

Photo-oxidation of Tanshinone II (6,7,8,9-Tetrahydro-1,6,6-trimethylphenanthro[1,2-*b*]furan-10,11-dione)

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Irradiation of the phenanthrofurandione tanshinone II (2) with u.v. light in the presence of air afforded 9-hydroxy-tanshinone (1), which had been isolated from a Chinese drug as a minor constituent. Two other products, an anhydride (3) and a lactone (4), were also obtained. The formation of these compounds was explained in terms of an intermediate 9,10-epidioxide (6), derived from tanshinone II by photoenolization and oxygenation.

IN the course of our studies on the constituents of the Chinese drug Tan-shen,^{1,2} the dried root of *Salvia miltiorrhiza* Bunge, 9-hydroxytanshinone II was detected as a minor constituent. This compound was not found to have optical activity in spite of its chiral structure.³ This finding raised the question of whether hydroxytanshinone (1) is a genuine constituent of the plant, or whether it is an artefact produced by photo-oxidation of tanshinone II (2). Tanshinone II is the most abundant component of the drug and is exposed to sunlight during the preparation of the latter.

After a solution of tanshinone II (2) in hexane had

† When methanol, ethanol, or benzene was used as solvent, most of the tanshinone II was recovered, even after prolonged irradiation.

¹ Y. Okumura, H. Kakisawa, M. Kato, and Y. Hirata, *Bull. Chem. Soc. Japan*, 1961, **34**, 895.

been exposed to sunlight for several days, t.l.c. showed a purple spot with the same R_F value as hydroxy-tanshinone (1). This finding prompted us to study the photo-oxidation of tanshinone II in detail, and we now describe the results.

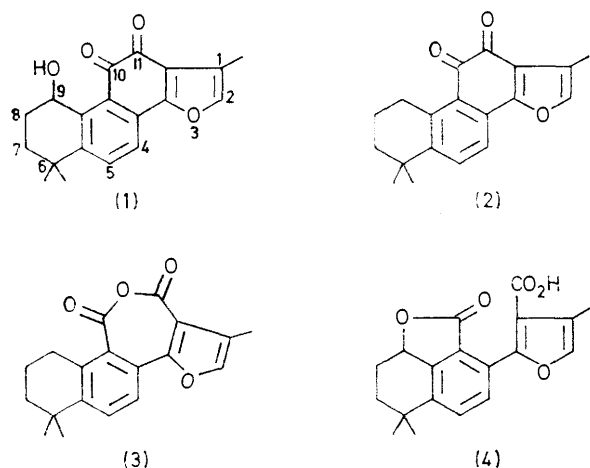
A stirred suspension of tanshinone II (2) in n-hexane was irradiated for 2 h in the presence of air with a high-pressure mercury lamp (450 W) through a Pyrex filter. The red colour smoothly faded, and a white solid was precipitated.† Three crystalline substances, A—C, were isolated by chromatography in yields of 3, 8, and 2%, respectively.

Compound A showed a green fluorescence when

² H. Kakisawa, T. Hayashi, and T. Yamazaki, *Tetrahedron Letters*, 1969, 301.

³ H. Kakisawa, T. Hayashi, I. Okazaki, and M. Ohashi, *Tetrahedron Letters*, 1968, 3231.

exposed to light of wavelength 365 nm. A molecular ion peak at m/e 310 in its mass spectrum indicated that



one oxygen atom had been incorporated. The u.v. spectrum had no maximum in the visible region, showing that the quinoid system had been destroyed. I.r. bands at 1786 and 1735 cm^{-1} indicated the presence of an unsaturated acid anhydride group. These properties together with the n.m.r. spectrum (see Experimental section) are in accord with the structure (3), which was confirmed by independent synthesis from tanshinone II (see later).

Compound B showed blue fluorescence in u.v. light, and had the molecular formula $\text{C}_{18}\text{H}_{16}\text{O}_4$. Its u.v. spectrum was similar to that of the anhydride (3), showing the presence of the same chromophore. An i.r. band at 1765 cm^{-1} suggested the presence of an $\alpha\beta$ -unsaturated γ -lactone group, and bands at 3500—2400 cm^{-1} and 1682 cm^{-1} are ascribable to an $\alpha\beta$ -unsaturated carboxy-group. These properties agreed with structure (4), which was confirmed by its n.m.r. spectrum (see Experimental section).

