

SYNTHESIS OF TANSHINONES

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Abstract—Tanshinone-II and cryptotanshinone have been synthesized from 1,2,4-trimethoxybenzene by fourteen steps.

TANSHINONE-II (II)¹ and cryptotanshinone (III),^{2,3} the diterpenoid quinones, have been isolated from the roots of *Salvia miltiorrhiza* Bunge⁴ together with other pigments, tanshinone-I (I),⁵ methyl tanshinonate⁶ and isotanshinones.⁷ The structures of these pigments have been determined from their spectral properties and degradative reactions.

Although the total syntheses of these compounds have been attempted⁸ since 1959, only in 1968 did King⁹ obtain the isomer IV instead of tanshinone-I (I). Recently the syntheses of these quinones have been achieved by Thomson¹⁰ and independently in

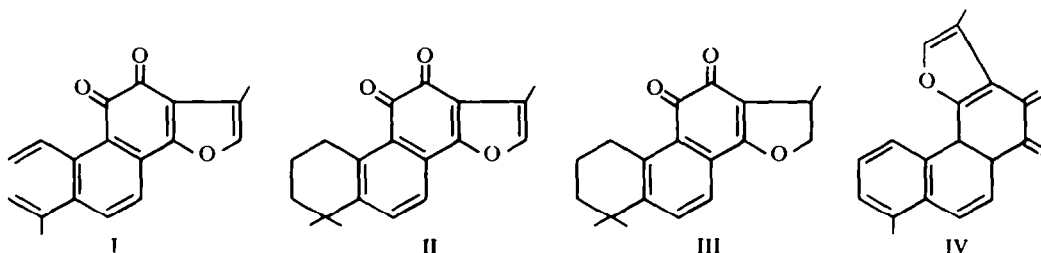


FIG 1

this laboratory.^{11a, b} The present paper describes in detail the synthesis of tanshinone-II and cryptotanshinone, which has been partly presented as a preliminary communication.^{11a}

Friedel-Crafts acylation of 1,2,4-trimethoxybenzene (V) with succinic anhydride afforded 2,4,5-trimethoxybenzoylpropionic acid (VI). Although acylation may have occurred at the C₃- or C₆-positions of the trimethoxybenzene, these were eliminated after inspection of the NMR spectrum: two peaks attributable to aromatic protons at δ 6.52 and 7.49 ppm show no splitting anticipated from *meta*- or *ortho*-coupling. Catalytic hydrogenation¹² of the benzoylpropionic acid (VI) in the presence of Pd-C and perchloric acid afforded a trimethoxyphenylbutyric acid (VII), which was converted into the trimethoxy- α -tetralone (VIII).

The tetralone (VIII) was condensed with ethyl γ -bromocrotonate by the Reformatsky reaction, and the initial product (IX) was directly converted by heating with

Pd-C into the naphthylbutyric ester (X). The structure of this product was first expected to be XII, but the elemental analysis and the mass spectrum show the elimination of one OMe group in the course of reaction. The NMR spectrum of the product shows a pair of *meta*-coupling doublets at δ 6.55 (1H, d, $J = 2$ Hz) and 6.96 (1H, d, $J = 2$ Hz) besides a 3-proton ABC-multiplet centred at 7.5 ppm in the aromatic region. This indicates that a OMe group at C₄ in the tetralone (VIII) has been replaced by an H atom and therefore, the structure X was assigned to the product.

Reaction of the ethyl ester (X) with methylmagnesium iodide and subsequent cyclodehydration of the resulting alcohol gave a tetrahydromethoxyphenanthrene (XI).*

