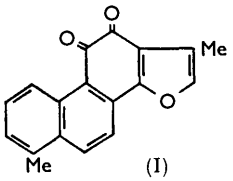
1008. *Tanshinones. Part I. The Synthesis of an Isomer of Tanshinone-I.*

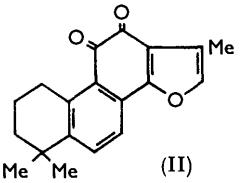
By T. J. King and G. Read.

The synthesis is described of 4,5-dihydro-3,8-dimethyl-4,5-dioxophenanthro[4,3-*b*]furan (IV), an isomer of tanshinone-I (I).

In 1930 Nakao [1] reported the isolation of three red crystalline pigments from the purgative drug " tan-shin " which is the dried roots of *Salvia miltorrhiza*. The pigments were called tanshinone-I, -II, and -III, and were identified as *o*-quinones. Takiura [2] later repeated their isolation and showed that tanshinone-III was a mixture of tanshinone-II with another pigment which he termed cryptotanshinone. Degradative work with the three pigments, including dehydrogenation [3] which shows that they all have the same skeleton, has led to the following structures being proposed for them, tanshinone-I (I), tanshinone-II (II), and cryptotanshinone (III). Most of the evidence on which these structures are



(I)



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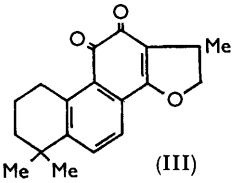

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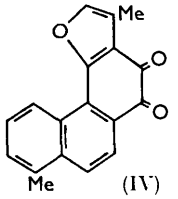

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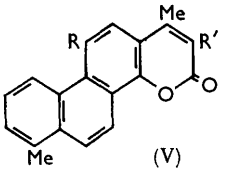

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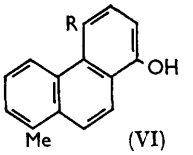


(VI)

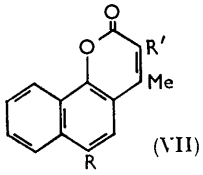
based has been obtained by Takiura [4] or by von Wesseley and his co-workers [4] and has been admirably summarised.[5] The possible biogenetic relationship of all these pigments to the diterpenes was first emphasised by Todd.[6]

[1] Nakao, *Bull. Shanghai Sci. Inst.*, 1930, V; Nakao and Fukushima, *J. Pharm. Soc. Japan*, 1934, **54**, 154.
[2] Takiura, *J. Pharm. Soc. Japan*, 1941, **61**, 475.
[3] Takiura, personal communication.
[4] (*a*) Takiura, *J. Pharm. Soc. Japan*, 1941, **61**, 482; 1943, **63**, 40; (*b*) Wessely and Wang, *Ber.*, 1940, **73**, 19; (*c*) Wessely and Bauer, *Ber.*, 1942, **75**, 617; (*d*) Wessely and Lauterbach, *Ber.*, 1942, **75**, 958.
[5] Thomson, " Naturally Occurring Quinones," Butterworths Sci. Publ. Ltd., London, 1957, p. 260.
[6] Todd, *Ann. Reports*, 1941, **38**, 209.

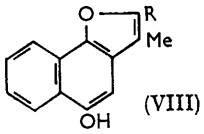
We were led by our interest in diterpene synthesis to attempt their synthesis and our initial aim was to prepare the fully aromatic tanshinone-I. In this we have been unsuccessful but we now record the synthesis of the isomer (IV).

A key intermediate in our proposed synthesis was the coumarin (V; R = OH, R′ = Cl or Br) which could be converted by standard methods into a hydroxyphenanthrofuran which should readily give the desired quinone by further oxidation. This key intermediate should be available from 1-hydroxy-8-methylphenanthrene (VI; R = H) by conversion into the coumarin (V; R = R′ = H) and subsequent Elbs persulphate oxidation and bromination. This route, though unambiguous, suffers from the disadvantage that the starting material is not readily available. Furthermore, a model experiment [7] with a simple analogue (VII; R = R′ = H) suggested that the Elbs oxidation of the pyrone (V; R = R′ = H) would be difficult. We accordingly attempted the synthesis of the intermediate pyrone (V; R = OH, R′ = Cl) directly from 1,4-dihydroxy-8-methylphenanthrene (VI; R = OH).

