Tetrahedron Letters No.5, pp. 301-304, 1969. Pergamon Press. Printed in Great Britain.

STRUCTURES OF ISOTANSHINONES

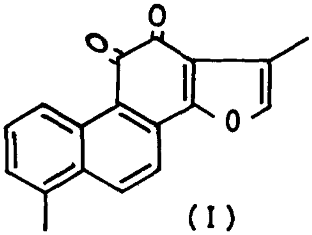
H.Kakisawa, T.Hayashi and T.Yamazaki
Department of Chemistry, Tokyo Kyoiku University
Otsuka, Tokyo, Japan

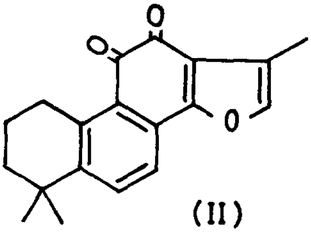
(Received in Japan 19 November 1968; received in UK for publication 16 December 1968)

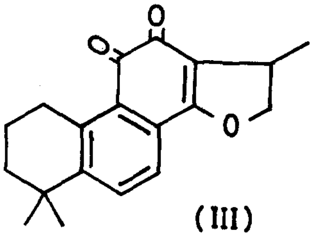
Many orange-red pigments were isolated from Chinese drug "tan-shen", the dried root of Salvia miltiorrhiza Bunge, and their structures have been determined by Japanese$^{1-3)}$and Austrian$^{4)}$chemists. All of these pigments have furo-1,2-naphthoquinone chromophore as shown in the structural representatives tanshinone-I(I), tanshinone-II(II) and cryptotanshinone(III), and were biogenetically classified as diterpenoid.$^{5)}$

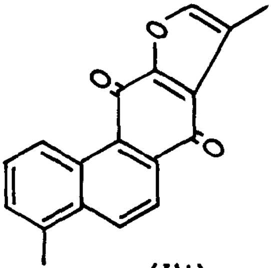
TLC analyses of the crude extract of tan-shen indicated the presence of more than ten colored components. Six of these were known pigments and identified as tanshinone-I,$^{4)}$ tanshinone-II,$^{2)}$ cryptotanshinone,$^{1)}$ hydroxytanshinone,$^{3)}$ tanshinone-IIB$^{6)}$ and methyl tanshinonate.$^{3)}$ Three of the remaining unknown pigments, designated isotanshinone-I, isotanshinone-II and isocryptotanshinone, were assigned structures (IV), (V) and (VI) respectively, based on the evidence described below.

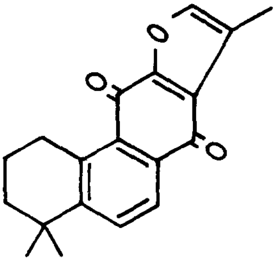
Isotanshinone-I, $C_{18}H_{12}O_3$(M^+ 276), mp 219°, has the same molecular formula with that of tanshinone-I(I), and ir spectrum of this orange-red pigment shows the presence of furan ring$^{9)}$(ν^{KBr}3150, 1530, 1030, 845 cm^{-1}) and p-quinonoid carbonyls (1660, 1585 cm^{-1}). The nmr spectrum shows a striking resemblance in many of its features to that of tanshinone-I, and exhibits that the former possesses a methyl group (δ 2.35, 3H, d, J=2 Hz) attached to a furan ring which is unsubstituted in the α-position (α-proton appears at δ 7.45, 1H, q, J=2 Hz), a methyl group (δ 2.70, 3H, s) bonded to an aromatic ring, and three aromatic protons (δ 7.50 and 9.50, 3H, m). However, there is a difference between the two spectra, whereas an AB-quartet of aromatic protons appears at δ8.00(J=8 Hz)

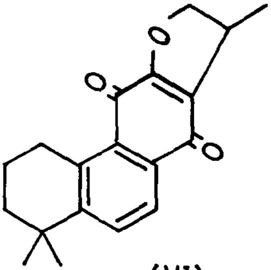

(I)


(II)


(III)


(IV)


(V)


(VI)

in the spectrum of tanshinone-I, the corresponding AB-quartet is shifted to low field (δ8.25, q, J=8 Hz) in that of isotanshinone-I. A conspicuous difference is seen in the uv spectra of these two pigments; tanshinone-I shows absorption maxima at 245(logε, 4.50), 330(3.60) and 420mμ(3.67), but isotanshinone-I shows at 234(4.58), 293(4.45), 346(3.78) and 450mμ(3.28). From these spectral properties, the structure of isotanshinone-I was deduced to IV. This structure was confirmed by direct comparison with the synthetic compound. Previously, we reported the total synthesis of tanshinones,7) in which the compound (IV) was synthesized as an intermediate and was converted into tanshinone-I(I). The natural isotanshinone-I was identical with this synthetic compound in all respects (ir, uv, nmr, t.l.c. and mixed melting point).

