to C_4, and the structure of the monoacetate was deduced to be IV. For confirmation of the structure, reduction product (III) was converted into a known compound (IX). Hydrogenation product (III) was first methylated by dimethyl sulfate to afford a monomethyl ether (V). Ether (V) was dehydrogenated by refluxing with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[6] to afford a furanonaphthyl ether (IX), which was identical with the synthetic compound (IX) prepared in the total synthesis of tanshinones.[5] Thus the structure of the air sensitive compound obtained by catalytic hydrogenation in acidic condition could be assigned to III.

Catalytic hydrogenation of tanshinone-II proceeded very rapidly to afford a colorless solution of the corresponding hydroquinone within a few minutes, when the reaction was allowed to stop just to obtain a mixture of tanshinone-II (VI) and cryptotanshinone (II). On the other hand, when the hydrogenation mixture was stirred in hydrogen atomosphere for a longer time (fifteen hours or more), the sole reaction product was monohydroxy compound (III). These observations show that a hydroquinone (X) produced from tanshinone-II is an intermediate of the hydrogenolysis reaction. Protonation to a carbon atom of hydroquinone (X) forms benzyl alcohol (XI), which would readily lose a hydroxy group in hydrogenolytic condition to give (XII). Protonated ketone (XII) loses a proton to afford the monohydroxy compound (III).

The *meta*-oriented two oxygen functions (C_1–O and C_3–O) in the hydroquinone (X) have a particularly important effect on the formation of carbon-protonated species (XI), because unsubstituted 1,2-naphthoquinone showed no hydrogenolytic removal of quinonoid oxygen atom even under much severer conditions, and the product expected from another protonated intermediate (XIII) was not detected from the reaction mixture. The same effect of two oxygen atoms situated in *meta* orientation was recently found[7] in alkoxy exchange reaction of naphthyl alkyl ethers. Thus, while 1-hydroxy-2, 4-dimethoxynaphthalene exchanges methoxy groups to give 1-hydroxy-2,4-diethoxynaphthalene in acidic ethanol through carbon-protonated species (XIV), 1,4-dimethoxy-naphthalene does not exchange in the same condition.

Experimental[8]

Hydrogenolysis of Tanshinone-II (VI). To a solution of 240 mg of tanshinone-II in ethanol (60 m*l*) were added 250 mg of palladium charcoal (5%) and 0.1 m*l* of concentrated hydrochloric acid. The mixture was stirred overnight at room temperature in hydrogen atmosphere. The solution was filtered and the filtrate was neutralized with saturated sodium bicarbonate solution and extracted with ether. Evaporation of the solvent afforded a white viscous oil which slowly changed into orange compound, cryptotanshinone, in the air.

Monoacetate(IV). The above reaction product (*ca.*

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[8] Melting points were measured by a mp apparatus, type MP-1, of Yamamoto Scientific Co. Ltd., and are uncorrected. The IR spectra were measured with a Hitachi EPI-S2. The UV spectra were measured with a Hitachi EPS-3T recording spectrometer in ethanol. The NMR spectra were measured with a Hitachi R-20 at 60 MHz in $CDCl_3$ solution using TMS as an internal reference.

100 mg) was dissolved in 1 m*l* of pyridine, acetic anhydride (2 m*l*) was slowly added, and the reaction mixture was stood overnight at room temperature. The solution was treated as usual, and the acetate was purified by repeated chromatography. $\lambda_{\max}^{\mathrm{EtOH}}$ 232 (sh), 244, 293, 303, 317 and 331 mμ. $\nu_{\max}^{\mathrm{CHCl_3}}$ 1760, 1640, 1600, 1580, 1100 and 1040 cm^{-1}. *m*/*e* 324.175 (M$^+$): calcd for $C_{21}H_{24}O_3$, *m*/*e* 324.172.

The acetate obtained from hydroxytanshinone under the same reaction conditions is identical with this acetate.

Monomethyl Ether (V). About 100 mg of the reaction product of the hydrogenation was dissolved in 5 m*l* of acetone. To this were added 0.2 m*l* of freshly distilled dimethyl sulfate and 1 g (excess amount) of finely pulverized potassium carbonate. After refluxing the mixture under nitrogen for three hours, the same amounts of potassium carbonate and dimethyl sulfate were added, and refluxed for another three hours. The reaction mixture was filtered off while hot, and the filtrate was evaporated to dryness *in vacuo* until crystals appeared. The crude crystals were purified by column chromatography(SiO_2) and the monomethyl ether was eluted with benzene-hexane (1 : 2), and then recrystallized from ethanol to give white crystals (70 mg): mp 125—125.5°C; Found: C, 80.59; H, 8.07%. Calcd $C_{20}H_{24}O_2$: C, 81.04; H, 8.16%. $\lambda_{\max}^{\mathrm{EtOH}}$ 224, 242 (sh), 248, 280, 283, 303, 317 and 332 mμ. $\nu_{\max}^{\mathrm{KBr}}$ 3090, 1635, 1603, 1520 and 1115 cm^{-1}. $\delta^{\mathrm{CHCl_3}}$ ppm, 1.34 (s, 6H), 1.35 (d, 3H, *J*=6 Hz), 1.8 (m, 4H), 3.00 (brt, 2H, *J*=6 Hz), 3.7 (m, 1H), 3.92 (s, 3H), 4.30 (q, 1H, *J*=9 and 6 Hz), 4.80 (t, 1H, *J*=9 Hz), 6.75 (s, 1H), 7.30 (d, 1H, *J*=8 Hz) and 7.70 (d, 1H, *J*=8 Hz).

Oxidation of Monomethyl Ether (V) with 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). To a solution of 39 mg of V in benzene (4.5 m*l*) was added 33 mg of DDQ. After the solution was refluxed under nitrogen for 75 min, separated hydroquinone was filtered off. Evaporation of the filtrate afforded white crystals (37 mg); mp 124—124.5°C (EtOH). The spectrum of UV and IR, and melting point were all identical with those of synthetic compound (IX), and the latter was not depressed in mixed melting. $\lambda_{\max}^{\mathrm{EtOH}}$ 240, 248, 255.5, 275 (sh), 286 (sh), 325 and 338 mμ. $\nu_{\max}^{\mathrm{KBr}}$ 3080, 1635, 1225 and 1115 cm^{-1}. $\delta^{\mathrm{CHCl_3}}$ ppm, 1.40 (s, 6H), 1.8 (m, 4H), 2.40 (d, 3H, *J*=1 Hz), 3.08 (brt, 2H, *J*=6 Hz) 3.98 (s, 3H), 6.80 (s, 1H), 7.35 (q, 1H, *J*=1 Hz), 7.45 (d, 1H, *J*=9 Hz) and 8.00 (d, 1H, *J*=9 Hz).

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