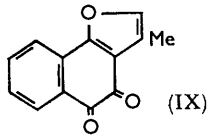
Model experiments with 1,4-dihydroxynaphthalene were encouraging. This compound was readily converted into the coumarin (VII; R = OH, R′ = Cl) by a Pechmann reaction with ethyl α-chloroacetoacetate, which in turn underwent ring contraction to the naphthofuran (VIII; R = CO_2H) with alkali. Oxidation with either selenium dioxide or, much better, potassium nitrosodisulphonate [8] then gave the *o*-quinone. Similar oxidation of the decarboxylated furan (VIII; R = H) was also satisfactory, and the product (IX) was reductively methylated to give an ether whose ultraviolet absorption closely resembled that of the leuco-dimethyl ether of tanshinone-II,[4d] confirming the supposition that they have a common chromophore.



(VII)



(VIII)



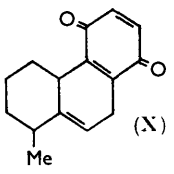
(IX)

The dihydroxymethylphenanthrene (VI; R = OH) needed for the synthesis has not been reported, but Robins and Walker [9] and Deno and Johnston [10] prepared the dione (X) by the Diels–Alder addition of benzoquinone to 3-methyl-2-vinylcyclohexene. We experienced some difficulty in repeating this preparation when using methanol as a solvent, as sometimes the only solid product was a high-melting non-ketonic material to which, on the basis of analysis and ultraviolet absorption, we assign the structure (XI). Robins [11] also had some failures with this reaction which he attributed to the presence of adventitious acid. When the addition was performed in benzene no difficulty was experienced. The diketone was rearranged to the quinol by short treatment with acid, and this was methylated, dehydrogenated, and demethylated to give the desired phenol. 1,4-Dihydroxyphenanthrene has been made by Grob *et al.*[12] in a similar way and we modified their method by carrying out the dehydrogenation with sulphur, which gives appreciably better yields than palladised charcoal.

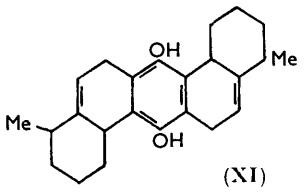
The Pechmann reaction with the diol (VI; R = OH) was expected to yield two products. Orientation effects might be expected to favour formation of the unwanted isomer (XII) but we hoped that they would not exclude the formation of appreciable amounts of the

[7] Bhevsar and R. D. Desai, *Indian J. Pharm.*, 1951, **13**, 200; cf. R. B. Desai and Sethna, *J. Indian Chem. Soc.*, 1951, **28**, 213.
[8] Teuber and Gotz, *Chem. Ber.*, 1954, **87**, 1236; 1956, **89**, 2654.
[9] Robins and Walker, *J.*, 1952, 642.
[10] Deno and Johnston, *J. Org. Chem.*, 1952, **17**, 1466.
[11] Robins, personal communication.
[12] Grob, Jundt, and Wicki, *Helv. Chim. Acta*, 1949, **32**, 2427.

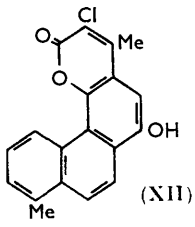
desired isomer (V; R = OH, R′ = Cl). We had expected to be able to separate the two possible products at this stage and to proceed with each separately. However, it appears that only one product is formed and this was shown to have the structure (XII).



(X)



(XI)



(XII)

Ring contraction of the pyrone took place easily and the product, characterised as the *O*-methyl ether methyl ester, was decarboxylated on good yield. The orientation of the product was determined at this stage by vigorous catalytic reduction, followed by dehydration and dehydrogenation with selenium. Depending on the position of attachment of the original pyrone ring to the phenanthrene skeleton the product should be retene or 6-isopropyl-1-methylphenanthrene. The product actually obtained was not isolated pure but its m. p. of 31—32°, undepressed by admixture with 6-isopropyl-1-methylphenanthrene, m. p. 45° (kindly supplied by Professor S. N. Slater), and its ultraviolet absorption which was identical over all peaks (eleven) with that of the authentic sample, left little doubt that it was substantially the 6-isopropyl isomer, and that therefore the parent furan had the opposite orientation to that suggested for the tanshinones.

As expected, oxidation of the furan with potassium nitrosodisulphonate took place smoothly to give the quinone (IV), which was very similar in appearance to tanshinone-I. The melting point was close to that of the natural pigment but was depressed on admixture with an authentic sample (kindly supplied by Professor K. Takiura). The new quinone, which was characterised as the quinoxaline, showed distinct differences in its ultraviolet absorption from that of the natural product.

Experimental

Except where otherwise indicated, ultraviolet absorption refers to ethanolic solutions. Light petroleum had b. p. 60—80°.