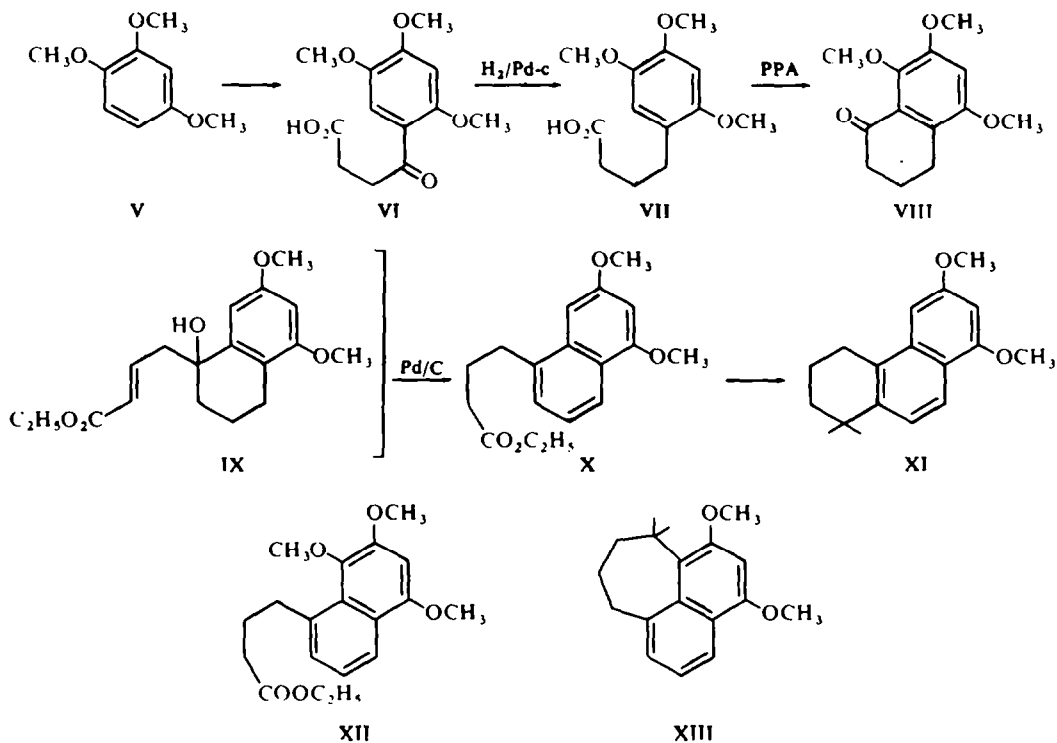


FIG 2

Previously, we devised a new synthetic method for constructing the furano group on a naphthoquinone system: 2-acetoxy-1,4-naphthoquinone (XV) was directly converted into a furo-1,4-naphthoquinone (XVII) by reaction with *N*-propenylmorpholine.¹³ This method was attempted for the synthesis of tanshinones.

Dimethoxyphenanthrene (XI) was converted into the corresponding phenanthrene-diol (XVIII). An attempt to oxidize the diol (XVIII) to hydroxynaphthoquinone (XIX) with Fremy's salt resulted in recovery of the starting diol. On oxidation with

* The NMR spectrum of this compound shows a pair of *meta*-coupling doublets at δ 6.85 (1H, d, $J = 2$ Hz) and 6.51 (1H, d, $J = 2$ Hz) besides a two-proton AB-quartet (8.05 and 7.32 ppm, $J = 9$ Hz) in the aromatic region. This also confirmed that the C₄-OCH₃ group in the tetralone (VIII) was removed in the course of Reformatsky reaction, and eliminated a possibility that the cyclodehydration product had a structure such as (XIII).

