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Synthesis of 2,2'-(Substituted Arylmethylene)bis(1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-dione) Derivatives

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Abstract: The reactions of tanshinone IIA with aromatic aldehydes have been investigated and several 2, 2'-(substituted arylmethylene) bis (1,6,6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]-furan-10, 11-dione) derivatives were obtained.

Keywords: Tanshinone IIA, aromatic aldehydes, reaction.

Tanshinones are a series of quinone diterpenes which are isolated from *Salvia miltiorrhiza* Bunge known as "Danshen" in Chinese traditional medicine. They have broad pharmacological activities, such as antibacterial, anti-tumor and anti-platelet aggregation[1]. Tanshinones' derivatives have been used to treat the coronary disease, cerebrovascular diseases as well as neurasthenic insomnia in clinic[2]. Tanshinone IIA is one of the main components of tanshinones and characterized by the presence of a furan ring and an *o*-quinone moiety, which are able to react with nucleophilic agents. In our previous work, we have systematically reported the reactions of cryptotanshinone and tanshinone IIA with amino compouds[3]. M. K. Qian *et al.* and C. J. Sun *et al*. reported the sulfonation[4] and Mannich reaction[5] of tanshinone IIA respectively, which indicated that the furan ring of tanshinone IIA was highly chemical activity and nucleophilicity. In this paper we described the reactions of tanshinone IIA with carbonyl groups of aromatic aldehydes.

Results and Discussion

The reactions of tanshinone IIA with aromatic aldehydes proceeded smoothly[8] in $CHCl_3$ in the presence of *p*-methyl benzene sulfonic acid to give the products as red solids under mild conditions. All products show absorption bands at about 1675, 1580, 1545, 1460 cm^{-1} in IR and 183.5s, 175.8s ppm in ^{13}C NMR, indicating that the *o*-quinone moiety still existed[6]. In ^{1}H NMR of tanshinone IIA, the α-H in furan ring showed representative

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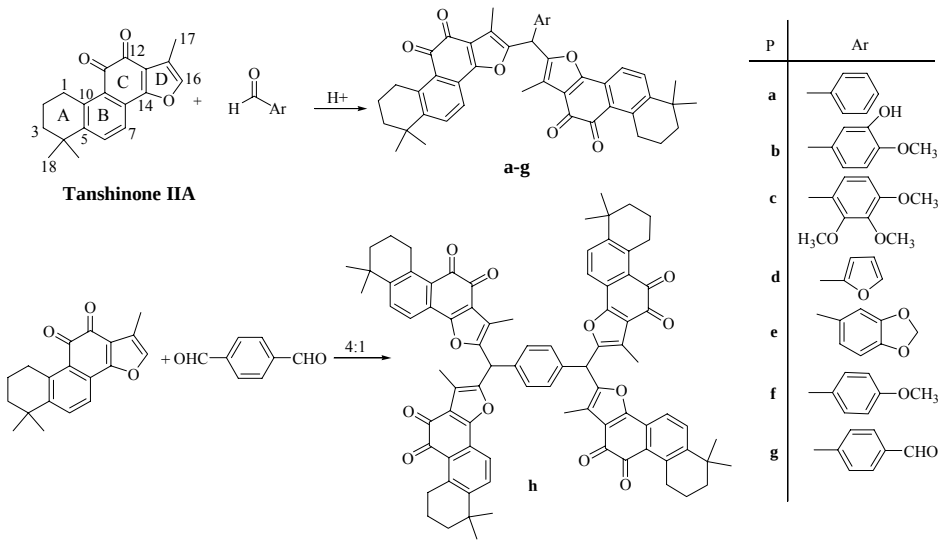
quadruple peaks at δ 7.21 ppm and the representative double peaks at δ 2.21 ppm belonged to the methyl group at furan ring[6]. Compared the ^{1}H NMR of the products with that of tanshinone IIA, the signals of **A-B** rings still existed, but the quadruple peaks of the α-H in furan ring had disappeared. The methyl group at furan ring showed only single peak instead of double peaks as it was in furan ring of tanshinone IIA, this indicated that the α-H in furan ring was replaced during the reaction. Besides, the signal at δ 5.6 ppm in ^{1}H NMR and the tertiary C at 40-60 ppm in ^{13}C NMR suggested a methine formed from the carbonyl C of aldehyde group. Combined IR, NMR and FAB-MS, the structures of **a-h** were assigned as 2, 2'-(substituted arylmethylene)bis (1, 6, 6-trimethyl-6,7,8,9-tetrahydrophenanthro[1,2-b]furan-10,11-dione)derivatives (**Scheme 1**).