3-Chloro-6-hydroxy-4-methyl-2-naphtho[1,2-b]*pyrone* (VII; R = OH, R′ = Cl).—84% Sulphuric acid (100 c.c.) was slowly added to a cold (10°) stirred paste of 1,4-dihydroxynaphthalene (10 g.) and ethyl α-chloroacetoacetate (15 c.c.). Stirring was continued for 18 hr. and the mixture was then poured into water (200 c.c.). The brown precipitate was extracted with boiling glacial acetic acid (200 c.c.) to remove impurities and the crude residual *pyrone* (12·6 g.) was collected. Extraction with ethyl acetate removed further coloured impurities to give a very sparingly soluble, pale brown product, m. p. 305—307°. It crystallised from acetic acid as yellow prisms, m. p. 310—311° (Found: C, 64·2; H, 3·5; Cl, 13·0. $C_{14}H_9ClO_3$ requires C, 64·5; H, 3·5; Cl, 13·6%), $\lambda_{max.}$ (in $CHCl_3$) 282 (ε 23,000), 291 (ε 27,000), 316 (ε 6500), and 383 mμ (ε 6500).

5-Hydroxy-3-methylnaphtho[1,2-b]*furan-2-carboxylic Acid* (VIII; R = CO_2H).—The above naphthopyrone (6 g.) was heated under reflux with 10% ethanolic potassium hydroxide (220 c.c.) under nitrogen for 6 hr. The solution was then diluted with water and acidified with hydrochloric acid. The product was collected in ether, and the acidic portion extracted with aqueous sodium hydrogen carbonate and crystallised from acetic acid (charcoal) as blades, m. p. 254—255° (decomp.), yield 69%. This and all other carboxyfurans made in this investigation gave low carbon values on analysis. The acid with diazomethane gave the O-*methyl ether methyl ester* which crystallised from acetic acid as prisms, m. p. 234—235° (Found: C, 71·1; H, 5·1. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%).

4,5-Dihydro-3-methyl-4,5-dioxonaphtho[1,2-b]*furan-2-carboxylic Acid.*—(*a*) A solution of

potassium nitrosodisulphonate (0·45 g.) in water (30 c.c.) containing 0·65M-potassium dihydrogen phosphate (7·5 c.c.) was added to a solution of the above hydroxyfurancarboxylic acid (0·15 g.) in acetone (13 c.c.). After 12 hr. at room temperature the acetone was evaporated under reduced pressure and the aqueous residue was acidified with concentrated hydrochloric acid (2 drops) and left in the refrigerator for 8 hr. The precipitated orange *quinone* was collected and crystallised from ethanol and finally ethyl acetate as prisms, m. p. 292—293° (decomp.) (Found: C, 65·1; H, 3·3. $C_{14}H_8O_5$ requires C, 65·6; H, 3·1%), $\lambda_{max.}$ 255 (ε 24,000), 277 (ε 26,000), and 431 mμ (ε 2000). It dissolved in concentrated sulphuric acid to give a purple solution which changed to blue-green. *o*-Phenylenediamine in glacial acetic acid gave the *quinoxaline* as yellow needles (from dioxan), m. p. 310—312° (Found: N, 8·4. $C_{20}H_{12}N_2O_3$ requires N, 8·5%).

(*b*) A solution of the naphthofuroic acid (0·2 g.) in dioxan (15 c.c.) containing water (1 drop) and selenium dioxide (0·15 g.) was boiled for 4 hr. When cold the solution was filtered and diluted with water (15 c.c.), and the precipitated impurity was removed. The residual solution was acidified and after two days deposited the above quinone (30 mg.), m. p. and mixed m. p. 291—292° (decomp.).

5-*Hydroxy*-3-*methylnaphtho*[1,2-b]*furan* (VIII; R = H).—The above furoic acid (1·7 g.) and copper bronze (1·5 g.) were heated to 250°/12 mm. The temperature was slowly raised to 265° and the volatile product was collected on a cold finger. The *naphthofuran* was purified by sublimation at 135°/0·05 mm. It formed colourless needles, m. p. 145—146° (53%) (Found: C, 79·2; H, 5·3. $C_{13}H_{10}O_2$ requires C, 78·8; H, 5·1%).