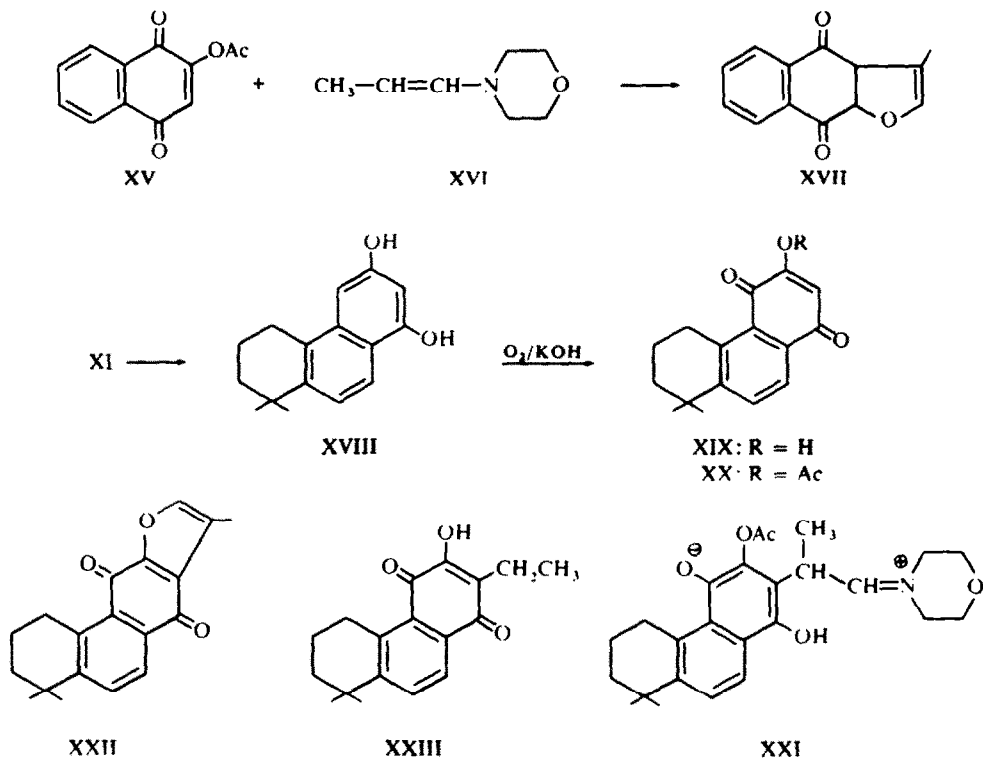


FIG 3

molecular oxygen in aqueous potassium hydroxide phenanthrediol (XVIII) afforded in good yield the hydroxyquinone (XIX), which was then converted into the acetate (XX). Although condensation of the acetate (XX) and morpholinoenamine (XVI) was examined under various conditions, the main product was not furo-1,4-naphthoquinone (XXII) but XXIII, which may have been produced from the initial adduct (XXI).

Consecutive treatment of the dimethoxyphenanthrene (XI) with butyllithium in diethyl ether and carbon dioxide produced the acid XXIV, which was converted into the methyl ester (XXV). This ester (XXV) was converted into the methyl ketone (XXVI) *via* two steps¹⁵ including treatment with dimethylsulphoxide anion to afford the sulphoxide (XXVII) and removal of the methanesulphonyl group with aluminum amalgam. The one OMe group of dimethoxy ketone (XXVI) was selectively cleaved by treating with boron trichloride to afford the ketophenanthrenol (XXVIII). The structure of this product was first expected to be XXVIII from the fact that the intermediate XXXII would be more stable than the other possible intermediate XXXIII, and the structure XXVIII was finally confirmed by conversion into tanshinone-II. Heating the ketophenanthrenol (XXVIII) with a mixture of ethyl bromoacetate and potassium carbonate under nitrogen followed by saponification gave the keto-carboxylic acid (XXIX). The furanophenanthrene (XXX) was obtained from the acid

