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Synthesis of Furonaphthoquinones

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The reaction of 2-acetoxy-1,4-naphthoquinone with *N*-(1-propenyl)morpholine in an ordinary atomsphere afforded 3-methylnaphtho[2,3-*b*]furan-4,9-quinone in a modest yield. When this reaction was carried out in an atmosphere of nitrogen, the reaction product was an aminodihydronaphthofuran XII, which was then converted into 3-methylnaphtho[1,2-*b*]-2,3-dihydrofuran-4,5-quinone by succesive treatments with ferric chloride, sodium borohydride, and sufuric acid.

Since the presence of orange-red pigments, the tanshinones, in the roots of *Salvia miltiorrhiza* Bunge was reported by Nakao in 1934,[1] more than ten tanshinones have been isolated from the roots, and their structures have been determined by various groups.[2] These pigments are classified into two groups according to their structural characters: the members of the first group have a furo-*o*-quinone chromophore, while those of the second group have a furo-*p*-quinone chromophore, as is shown by the examples of cryptotanshinone (I)[2a] and isotanshinone-II (II)[2b] respectively.

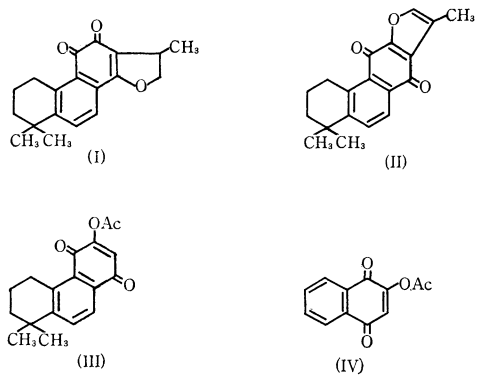

Fig. 1

These tanshinones seem to be synthesized from an intermediate (III) through constructing an appropriate furan group fused to the quinone ring. To develop a synthetic route from the intermediate (III) to the tanshinones, some attempts have been made with a model compound; the present report will deal with a new synthesis of 3-methylnaphtho[1,2-*b*]-furan-4,9-quinone (VIII) and 3-methylnaphtho[1,2-*b*]-2,3-dihydrofuran-4,5-quinone (XV) from 2-acetoxy-1,4-naphthoquinone.

For the synthesis of furonaphthoquinones from the acetoxynaphthoquinone (IV), it is preferable to introduce at the C-3 position of the quinone, an isopropyl group bearing an appropriate oxygen function. The reaction of the quinone with an enamine made from propionaldehyde was expected to give either formylethylnaphthol or an equivalent addition compound. Although a reaction of enamine with unsubstituted quinone (V) has been reported by Brannock *et al.*[3] to give a cyclic addition compound such as VI, no reaction of an acyloxyquinone with an enamine has yet been reported.

When 2-acetoxy-1,4-naphthoquinone (IV) was allowed to react with an equivalent amount of 4-(1-propenyl)morpholine (VII)[4] in methanol, there was obtained, by direct crystallization, a nitrogen-free product, $C_{13}H_8O_3$, in a 44% yield. The structure of this yellow product was identified as 3-methylnaphtho[2,3-*b*]furan-4,9-quinone (VIII) from its spectral properties. The IR spectrum of the product shows a quinonoid carbonyl absorption at 1675 cm^{-1} besides furano absorptions[5] at 3150, 1590, and 1525 cm^{-1}. The presence of the furan group in the reaction product was supported by its NMR spectrum, which exhibits the signal of a methyl group at 2.36 (3H, d. J=2 Hz) and that of an olefinic proton at 7.45 (1H, q. J= 2 Hz), attributable to the coincidence with the CH_3–C=CH–O– group, in addition to aromatic protons at 7.65 and 8.05. The UV spectrum of

1) M. Nakao and T. Fukushima, *J. Pharm. Soc. Jap.*, **54**, 154 (1934).

2) a) K. Takiura, *ibid.*, **61**, 482 (1941). b) F. von Wessely and S. Wang, *Ber.*, **73**, 19 (1940). c) Y. Okumura, H. Kakisawa, M. Kato and Y. Hirata, This Bulletin, **34**, 895 (1961). d) H. Kakisawa, T. Hayashi and T. Yamazaki, *Tetrahedron Lett.*, **1969**, 301.