4,5-*Dihydro*-3-*methyl*-4,5-*dioxonaphtho*[1,2-b]*furan* (IX).—The above furan (1·05 g.) was oxidised with potassium nitrosodisulphonate (3·2 g.) as described for the related acid above. The *quinone* (0·95 g.) crystallised from aqueous acetone as red blades, m. p. 168° (Found: C, 73·6; H, 3·8. $C_{13}H_8O_3$ requires C, 73·6; H, 3·8%), $\lambda_{max.}$ 247 (ε 19,000), 265 (ε 26,000), 270 (ε 22,000), 455 mμ (ε 2000). The derived *quinoxaline*, prepared in acetic acid, crystallised as yellow needles, m. p. 175° (from ethanol) (Found: C, 80·6; H, 4·2; N, 9·6. $C_{19}H_{12}N_2O$ requires C, 80·3; H, 4·25; N, 9·8%). A solution of the quinone in concentrated sulphuric acid was green, becoming purple and finally brown.

4,5-*Dimethoxy*-3-*methylnaphtho*[1,2-b]*furan*.—The last-mentioned quinone (0·4 g.) in ethanol (20 c.c.) was hydrogenated at room temperature and pressure over palladium black. 1 Mol. of hydrogen was absorbed, and dimethyl sulphate (20 c.c.) and 20% aqueous sodium hydroxide (40 c.c.) were then added. After 2·5 hr. the solution was diluted and extracted with ether, and the extract washed (dilute hydrochloric acid and water), dried and distilled. The fraction with b. p. 110—120° (bath)/0·08 mm. was filtered in light petroleum through a short column of alumina and redistilled [b. p. 118—122° (bath)/0·1 mm.]. The *dimethyl ether* so obtained solidified (m. p. 51—52°) but could not be crystallised (Found: C, 74·6; H, 5·9. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8%); it had $\lambda_{max.}$ 259 (ε 30,000), 323 (ε 9000), 340 mμ (ε 4000).

1,2,3,4,6,7b,8,9,10,11,13,14b-*Dodecahydro*-7,14-*dihydroxy*-4,11-*dimethyldibenz*[a,h]*anthracene* (XI).—On some occasions a solution of the methylvinylcyclohexene mixture from the dehydration of 2-methyl-1-vinylcyclohexanol and benzoquinone in methanol deposited, not the Diels–Alder adduct, but the *dibenzanthracene derivative* which separated from light petroleum as colourless needles, m. p. 197—198° (Found: C, 82·3; H, 8·5. $C_{24}H_{30}O_2$ requires C, 82·2; H, 8·6%), $\lambda_{max.}$ 249 (ε 6700) and 299 mμ (ε 1300). Acetic anhydride in pyridine gave the *diacetate*, prisms (from ethanol), m. p. 223—225° (Found: C, 77·1; H, 7·8. $C_{28}H_{34}O_4$ requires C, 77·4; H, 7·9%).

5,6,7,8,10,13-*Hexahydro*-1,4-*dimethoxy*-8-*methylphenanthrene*.—The corresponding diphenol [10] (28 g.) was methylated by dimethyl sulphate (45 g.) and potassium carbonate (90 g.) in boiling acetone (1 l.) for 30 hr. Most of the acetone was then evaporated, the residue was diluted with water, and the product was collected with ether. The extract was washed with aqueous sodium hydroxide and then dilute hydrochloric acid and water, dried, and distilled. The *dimethyl ether* (29 g., 92%) distilled as a colourless oil, b. p. 148—149°/4·5 mm., which separated from acetone as large prisms, m. p. 66—67° (Found: C, 79·2; H, 8·8; OMe, 20·2. $C_{17}H_{22}O_2$ requires C, 79·0; H, 8·6; 2OMe, 19·4%).

1,4-*Dimethoxy*-8-*methylphenanthrene*.—The above dimethyl ether (1·6 g.) was heated with sulphur (0·6 g.) at 200—220° for 3 hr. The mixture was triturated with ethanol, and the solid product was chromatographed on alumina from which light petroleum–benzene (95 : 1) eluted the *dimethoxyphenanthrene* (1·0 g.); this crystallised from ethanol as needles, m. p. 124° (Found:

C, 80·7; H, 6·5; OMe, 24·5. $C_{17}H_{16}O_2$ requires C, 80·9; H, 6·4; 2OMe, 24·6%), $\lambda_{max.}$ 240 (ε 52,000), 286 (ε 22,000), 309 (ε 10,000), 351 (ε 4500), and 368 mμ (ε 5000). The *picrate* formed brown needles (from ethanol), m. p. 168—170° (Found: C, 56·9; H, 4·1. $C_{17}H_{16}O_2,C_6H_3N_3O_7$ requires C, 57·4; H, 4·0%).