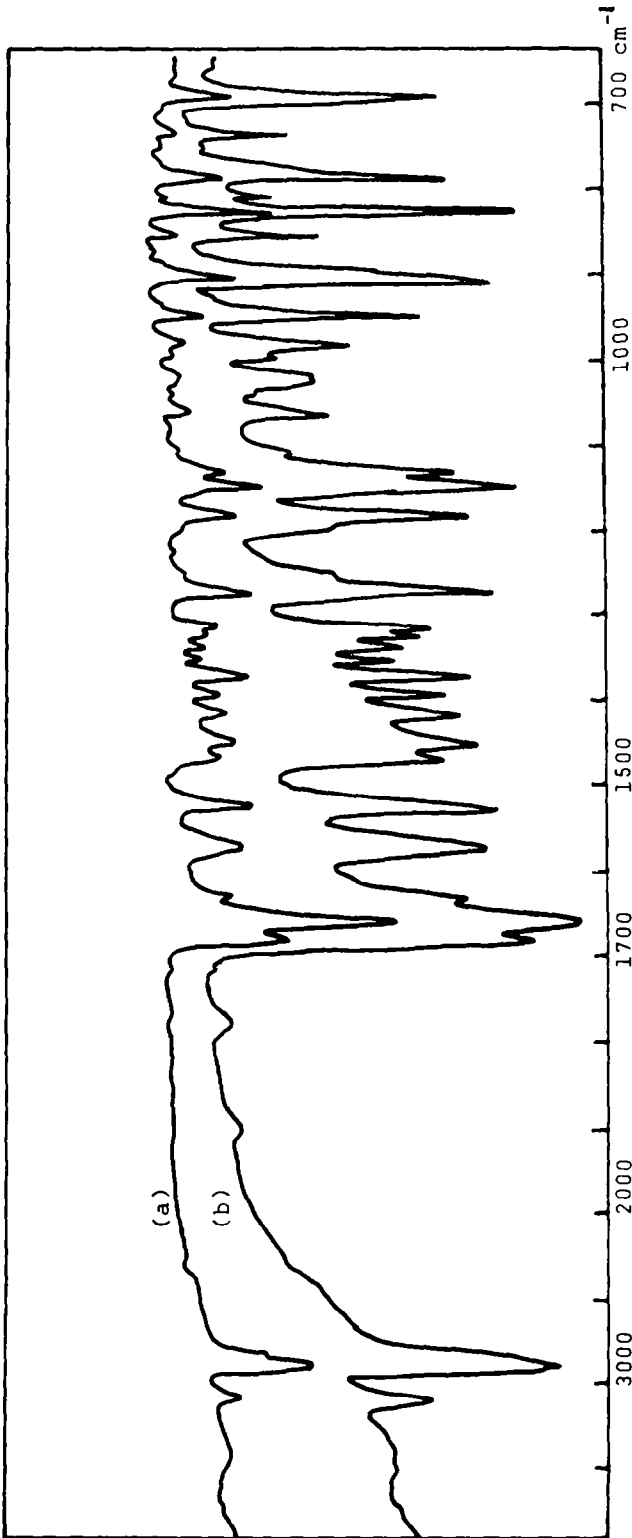


FIG. 2. The IR spectra of the natural (a) and synthetic (b) tanshinone-II.

and perchloric acid (0.8 ml) was added. After stirring under H_2 for 2 days at room temp, the soln was filtered and the residual catalyst was washed with ACOH. To the filtrate was added KOAc (3 g) and the resulting gray ppt was filtered off and washed with ACOH several times. The neutralized filtrate was evaporated under reduced pressure to about 30 ml, then water was added to separate the white crystals. These were filtered off and the filtrate was extracted with ether, yielding 5.3 g (91%), m.p. 78–80°; $\nu_{\max}^{CHCl_3}$ 3000, 1700 cm^{-1} . (Found: C, 61.62; H, 7.01; Calc. for $C_{13}H_{18}O_3$: C, 61.40; H, 7.14%).

Trimethoxytetralone (VIII). P_2O_5 (11.3 g) was added to vigorously stirred phosphoric acid (9.3 g) keeping the temp below 60° and the resulting mixture was stirred for 6 hr at 80 to 90°. A soln of VII (1 g) in CH_2Cl_2 (2 ml) was added with vigorous stirring to the polyphosphoric acid keeping the temp at 60 to 70°. After 20 min, the mixture was cooled in an ice-bath and 25 ml ice-water was added to afford a yellow green ppt. The ppt was collected and washed with water. Recrystallization from EtOH yielded 0.9 g pale yellow needles (93%), m.p. 104–106°; $\nu_{\max}^{CHCl_3}$ 1670, 1590 cm^{-1} ; NMR, δ 2.09 (2H, t, $J = 7$ Hz), 2.68 (4H, m), 3.73 (3H, s), 3.79 (3H, s), 3.82 (3H, s), 6.58 (1H, s). (Found: C, 66.32; H, 7.01; Calc. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83%).