Scheme 1



Tanshinone IIA reacted with substitued phenyl aldehydes to form correspoding products in high yied(75-85%), but when it was treated with furaldehydes, the yield was only 45%. It might be that the unstable and active property of furaldehydes brought too many side reactions. According to our experiments, this reaction needed to be catalyzed by proton acids such as *p*-methyl benzene sulfonic acid or Lewis acids such as $ZnCl_2$. Among them, *p*-methyl benzene sulfonic acid had the best catalyzing effect, for that it was anhydrous and had better solubility in organic solvents. Sulfuric acid and hydrochrolic acid usually contained water which would be unfavorable for this reaction, concentrated sulfuric acid could destroy tanshinones and hydrogen chloride was easy to escape from the reaction system. Lewis acid was also not a good choice because it could coordinate with tanshinones and the solubility in organic solvents was bad[7]. Tanshinone IIA hardly reacted with aqueous formaldehyde and aqueous acetaldehyde because water could inhibit the reaction. Tanshinone IIA also could react with other fatty aldehydes, but with too many side-products which were hard to be separated. Interestingly, when the molar ratio of tanshinone IIA to terephalicaldehyde was 2:1, the

main reaction product was bis-substituted derivative **g**, and when it was 4:1, the main reaction product was tetra-substituted derivative **h**. This reaction responsed the highly chemical activity and nucleophilicity of furan ring in tanshinone IIA.

The reactions of tanshinones with amino group and carbonyl group indicate that tanshinones not only can act as nucleophilic groups, meanwhile as electrophilic groups. This character responses for their all kinds of pharmacological activities. It was thought before that the pharmacological activities of tanshinones were mainly connected with their highly electropositive quinone structure[6]. However, this reaction suggests that the furan ring of tanshinone might also play an important role in its activities by recognizing electrophilic groups in organism. Further investigation is needed to support this hypothesis.

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8. General procedure :Supercritical extract of *Salvia miltiorrhiza* Bunge was purified by silica gel column chromatography by stepwise elution using the mixture of ethyl acetate/petroleum ether (2:98-5:95) as eluent to yield highly purified tanshinone IIA.

   The solution of tanshinone IIA (294 mg, 1 mmol), aromatic aldehyde (0.6 mmol) and *p*-methylbenzene sulfonic acid (40 mg) in 25 mL $CHCl_3$ was stirred at about 50-60℃ for about 12 h (the reaction progress can easily be followed by TLC). After reaction, the mixture was allowed to cool to room temperature and was washed with 3×100 mL water. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was isolated with column chromatography of silica gel to afford the products. [eluent: ethyl acetate/petroleum (8:92 to 19:81)]
9. Spectra data(The serial number of atoms in ^1H NMR is written according to the conventional name of tanshinone showed in **Scheme 1**.):

   a: 286 mg, yied 85%; m.p. 176.9℃(decomposed); $C_{45}H_{40}O_6$, found(calcd.): C, 79.67(79.86), H 5.81(5.96); IR(KBr): 2930，1675，1581，1544，1457，1197 cm^{-1}; ^1H NMR(300MHz, $CDCl_3$, δ ppm): 7.60(d, 2H, *J*=8.1Hz, H-6), 7.46(d, 2H, *J*=8.4Hz, H-7), 7.26-7.39(m, 5H, Ar-H), 5.64 (s, 1H, CH), 3.18(t, 4H, *J*=6.3Hz, H-1), 1.74 -1.85(m, 4H, H-2), 1.64-1.68(m, 4H, H-3)，2.21 (s, 6H, H-17), 1.30(s, 12H, H-18, 19); ^{13}C NMR-DEPT(300MHz, $CDCl_3$, δ ppm): 183.5s, 175.8s, 160.6s, 150.5s, 150.4s, 144.7s, 137.1s, 133.7d, 129.1d, 128.1d, 127.9d, 127.4s, 126.6s, 120.8s, 120.4d, 117.9s, 41.0d, 38.1t, 35.0s, 32.2q, 30.2t, 19.5t, 9.2q; FAB-MS (*m/z*): 677 $(M+1)^+$.

   b: 289 mg, yied 80%, m.p. 174.5℃(decomposed); $C_{46}H_{42}O_8$, found(calcd.): C 76.28(76.44), H 5.65(5.86); IR(KBr): 2931，1674，1580，1544，1461，1172 cm^{-1}; ^1H NMR(300MHz, $CDCl_3$, δ ppm): 7.60(d, 2H, *J*=7.5Hz, H-6), 7.46(d, 2H, *J*=7.5Hz, H-7), 6.75-6.91(m, 3H, Ar-H), 5.57(s, 1H, CH), 5.62(s, br, 1H, OH), 3.86(s, 3H, OCH_3), 3.18(t, 4H, *J*=6.3Hz, H-1), 1.78-1.80