3-*Chloro*-6-*hydroxy*-4,9-*dimethyl*-2-*phenanthro*[4,3-b]*pyrone* (XII).—The above methyl ether (1·0 g.) was heated with pyridine hydrochloride (3·4 g.) at 170—190° for 4 hr. The addition of water then precipitated the phenanthrenediol (0·84 g.), sufficiently pure for use in the next stage. A paste of the diol (1 g.) and ethyl α-chloroacetoacetate (3·5 c.c.) was treated at 0° with 88% sulphuric acid (20 c.c.), and after 24 hr. at room temperature was diluted with water, to give the solid *chloropyrone* (100%) which sublimed at 210°/5 × 10^{-5} mm. as yellow needles, m. p. 280—300° (charring) (Found: C, 70·2; H, 4·2; Cl, 11·3. $C_{19}H_{13}ClO_3$ requires C, 70·3; H, 4·0; Cl, 10·9%), $\lambda_{max.}$ 257 (ε 35,000), 283 (ε 26,000), 340 (ε 9000), 353 (ε 10,000), 396 (ε 9000), and 413 mμ (9300).

5-*Hydroxy*-3,8-*dimethylphenanthro*[4,3-b]*furan*-2-*carboxylic Acid*.—The above chloropyrone (1·5 g.) was heated at the b. p. under nitrogen with alcoholic 10% potassium hydroxide (75 c.c.) for 5 hr. The solution was then diluted, acidified, and extracted with ether. The acidic part of the product was extracted from the ether with aqueous sodium hydrogen carbonate, and acid then liberated the furan-carboxylic acid as a flocculent precipitate (1·05 g.). Diazomethane gave the O-*methyl ether methyl ester* which separated from acetic acid as pale yellow prisms, m. p. 306—307° (decomp.) (Found: C, 75·1; H, 5·3. $C_{21}H_{18}O_4$ requires C, 75·4; H, 5·4%).

5-*Hydroxy*-3,8-*dimethylphenanthro*[4,3-b]*furan*.—The above acid (1·0 g.) and copper bronze (3 g.) were heated to 220°/14 mm. The temperature was raised during 30 min. to 280° and the crude *furan* was collected on a cold finger. Resublimation at 170°/0·1 mm. gave the product (0·49 g.) as needles, m. p. 223° (Found: C, 82·2; H, 5·5. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·4%).

Orientation of 5-*Hydroxy*-3,8-*dimethylphenanthro*[4,3-b]*furan*.—The above furan (0·25 g.) was hydrogenated in methylcyclohexane over Raney nickel at 200°/200 atm. for 3 hr. Removal of catalyst and solvent then left a clear oil transparent to ultraviolet light. This oil was dehydrated with potassium hydrogen sulphate at 180° for 30 min. and finally heated with selenium at 340—350° for 12 hr. Distillation then gave a product which crystallised from methanol and then aqueous ethanol as plates, m. p. 31—32°, raised to 32—34° on admixture with 6-isopropyl-1-methylphenanthrene (m. p. 45—46°). The ultraviolet spectrum of both hydrocarbons showed eleven peaks at the same wavelengths, the intensities of each peak also being nearly identical.

4,5-*Dihydro*-3,8-*dimethyl*-4,5-*dioxophenanthro*[4,3-b]*furan* (IV).—The above phenanthrofuran (100 mg.) was oxidised with potassium nitrosodisulphonate (0·38 g.) as previously described. The *quinone* crystallised from acetic acid as dark red prisms (98 mg.), m. p. 230—232°, raised to 233—234° by crystallisation from toluene (Found: C, 77·9; H, 4·7. $C_{18}H_{12}O_2$ requires C, 78·2; H, 4·4%). The m. p. was depressed to 194—202° on admixture with tanshinone-I (m. p. 230—231°). The derived *quinoxaline* was formed in acetic acid and crystallised from ether as yellow needles, m. p. 252—253° (Found: C, 82·3; H, 4·5; N, 8·15. $C_{24}H_{16}N_2O$ requires C, 82·7; H, 4·6; N, 8·05%); tanshinone-I quinoxaline has m. p. 231°. The ultraviolet spectrum of the quinone (in CH_2Cl_2) had $\lambda_{max.}$ 230 (ε 28,000), 295 (ε 30,000), 305 (ε 29,000), 364 (ε 4000), and 540 mμ (ε 3000); under the same conditions tanshinone-I had peaks at 245 (ε 39,000), 280 (ε 20,000) and 418 mμ (ε 6000).

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