Dimethoxynaphthylbutyric ester (X). To activated Zn (33.2 g) covered with 80 ml dry benzene was added 20.0 g of dried mercuric chloride. After standing for 30 min at room temp, a soln of VIII (40 g), ethyl γ -bromocrotonate (40 g), ether (80 ml) and dry benzene (80 ml) was added all at once. Iodine crystals were then added at the bath temp 65°. Reaction started and reflux was continued without heating for several min. To this mixture 3 additional portions of activated Zn (16 g), ethyl γ -bromocrotonate (10 g) and a trace of iodine was added every hr while the mixture was heated under reflux. After addition of the final portion, the mixture was heated under reflux for a further 3 hr. The mixture was cooled in an ice bath and then poured onto ice followed by acidification with ACOH and extracted with ether. The organic layer was washed with $NaHCO_3$ aq and then with water. The solvent was evaporated under reduced pressure and the residue was dried in vacuum to afford IX, which was directly converted into X.

A mixture of IX and 10% Pd-C (40 g) was heated in a metal bath at 280 to 290° under N_2 for 3 hr. After cooling, ether was added and the catalyst was filtered off and washed with ether. The filtrate was evaporated and the residual oil was distilled under vacuum (0.8 mm) at 200–210°. After standing at room temp, this oily distillate crystallized, and recrystallization from ether afforded white crystals, m.p. 68–69°; $\nu_{\max}^{CHCl_3}$ 1720, 1630 cm^{-1} ; NMR δ 1.20 (3H, t, $J = 7$ Hz), 2.00–2.50 (4H, m), 3.03 (2H, t, $J = 7$ Hz), 3.95 (6H, s), 4.15 (2H, q, $J = 7$ Hz), 6.55 (1H, d, $J = 3$ Hz), 6.96 (1H, d, $J = 3$ Hz), 7.55 ppm (3H, m); λ_{\max}^{EtOH} 237 (ϵ 38,500), 284 (4400), 295 (4500), 320 (1500), 334 μ (1700). (Found: C, 71.39; H, 7.44; Calc. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33%).

Dimethoxydimethyltetrahydrophenanthrene (XI). To a Grignard reagent made from Mg (16.2 g) and MeI (94 g) in ether (300 ml), a soln of X (10 g) in abs ether (100 ml) was added and the mixture was heated under reflux for 1 hr and then cooled in an ice bath. Water was added to the cooled mixture which was saturated with ammonium sulfate until the decomposition ceased. The mixture was extracted with ether and the organic layer was washed with water. After drying over Na_2SO_4 , the solvent was evaporated. To the residue (ca 10 g) 85% H_2SO_4 (10 ml) was added dropwise with ice cooling and stirring. After stirring for 10 hr at room temp, the viscous black mixture was poured into ice-water and the aqueous mixture was extracted with ether. The ether extract was washed with water, dried with Na_2SO_4 and evaporated. The crystalline residue was recrystallized from EtOH to give 3.1 g of XI (34% from the ester X), m.p. 158°; $\nu_{\max}^{CCl_4}$ 1625 cm^{-1} ; NMR, δ 1.36 (6H, s), 1.70–2.0 (4H, m), 3.05 (2H, br, t), 3.92 (3H, s), 3.95 (3H, s), 6.85 (1H, d, $J = 3$ Hz), 6.51 (1H, d, $J = 3$ Hz), 7.37 (1H, d, $J = 8$ Hz), 8.05 ppm (1H, d, $J = 8$ Hz); λ_{\max}^{EtOH} 238 (19,000), 284 (1800), 295 (1800), 331 m (350). (Found: C, 79.52; H, 7.97; Calc. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20%).

Hydroxynaphthoquinone (XIX). A mixture of XI (3 g) and pyridinium hydrochloride (21 g) was heated at 205–210° for 5 hr. After cooling, water was added to give crude XVIII which was dissolved immediately in 25 ml dioxan. A mixture made from this soln and 1.5 N KOH (20 ml) was stirred in an atmosphere of O_2 ; the rate of absorption of O_2 was slow but the soln changed to dark-red. After 180 ml of O_2 was consumed, absorption was stopped. The mixture was extracted with ether and the organic layer discarded. The acidified aqueous layer was extracted with ether, and the ether extract was evaporated to give dark yellow crystals. The crude crystals were dissolved in benzene and purified through a silicic acid column. The benzene eluate was evaporated to give bright yellow crystals which were recrystallized from EtOH to afford 2 g needles, m.p. 165–167°; ν_{\max}^{KBr} 3400, 1660, 1570 cm^{-1} ; λ_{\max}^{EtOH} 248 (ϵ 6100), 255 (72,000), 290 (4700), 360 μ (1500). (Found: C, 74.78; H, 6.39; Calc. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29%).