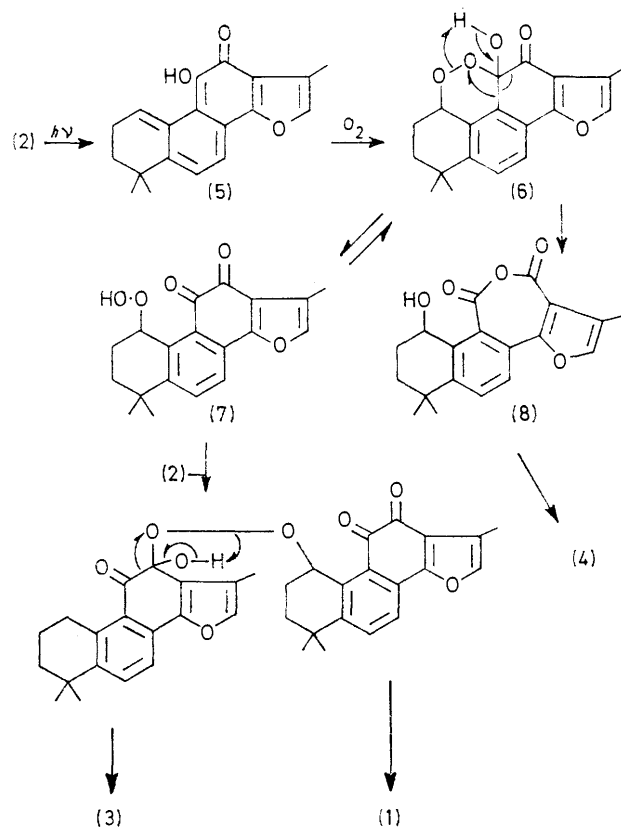
Compound C was identical with hydroxytanshinone (1) in its i.r. spectrum and thin-layer and high speed liquid chromatographic behaviour (μ -Porasil; chloroform). This supports the idea that hydroxytanshinone (1) is an artefact formed from tanshinone II (2) by the action of sunlight.

A possible mechanism of photo-oxidation of tanshinone II is outlined in the Scheme. Photoenolization of the quinone (2) [to the enol (5)] and subsequent oxygenation give the peroxide (6). This type of photo-oxygenation has been reported for anthraquinones.⁴⁻⁶ The peroxide (6) is convertible into the three photoproducts as follows. Migration of the carbonyl group to an electron-deficient oxygen atom leads to the hydroxy-anhydride (8), which rearranges to give the lactonic acid (4). Ring cleavage of the hemiketol group of the peroxide (6) produces a hydroperoxide (7), a Baeyer-Villiger-type

⁴ N. C. Yang and C. Rivas, *J. Amer. Chem. Soc.*, 1961, **83**, 2213.

⁵ K. R. Huffman, M. Loy, and E. F. Ullman, *J. Amer. Chem. Soc.*, 1965, **87**, 5417; W. A. Henderson, jun., and E. F. Ullman, *ibid.*, p. 5424.

reaction of which with tanshinone II (2) results in both hydroxytanshinone (1) and the anhydride (3). The participation of the hydroperoxide (7) is supported by the finding that the Baeyer-Villiger reaction of tanshinone II (2) with *m*-chloroperbenzoic acid⁷ also affords the anhydride (3).



SCHEME

EXPERIMENTAL

I.r. spectra were recorded with a Hitachi 215 grating spectrophotometer, and u.v. spectra with a Hitachi EPS-3T spectrophotometer. N.m.r. spectra were taken with a Hitachi H 60 instrument. Mass spectra were measured with a JEOL JMS-01SG double-focusing spectrometer. Column chromatography was performed with Merck Kieselgel 60. Thin and preparative layer chromatography were carried out with Merck Kieselgel GF₂₅₄. High-speed liquid chromatography was carried out with a Waters ALC/GPC 202/401 instrument (1/4 in \times 1 ft column packed with μ -Porasil).

n-Hexane was washed with concentrated sulphuric acid (three times), water, and sodium hydrogen carbonate solution, dried (CaCl_2), and distilled. The amount of impurity in the tanshinone II (m.p. 189—191°) was confirmed as $\leq 0.1\%$ by high-speed liquid chromatography.