3) K. C. Brannock, R. D. Burpitt, H. E. Davis and H. S. Pridgen, *J. Org. Chem.*, **29**, 2579 (1964).

4) Propenylmorpholine (VII) was made according to the method explored by C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936).

5) M. Yamaguchi and A. Fujino, "Kagaku no Ryoiki," Supplement No. 3, Nankodo, Tokyo, (1954), p. 101.

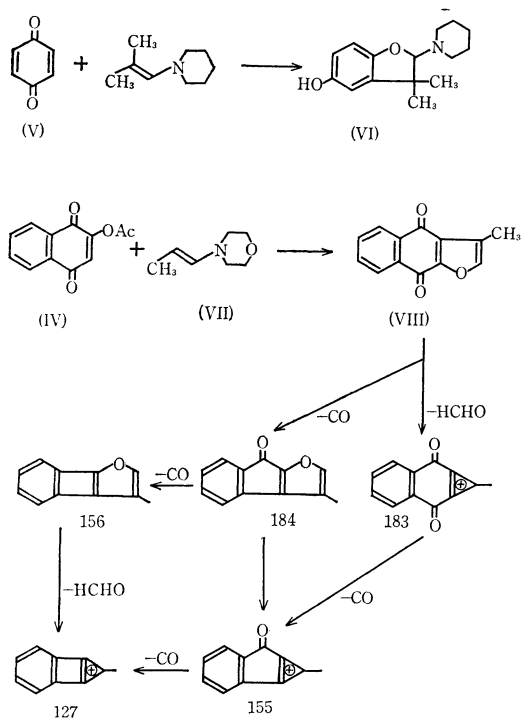

Fig. 2

the product, λ_{max} 246 (21500 sh), 251 (22000), 268 (6100), 305(4100) and 360 nm (4300), is almost superimposable upon that of isotanshinone-II (II), which has a naphtho[2,3-*b*]furan-4,9-quinone chromophore. The mass spectrum shows main peaks at 212, 184, 183, 156, 155, and 127 mu; these fragmentation patterns are characteristic[6] of the 3-methylnaphtho[2,3-*b*]furan-4,9-quinone derivatives. This reaction, which has made possible the synthesis of the furo-*p*-quinone by a simple reaction from 2-acetoxy-1,4-naphthoquinone, will be useful for the synthesis of isotanshinones.[7]

The above addition reaction of the enamine (VII) to the acetoxynaphthoquinone (IV) was expected first to afford an aminodihydronaphthofuran, either XI or XII, by the nucleophilic addition of the enamine to the quinone and by subsequent cyclization, but the fact that the furonaphthoquinone (VIII) was formed without any oxidative reagent makes it obvious that air oxidation must have taken place during the condensation process. Therefore, the condensation of 4-(1-propenyl)morpholine (VII) to 2-acetoxy-1,4-naphthoquinone (IV) in an atmosphere of nitrogen has been attempted in order to obtain the intermediates, XI and/or XII. The reaction product was formed of white crystals having a molecular composition of $C_{19}H_{21}O_5N$; the UV spectrum (λ_{max} 246 and 305 nm) indicates the presence of a naphthol group, while the IR spectrum (ν_{max} 3350 and 1750 cm^{-1}) shows the presence of hydroxy and enol-acetate groups. Although two structures XI and XII were possible for the reaction product, the possibility of structure XI was disregarded in the following reactions. The oxidation of the adduct XII with ferric chloride gave a substance shown to be XIII. Three carbonyl absorptions, at 1780, 1720, and 1660 cm^{-1}, in the IR spectrum of XIII point to the presence of enol-acetate, unconjugated aldehyde, and quinonoid carbonyl groups respectively, and the NMR spectrum shows the presence of a formylethyl group at 1.35 (3H, d. J=8 Hz), 3.75 (1H, q. J=8 Hz), and 9.6 (1H, s), and of an acetyl group at 2.31 (3H, s). The UV spectrum of the oxidation product, showing absorption maxima at 248, 268, and 335 nm, is almost the same as that of 2-acetoxy-1,4-naphthoquinone.