Acetoxynaphthoquinone (XX). A soln of XIX (2 g) and a trace of $ZnCl_2$ in Ac_2O (18 ml) was kept at room temp for

30 min and then boiled for 2 min. The cooled soln was poured into water to give a yellow ppt which was extracted with ether. The ether soln was treated as usual and the crude product was recrystallized from EtOH to give 2.2 g of yellow crystals (95%); m.p. 114–115°; $\nu_{\text{max}}^{\text{KBr}}$ 1780, 1670, 1570 cm^{-1} ; $\lambda_{\text{max}}^{\text{EtOH}}$ 253 (ϵ 32000), 268 (1000), 364 $\text{m}\mu$ (400); NMR, δ 1.31 (6H, s), 1.70 (4H, m), 2.38 (3H, s), 3.20 (2H, t, $J = 6$ Hz), 6.54 (1H, s), 7.60 and 7.85 ppm (2H, ABq, $J = 8$ Hz). (Found: C, 72.39; H, 6.14; Calc. for $\text{C}_{18}\text{H}_{18}\text{O}_4$: C, 72.46; H, 6.08%).

Ethylhydroxyphenanthrenequinone (XXIII). To a suspension of XX (1.2 g) in 0.5 ml EtOH, 0.7 g *N*-propenylmorpholine¹⁷ was added dropwise with stirring at room temp followed by standing at 20° overnight. The red soln was purified with silica gel chromatography to give a yellow compound. Recrystallization from EtOH gave 1 g yellow crystals (88%); m.p. 165–167°; $\nu_{\text{max}}^{\text{KBr}}$ 3400, 1655, 1570 cm^{-1} ; $\lambda_{\text{max}}^{\text{EtOH}}$ 257, 292, 360 $\text{m}\mu$; NMR, δ 0.96 (3H, t, $J = 8$ Hz), 1.30 (6H, s), 1.71 (4H, m), 2.20 (2H, q, $J = 8$ Hz), 3.25 (2H, t, $J = 6$ Hz), 7.70 and 8.00 (2H, ABq, $J = 9$ Hz), 8.40 ppm (1H, brs). (Found: C, 76.33; H, 6.77; Calc. for $\text{C}_{18}\text{H}_{20}\text{O}_3$: C, 76.03; H, 7.09%).

Dimethoxyphenanthrenecarboxylic acid (XXIV) and the ester (XXV). To Li wire (6.88 g) in abs ether (160 ml), a soln of *n*-BuBr (55.2 g) in abs ether (80 ml) was added gradually with cooling at -10° under a N_2 stream. After all the soln had been added the mixture was stirred for 20 hr maintaining the temp at -10° or below. A soln of XI (5 g) in ether (400 ml) was added rapidly and the mixture was refluxed for 24 hr, cooled to room temp, and poured into a mixture of excess dry ice in abs ether to produce a brown ppt. The ethereal soln was kept at room temp for 1 hr, then water was added, the aqueous layer was separated and the organic layer was extracted with dil NaOH aq. The combined aqueous soln was acidified and extracted with ether. The ether soln was dried and evaporated to give white crystals. Without purification, this acid (XXIV) was esterified with diazomethane to give 3.4 g crude XXV. The white crystals were recrystallized from MeOH: m.p. 130°, $\nu_{\text{max}}^{\text{CCl}_4}$ 1720, 1620 cm^{-1} ; NMR, δ 1.24 (6H, s), 1.80 (4H, m), 3.00 (2H, t, $J = 6$ Hz), 3.90 and 3.95 (9H, two s), 7.55 ppm (2H, ABq, $J = 8$ Hz); $\lambda_{\text{max}}^{\text{EtOH}}$ 240 (ϵ 55,000), 274 (4500), 284 (4800), 295 (sh. 3600), 333 $\text{m}\mu$ (1600). (Found: C, 72.73; H, 7.72%; Calc. for $\text{C}_{20}\text{H}_{24}\text{O}_4$: C, 73.14; H, 7.37%).