(m, 4H, H-2), 1.65-1.68(m, 4H, H-3), 2.21(s, 6H, H-17), 1.30(s, 12H, H-18, 19); ^{13}C NMR-DEPT(300MHz, $CDCl_3$, δ ppm): 183.4s, 175.8s, 160.6s, 150.8s, 150.4s, 147.1s, 145.5s, 144.7s, 133.7d, 128.7s, 127.3s, 126.6s, 121.1s, 120.8d, 120.4d, 117.7s, 114.9d, 110.9d, 56.4q, 40.8d, 38.1t, 35.0s, 32.2q, 30.2t, 19.5t, 9.2q; FAB-MS (*m/z*): 723(M+1)$^+$.

c: 318mg, yied 83%; m.p. 153.6℃(decomposed); $C_{48}H_{46}O_9$, found(calcd.): C 74.95(75.18), H 5.87(6.05); IR(KBr): 2931, 1674, 1580, 1543, 1493, 1463, 1198, 1172 cm^{-1}; ^{1}H NMR(300MHz, $CDCl_3$, δ ppm): 7.60(d, 2H, *J*=8.4Hz, H-6), 7.47(d, 2H, *J*=8.4Hz, H-7), 7.00(d, 1H, *J*=8.4Hz, Ar-H), 6.65(d, 1H, *J*=8.4Hz, Ar-H), 5.93(s, 1H, CH), 3.88(s, 3H, OCH3), 3. 87(s, 3H, OCH3), 3.81(s, 3H, OCH_3), 3.18(t, 4H, *J*=6.3Hz, H-1), 1.76-1.82(m, 4H, H-2), 1.65-1.68 (m, 4H, H-3), 2.21(s, 6H, H-17), 1.31(s, 12H, H-18, 19); ^{13}C NMR-DEPT(300MHz, $CDCl_3$, δ ppm): 183.6s, 175.9s, 160.4s, 153.7s, 151.4s, 150.9s, 150.3s, 144.7s, 133.7d, 127.5s, 126.6s, 123.5d, 123.2s, 120.8s, 120.4d, 117.1s, 107.4d, 61.0q, 56.3d, 38.1t, 34.7s, 32.2q, 30.2t, 19.5t, 9.1q; FAB-MS (*m/z*): 767(M+1)$^+$.

d: 148mg, yied 45%; m.p. 112.1℃(decomposed); $C_{43}H_{38}O_7$, found(calcd.): C 77.59(77.46), H 5.83(5.74); IR(KBr): 2929, 1674, 1581, 1544, 1460, 1197, 1171 cm^{-1}; ^{1}H NMR(300MHz, $CDCl_3$, δ ppm): 7.61(d, 2H, *J*=8.4Hz, H-6), 7.49(d, 2H, *J*=8.4Hz, H-7), 7.42(d, 1H, furan-H), 6.37-6.40(m, 1H, furan-H), 6.23(d, 1H, furan-H), 5.68(s, 1H, CH), 3.17(t, 4H, *J*=6Hz, H-1), 1.77-1.81(m, 4H, H-2), 1.63-1.67(m, 4H, H-3), 2.22(s, 6H, H-17), 1.30(s, 12H, H-18, 19); ^{13}C NMR-DEPT(300MHz, $CDCl_3$, δ ppm): 183.5s, 175.8s, 160.7s, 150.5s, 149.2s, 148.4s, 144.8s, 142.8d, 133.7d, 127.3s, 126.7s, 120.7s, 120.4d, 118.1s, 110.9d, 108.8d, 53.8d, 38.1t, 35.0s, 32.2q, 30.2t, 19.5t, 8.9q; FAB-MS(*m/z*): 667(M+1)$^+$.

e: 302mg, yied 84%, mp. 186.2℃(decomposed); $C_{46}H_{40}O_8$, found(calcd.): C 76.57(76.65), H 5.71(5.59); IR(KBr): 2929, 1674, 1582, 1545, 1487, 1443, 1197 cm^{-1}; ^{1}H NMR(300MHz, $CDCl_3$, δ ppm): 7.60(d, 2H, *J*=8.1Hz, H-6), 7.47(d, 2H, *J*=8.1Hz, H-7), 6.69-6.79(m, 3H, Ar-H), 5.97(s, 2H, -O-CH_2-O-), 5.53(s, 1H, CH), 3.18(t, 4H, *J*=6.3 Hz, H-1), 1.76-1.82(m, 4H, H-2), 1.63-1.68(m, 4H, H-3), 2.21(s, 6H, H-17), 1.30(s, 12H, H-18, 19); ^{13}C NMR-DEPT (300MHz, $CDCl_3$, δ ppm): 183.5s, 175.8s, 160.6s, 150.5s, 150.4s, 148.4s, 147.3s, 144.7s, 133.7d, 130.9s, 127.3s, 126.7s, 121.4d, 120.7s, 120.4d, 117.7s, 108.7d, 101.6t, 40.7d, 38.1t, 35.0s, 32.2q, 30.2t, 19.5t, 9.2q; FAB-MS (m/z): 721(M+1)$^+$.