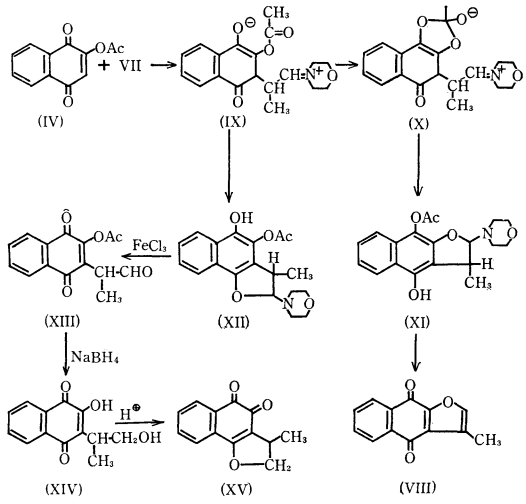

Fig. 3

The sodium borohydride reduction of XIII and the subsequent base hydrolysis of the acetyl group afforded a diol XIV (ν_{max} 3400, 1660 cm^{-1}). The diol XIV was prepared directly from the aminodihydrofuran (XI) by alkaline hydrolysis followed by reduction with sodium borohydride in an ordinary atmosphere. The treatment of the diol (XIV) with cold sulfuric acid in ethanol afforded, selectively, 3-methyldihydronaphtho[1,2-*b*]-2,3-dihydrofuran-4,5-quinone (XV), whose structure was confirmed by spectral data. The IR absorption bands at 1680, 1650, and 1625 cm^{-1} are compatible with the *o*-naphthoquinone. The NMR spectrum has signals at 1.36 (3H, d, J=8 Hz) and 3,40—5.06 (3H, m) assignable to the CH_3–CH–CH_2–O–

6) T. Hayashi, Y. Inouye, M. Ohashi, H. Kakisawa, A. Tatematsu and S. Kinoshita, *Org. Mass Spect.*, **2**, (1970), in press.

7) Recently this reaction has been applied to the synthesis of matsurinone, a natural product having the structure of 3,5-dimethylnaphtho[2,3-*b*]furan-4,9-quinone; H. Kakisawa and Y. Inouye, *Tetrahedron Lett.*, **1969**, 1929.

grouping besides those due to aromatic protons at 7.60 (2H, m) and 8.10 (2H, m). Finally, the structure (XV) is established by the UV spectrum (λ_{max} 262, 333, and 460 nm), whose shape is very similar to that of cryptotanshinone (I). This synthetic method from IV to XV can be applied to the total synthesis of cryptotanshinone.

Experimental

All the melting points are determined in a liquid bath and are uncorrected. The infrared spectra were measured on a Hitachi EPI-S2 spectrophotometer as KBr disks. The UV spectra were determined on a Hitachi EPS-3T spectrometer, and the NMR spectra were recorded on Hitachi R-20 spectrometer, with tetramethylsilane as the internal standard.

3-Methylnaphtho[2,3]furan-4,9-quinone (VIII). 4-(1-Propenyl)morpholine (0.32 g) was added to an ice-cooled mixture of 0.54 g of 2-acetoxyl-1,4-naphthoquinone and 2 m*l* of methanol. The reaction mixture was allowed to stand for 2 hr at room temperature, and then left in a refrigerator overnight in order to separate crystals. The crystals were collected and recrystallized from ethanol to give 0.235 g (44%) of light yellow needles; mp 206°C; λ_{max}^{EtOH} (ε) 246^{sh} (21500), 251 (22000), 268^{sh} (6100), 305 (4100), 360 nm (4300); ν_{max} 3150, 1675, 1590, 1525, 1020 cm^{-1}; NMR ($CDCl_3$) 2.36 (3H, d, J=2 Hz), 7.45 (1H, q, J=2 Hz), 7.65 (2H, m), 8.05 (2H, m); MS 212, 184, 183, 157, 156, 155, 128, 126, 105, 102, 77 mu.

Found: C, 73.69; H, 3.88%. Calcd for $C_{13}H_8O_3$: C, 73.58; H, 3.80%.