Methylketone (XXVI). A mixture of NaH (96 mg) and dry DMSO (4 ml) was heated at 70 to 73° in an atmosphere of N_2 until the evolution of H_2 ceased. After cooling, THF (3 ml) was added to the above pale yellow soln followed by addition of 300 mg of XXV (300 ml) in THF (3 ml). The mixture was heated at 60 to 65° for 1 hr and, after cooling, it was poured into water followed by chloroform extraction. The chloroform extract was concentrated under reduced pressure to produce a brown residue, IR spectrum of which exhibited peaks at 1680 and 1620 cm^{-1} . To the residue dissolved in THF and water (1:1) was added at 0° aluminum amalgam which was prepared by stirring Al strips and 2% mercuric chloride soln and then washed with alcohol and ether. The mixture was stirred at 0° for 10 min followed by filtration to remove the inorganic ppt. After evaporating the THF under reduced pressure, the filtrate was extracted with ether to yield a mixture of XXVI and its corresponding alcohol. For oxidation of the alcohol to XXVI, the mixture dissolved in 2 ml pyridine was treated with 0.3 g CrO_3 in 7 ml pyridine at 0°. The oxidation was completed by stirring at room temp for 70 min. To this mixture was added water and the resulting brown soln was extracted with ether. The ether extract was washed with water, dried and evaporated to give a brown residue, which was purified by alumina chromatography. The fractions eluted with benzene–chloroform (1:1) afforded white crystals, which were recrystallized from MeOH to give 110 mg of XXVI, m.p. 112–113°; $\nu_{\text{max}}^{\text{KBr}}$ 1700, 1620 cm^{-1} ; $\lambda_{\text{max}}^{\text{EtOH}}$ 284 (ϵ 4800), 332 $\text{m}\mu$ (1300); NMR, δ 1.25 (6H, s), 1.78 (4H, m), 2.54 (3H, s), 3.00 (2H, t, $J = 6$ Hz), 3.88 (3H, s), 3.90 (3H, s), 7.35 and 7.80 ppm (2H, ABq, $J = 7$ Hz). (Found: C, 76.70; H, 7.80; Calc. for $\text{C}_{20}\text{H}_{24}\text{O}_3$: C, 76.89; H, 7.74%).

Acetylmethoxyphenanthrenol (XXVIII). To a 3-necked flask dried and cooled to -70° by dry ice–acetone were added successively CH_2Cl_2 (2 ml) and excess BCl_3 . To this soln was added a soln of XXVI (150 mg) in CH_2Cl_2 (6 ml) cooled at 0°, and the mixture allowed to stand at room temp for 1 hr. After evaporation of BCl_3 from the red mixture under reduced pressure, water was added and the products were extracted with chloroform. Recrystallization from EtOH gave 85 mg of yellow needles (57%); m.p. 193–194°; $\nu_{\text{max}}^{\text{CHCl}_3}$ 1620 cm^{-1} ; $\lambda_{\text{max}}^{\text{EtOH}}$ 226 (ϵ 11,800), 271 (16,000), 302 (3900), 313 (3100), 365 $\text{m}\mu$ (3800); NMR, δ 1.30 (6H, s), 1.70–2.20 (4H, m), 2.68 (3H, s), 2.90 (2H, t, $J = 6$ Hz), 3.88 (3H, s), 6.52 (1H, s), 7.25 and 8.10 (2H, ABq), 14.78 ppm (1H, s). (Found: C, 76.19; H, 7.51; Calc. for $\text{C}_{19}\text{H}_{22}\text{O}_3$: C, 76.48; H, 7.43%).