Irradiation of Tanshinone II (2).—Tanshinone II (502 mg) was added to *n*-hexane (450 ml), and the mixture was stirred for 0.5 h. The suspension was then irradiated with a 450 W high-pressure mercury lamp (Ushio) at room

⁶ P. Yates, A. C. Mackay, and F. X. Garneau, *Tetrahedron Letters*, 1968, 5389.

⁷ P. Karrer and L. Schneider, *Helv. Chim. Acta*, 1947, **30**, 859.

temperature for 2 h. A white solid (387 mg) was filtered off and the filtrate was concentrated, yielding a red oil (252 mg). The oil was chromatographed on silica gel (20 g); elution with hexane-chloroform (5:2) afforded 6,7,8,9-tetrahydro-1,6,6-trimethylfuro[3,2-c]naphth[2,1-e]oxepin-10,12-dione (3) (15 mg) as a colourless oil, which crystallized from benzene; m.p. 137–140° (Found: *m/e*, 310.121. $C_{19}H_{18}O_4$ requires *M*, 310.119): ν_{\max} (KBr) 3 154 (furan), 1 786 (C=O), 1 735 (C=O), 1 604 (aromatic C=C), and 1 537 cm^{-1} (furan); λ_{\max} (EtOH) 237 (log ϵ 4.00), 270 (3.80), 306 (3.97), and 325 nm (3.93); *m/e* 310 (M^+), 295 ($M^+ - CH_3$), 282 ($M^+ - CO$), 267 (295 - CO), 251 (295 - CO₂), and 223 (251 - CO); δ (CDCl₃) 1.32 (6 H, s, 2 × Me), 1.1–2.0 (4 H, m, CH₂·CH₂), 2.27 (3 H, d, *J* 1 Hz, furan Me), 2.89 (2 H, t, *J* 6 Hz, benzylic CH₂), 7.32 (1 H, q, *J* 1 Hz, furan H), and 7.63 (2 H, s, ArH). Further elution with hexane-chloroform (1:1) and chloroform yielded a red oil (147 mg), which was again chromatographed on neutral alumina (22 g). Elution with benzene-ether (5:1) gave crude 9-hydroxytanshinone (1) (13 mg), which was purified by preparative t.l.c. with benzene-ether (5:1) as eluant. The resulting powder was recrystallized from ethanol yielding 9-hydroxytanshinone (2 mg) as purple needles, m.p. 184–186° (lit.,³ 187°), identical with an authentic sample (i.r., t.l.c., and high-speed liquid chromatography).

The solid precipitate (387 mg) was chromatographed on

silica gel (15 g); elution with chloroform gave an unidentified oil, and elution with chloroform-ether (8:2) yielded a light brown oil, which fluoresced in u.v. light (365 nm). Recrystallization from ether afforded 2-(6,7,8,8a-tetrahydro-6,6-dimethyl-2-oxonaphtho[1,8-bc]furan-3-yl)-4-methylfuran-3-carboxylic acid (4) (38 mg), m.p. 186–188° (Found: *m/e*, 326.112. $C_{19}H_{18}O_5$ requires *M*, 326.115); ν_{\max} (KBr) 3 600–2 400br (CO₂H), 1 765 (lactone C=O), 1 682 (conj. CO₂H), and 1 552 cm^{-1} (furan); λ_{\max} (EtOH) 239 (log ϵ 4.14), 298 (3.79), and 325 nm (3.92); δ (CDCl₃) 1.20 (3 H, s), 1.40 (3 H, s), 2.22br (3 H, s, furan Me), 5.18 (1 H, dd, *J* 10 and 5 Hz, CH·O·C=O), 7.30br (1 H, q, *J* 0.5 Hz, furan H), 7.55 (2 H, ABq, *J* 8 Hz, ArH), and 8.0br (1 H, CO₂H).

Preparation of the Anhydride (3).—*m*-Chloroperbenzoic acid (200 mg) was added to a solution of tanshinone II (38 mg) in dry dichloromethane (3 ml), and the mixture was stirred at room temperature for 3 h. The resulting mixture was diluted with ether, washed with aqueous sodium hydrogen carbonate, water, and brine, dried (Na₂SO₄), and evaporated, giving a red oil (32 mg). The oil was purified by preparative t.l.c. (chloroform as eluant) giving a semi-solid (4 mg), whose u.v., n.m.r., and i.r. spectra were identical with those of the anhydride (3) obtained by the photo-oxidation.

[6/390 Received, 25th February, 1976]