Isotanshinone-II, mp 208°, has the composition $C_{19}H_{18}O_3$(M^+ 294), and hence this yellow pigment is an isomer of tanshinone-II(II). Infra-red spectrum of this pigment shows the presence of furan ring (ν^{KBr}3150, 1530, 1030, 840 cm^{-1})9) and of p-quinonoid carbonyls (1655, 1585 cm^{-1}). The nmr spectra of isotanshinone-II and tanshinone-II are very similar and establish that the former possesses geminal dimethyl group (δ 1.30, 6H, s), a methyl group (δ 2.32, 3H, d, J=1.7 Hz) bonded to a furan ring which is unsubstituted in the α-position (α-proton appears at δ 7.50, q, J=1.7 Hz) and methylene groups (δ 1.7, m, 4H and 3.35, m, 2H). However, major difference is seen in the aromatic region where the AB-quartet centered at δ 7.48(J= Hz) of tanshinone-II is shifted to low field (δ 7.90, AB-q, J=8.5 Hz) in the spectrum of isotanshinone-II. The uv spectrum of isotanshinone-II [λ_{max}^{EtOH} 227(log ε, 4.02), 253(4.33), 256(4.34), 303(3.59) and 361mμ(3.63)] is also different from that of tanshinone-II [λ_{max}^{EtOH} 224(4.34), 252(4.30), 269(4.44), 352(3.22) and 460mμ(3.43)]. These properties show that whereas tanshinone-II has furo-1,2-naphthoquinone, isotanshinone-II has furo-1,4-naphthoquinone chromophore and full structure (V). The structure (V) was ascertained by direct comparison with the synthetic compound which had been prepared as an intermediate in the total synthesis7) of tanshinone-II.

Isocryptotanshinone, $C_{19}H_{20}O_3$(M^+ 296), mp 121°, shows characteristic uv absorption maxima8) at 251(3.97), 258(4.10), 299(3.79) and 365mμ(3.30) in ethanol, and the ir absorptions at 1665, 1645 cm^{-1}. These spectral properties suggest the presence of 1-alkoxy-1,4-naphthoquinone group in this pigment. The nmr spectrum of isocryptotanshinone indicates the presence of a geminal dimethyl group (δ 1.30, 6H,s), a methyl (δ 1.35, 3H, d, J=7 Hz) bonded to methyne group (δ 3.65, 1H, m), three methylene groups (δ 1.65, 4H, m, and 3.25, 2H, br.t), methylene (δ 4.54, 2H, dq, J=10, 9 and 6 Hz) bonded to an oxygen atom, and aromatic protons (δ 7.75, 2H, ABq, J=8 Hz). This nmr spectrum is very similar to that of cryptotanshinone except that the signals for AB pattern of two aromatic protons appear at lower field than those of cryptotanshinone (δ 7.60, J=8.5 Hz). Accordingly, we assigned the structure (VI) to isocryptotanshinone which was consistent with its optical activity ($[\alpha]_D^{dioxane}$ +55.6°). The structure (VI) was confirmed through comparison of its ir, uv and nmr spectra with those of the synthetic compound which had been prepared as an intermediate in the total synthesis7) of cryptotanshinone.

Acknowledgement: The authors are grateful to Dr. H.Mishima, Sankyo Co., Ltd. for the generous supply of the material from which isotanshinones were isolated, and also to Professor A.Tatematsu of Meijo University and Dr. K.Yamada of Nagoya University for the measurments of mass spectra.

REFERENCES

1) K.Takiura, *J. Pharm. Soc. Japan*, **61**, 482 (1941).

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

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

4) F.von Wessely and S.Wang, *Ber.*, **73**, 19 (1940).

5) C.H.Brieskorn, A.Fuchs, J.Bredenberg, J.D.McChesney and E.Wenkert, *J. Org. Chem.*, **29**, 2293 (1964).

6) A.C.Baillie and R.H.Thomson, *J. Chem. Soc.*(*C*), 48 (1968).

7) H.Kakisawa and Y.Inouye, *Chem. Comm.* in press.

8) J.E.Little, T.J.Sproston and M.W.Foote, *J. Biol. Chem.* **174**, 335 (1948).

9) M.Yamaguchi and A.Fujino, "Kagaku no Ryoiki", Supplement No. 3, 101 (1954), Nankodo, Japan.