f: 303mg, yied 86%; mp. 175.2℃(decomposed); $C_{46}H_{42}O_7$, found(calcd.): C 77.91(78.17), H 5.89(5.99); IR(KBr): 2932，1673，1512，1461，1200，1176 cm^{-1}; ^{1}H NMR(300MHz, $CDCl_3$, δ ppm): 7.59(d, 2H, *J*=8.4Hz, H-6), 7.46(d, 2H, *J*=8.4Hz, H-7), 7.19(d, 2H, *J*=8.7Hz, Ar-H), 6.89(d, 2H, *J*=8.7Hz), 5.58(s, 1H, CH), 3.82(s, 3H, OCH_3), 2.20(s, 6H, H-17), 3.18(t, 4H, *J*=6.3Hz, H-1), 1.76-1.84(m, 4H, H-2), 1.63-1.68(m, 4H, H-3), 1.30(s, 12H, H-18, 19); ^{13}C NMR-DEPT(300MHz, $CDCl_3$, δ ppm): 183.5s, 175.9s, 160.8s, 150.8s, 150.4s, 144.7s, 133.7d, 129.3d, 127.4s, 126.7s, 120.8s, 120.4d, 117.6s, 114.5d, 55.6q, 40.4d, 38.2t, 35.0s, 32.2q, 30.2t, 19.5t, 9.2q; FAB-MS (*m/z*):707(M+1)$^+$.

g: 267 mg, yied 75%; mp. 187.5℃(decomposed); $C_{46}H_{40}O_7$, found(calcd.): C 78.30(78.39), H 5.65(5.72); IR(KBr): 2931, 1690, 1675, 1607, 1544, 1460, 1199 cm^{-1}; ^{1}H NMR(300MHz, $CDCl_3$, δ ppm): 10.02(s, 1H, CHO), 7.89(d, 2H, J=8.1Hz, H-6), 7.60(d, 2H, *J*=8.1Hz, H-7), 7.46(d, 2H, *J*=2.1Hz, Ar-H), 7.43(d, 2H, *J*=2.1Hz, Ar-H), 5.70(s, 1H, CH), 2.24(s, 6H, H-17), 3.19(t, 4H, *J*=6Hz, H-1), 1.78-1.82(m, 4H, H-2), 1.64-1.68(m, 4H, H-3), 1.30, 1.29(s, 12H, H-18, 19); ^{13}C NMR-DEPT(300MHz, $CDCl_3$, δ ppm): 191.6d, 183.3s, 175.7s, 160.9s, 150.6s, 149.4s, 144.8s, 144.0s, 136.0s, 133.7d, 130.5d, 128.9d, 127.1s, 126.7s, 120.7s, 120.4d, 118.4s, 41.0d, 38.1t, 35.0s, 32.2q, 30.2t, 19.5t, 9.2q; FAB-MS(*m/z*): 705(M+1)$^+$.

h: 252mg, yied 80%; mp.240.6 ℃(decomposed); $C_{84}H_{74}O_{12}$, found(calcd.): C 79.19(79.10), H 5.78(5.85); IR(KBr): 2929, 1675, 1582, 1544, 1460, 1198 cm-1; ^{1}H NMR(300MHz, $CDCl_3$, ppm): 7.60(d, 4H, *J*=8.4 Hz, H-6), 7.46(d, 4H, *J*=8.4Hz, H-7), 7.27(d, 4H, *J*=3.6Hz, Ar-H), 5.64(s, 2H, CH), 3.17(t, 8H, *J*= 6.3Hz, H-1), 2.22(s, 12H, H-17), 1.78-1.80(m, 8H, H-2), 1.64-1.68(m, 8H, H-3), 1.30(s, 24H, H-18, 19); ^{13}C NMR-DEPT(300MHz, $CDCl_3$, δ ppm): 183.4s, 175.9s, 160.8s, 150.6s, 150.2s, 144.9s, 136.9s, 133.8d, 128.8d, 127.3s, 126.7s, 120.8s, 120.5d, 118.1s, 40.6d, 38.1t, 35.1s, 32.3q, 30.4t, 19.5t, 9.4q; FAB-MS (*m/z*): 1276 (M+1)$^+$.

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