Ketocarboxylic acid (XXIX). A mixture of ethyl bromoacetate (0.2 ml), K_2CO_3 (0.5 g) and XXVIII (100 mg) in acetone (20 ml) was refluxed for 20 hr under a N_2 stream followed by filtration of inorganic salts. Evaporation of the filtrate gave a brown oil, IR spectrum of which showed peaks at 1720, 1675, 1620 cm^{-1} (liq. film). This oil was dissolved in 14 ml acetone and 7.5 ml 5% Na_2CO_3 aq was added. After heating on a water bath for 3 hr in an atmosphere of N_2 , the mixture was cooled and acetone was removed

under reduced pressure. The residual aqueous soln was extracted with ether, and the aqueous layer was acidified with dil HCl to afford a white ppt which was extracted with ether. Evaporation of the ether gave a white solid, which was recrystallized from benzene to afford white needles (100 mg), m.p. 176–178°; $\nu_{\text{max}}^{\text{KBr}}$ 3200, 1760, 1680, 1620 cm^{-1} ; $\lambda_{\text{max}}^{\text{EtOH}}$ 235 (ϵ 55,000), 284 (8300), 333 $\text{m}\mu$ (2000); NMR, δ 1.37 (6H, s), 1.80 (4H, m), 2.61 (3H, s), 3.03 (2H, t, $J = 7$ Hz), 3.95 (3H, s), 4.75 (2H, s), 7.09 (1H, s), 7.41 and 7.90 (2H, two ds, $J = 9$ Hz), 8.70 ppm (1H, brs). (Found: C, 70.72; H, 6.56%; Calc. for $\text{C}_{21}\text{H}_{24}\text{O}_5$: C, 70.76; H, 6.79%).

Furanophenanthrene (XXX). A mixture of XXIX (0.1 g), fused NaOAc (0.3 g) and Ac_2O (3 ml) was heated under reflux for 3 hr in an atmosphere of N_2 . After cooling, the mixture was poured into ice-water, and the resulting white ppt was collected, and recrystallized from EtOH to give 50 mg of white crystals (63%), m.p. 124–125°; $\nu_{\text{max}}^{\text{KBr}}$ 1620 cm^{-1} ; $\lambda_{\text{max}}^{\text{EtOH}}$ 240 (ϵ 19,300), 248 (44,000), 256 (60,600), 324 (59,000), 338 $\text{m}\mu$ (4300); NMR, δ 1.40 (6H, s), 1.8 (4H, m), 2.40 (3H, d, $J = 1$ Hz), 3.08 (2H, brt, $J = 6$ Hz), 3.98 (3H, s), 6.80 (1H, s), 7.35 (1H, q, $J = 1$ Hz), 7.45 (d, 1H, $J = 9$ Hz), 8.00 ppm (1H, d, $J = 9$ Hz). (Found: C, 81.39; H, 7.57; Calc. for $\text{C}_{20}\text{H}_{22}\text{O}_2$: C, 81.60; H, 7.53%).

Furophenanthrenol (XXXI). To a soln of XXX (50 ml) in abs ether (0.6 ml), a Grignard reagent which was prepared from Mg (0.07 g) and MeI (0.6 g) was added. The solvent was completely removed *in vacuo* at 100° N_2 gas was admitted to the vessel and the residual mixture was heated at 175 to 180° for 40 min. The evolution of methane ceased within a short time. To the cooled mixture EtOAc was added to decompose excess Grignard reagent. After addition of H_2SO_4 aq, the mixture was extracted with ether, and usual treatment of the ether extract afforded white crystals, the IR of which showed absorption at 3200 cm^{-1} .

Tanshinone-II (II). To a soln of XXXI (50 mg) in acetone (3 ml) a soln of excess Fremy's salt in 2 ml water was added. After allowing to stand at room temp overnight, the mixture was extracted with ether. The ether layer was washed with water, dried over MgSO_4 and evaporated under reduced pressure to afford the starting material and a small amount of II. The furanophenanthrenol XXXI was slowly autoxidized to give tanshinone-II (II), which was identical with the natural tanshinone-II in all respects (UV, IR spectra, m.p. and mixed m.p.).

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