2,3-Dihydro-4-acetoxy-5-hydroxy-3-methyl-2-morpholinonaphtho[1,2-*b*]furan (XII). Into a suspension of 2-acetoxy-1,4-naphthoquinone (100 mg) in 0.5 m*l* of methanol was gradually stirred 60 mg of 4-(1-propenyl)morpholine in an atmosphere of nitrogen. The yellow quinone thus dissolved, and white crystals were separated. After standing in a refrigerator for 24 hr, the crystals were filtered and washed with ether several times to give 65 mg (40%) of aminodihydronaphthofuran (XII). Although the product was difficult to purify by recrystallization, the crystals were pure enough for further experiments; mp 150—151°C; λ_{max}^{EtOH} (ε) 246 (48500), 305 (6700) nm; ν_{max}^{KBr} 3350, 1750, 1640, 1590 cm^{-1}.

Found: C, 67.03; H, 6.37; N, 4.26%. Calcd for $C_{19}H_{21}O_5N$: C, 66.46; H, 6.16; N, 4.08%.

2-(3-Acetoxy-1,4-naphthoquinonyl)propionaldehyde (XIII). A solution of 250 mg of ferric chloride hexahydrate and 0.6 m*l* of hydrochloric acid was stirred, drop by drop, into a suspension of 120 mg of aminodihydronaphthofuran (XII) in an atmosphere of nitrogen. After the reaction mixture had then been stirred for 10 min at room temperature, the solution turned orange-red; the mixture was then extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo* to afford oil; λ_{max}^{EtOH} 248, 268, 335 nm; $\nu_{max}^{CHCl_3}$ 1780, 1720, 1660 cm^{-1}; NMR ($CDCl_3$) 1.35 (3H, d, J=8 Hz), 2.31 (93H, s), 3.75 (1H, q, J=8 Hz), 7.7 (2H, m), 8.1 (2H, m), 9.61 (1H, s).

2-(3-Hydroxy-1,4-naphthoquinonyl)-1-propanol (XIV). To a solution of 95 mg of naphthoquinonylpropionaldehyde (XIII) in 5 m*l* of ethanol, was added 25 mg of sodium borohydride dissolved in 5 m*l* of methanol. After stirring at room temperature for 10 min, 2 m*l* of 2N sodium hydroxide solution was added and the mixture was stirred for a further 10 min. The deep red reaction mixture was neutralized with dilute hydrochloric acid and extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to give naphthoquinonylpropanol (XIV): $\nu_{max}^{CHCl_3}$ 3400 1660, 1590 cm^{-1}.

This diol XIV was made directly from the adduct XII. To a suspension of the adduct XII (165 mg) in 12 m*l* of ethanol was added 8 m*l* of a 0.1N aqueous potassium hydroxide solution, whereupon the solution turned deep red. After the solution had then been stirred for 1 hr at room temperature, the solution was acidified with dilute hydrochloric acid and extracted with ether. The ether extract was washed with water, dried and evaporated *in vacuo*. The residue was dissolved in 10 m*l* of ethanol and treated with excess sodium borohydride dissolved in aqueous ethanol. After standing for 1 hr at room temperature, the solution was treated with dilute hydrochloric acid and extracted with ether. The treatment of the ether solution as usual afforded oil (50 mg) whose IR spectrum was the same as that of the diol (XIV).

3-Methylnaphtho[1,2-*d*]-2,3-dihydrofuran-4,5-quinone (XV). A solution of 75 mg of diol (XIV) in 1 m*l* of ethanol was treated with a mixture of sulfuric acid and ethanol (1 : 1) at 80°C. After 5 min, the mixture was poured into ice water to give a red solution. The aqueous solution was then extracted with ether. The ether extract was washed with water, dried over magnesium sulfate, and evaporated to give red crystals. Recrystallization from ethanol yielded furonaphthoquinone (XV) (50 mg); mp 150—151°C; λ_{max}^{EtOH} (ε) 253^{sh} (12600), 262 (16800), 271^{sh} (14500), 288^{sh} (4100), 333 (1400), 460 nm (1500); $\nu_{max}^{CHCl_3}$ 1680, 1650, 1625 cm^{-1}; NMR ($CDCl_3$) 1.36 (3H, d, J=8.0 Hz), 3.40—5.06 (3H, m), 7.60 (2H, m), 8.10 (2H, m).