*Tetrahedron* Vol. 24, pp 3237 to 3240. Pergamon Press. 1968 Printed in Great Britain

# SYNTHESIS OF TETRA-O-METHYL DISTEMONANTHIN AND RELATED DEHYDROPELTOGYNANDIONES

A. C. JAIN, V. K. KHANNA, P. D. SARPAL and T. R. SESHADRI
Department of Chemistry, University of Delhi, Delhi-7, India

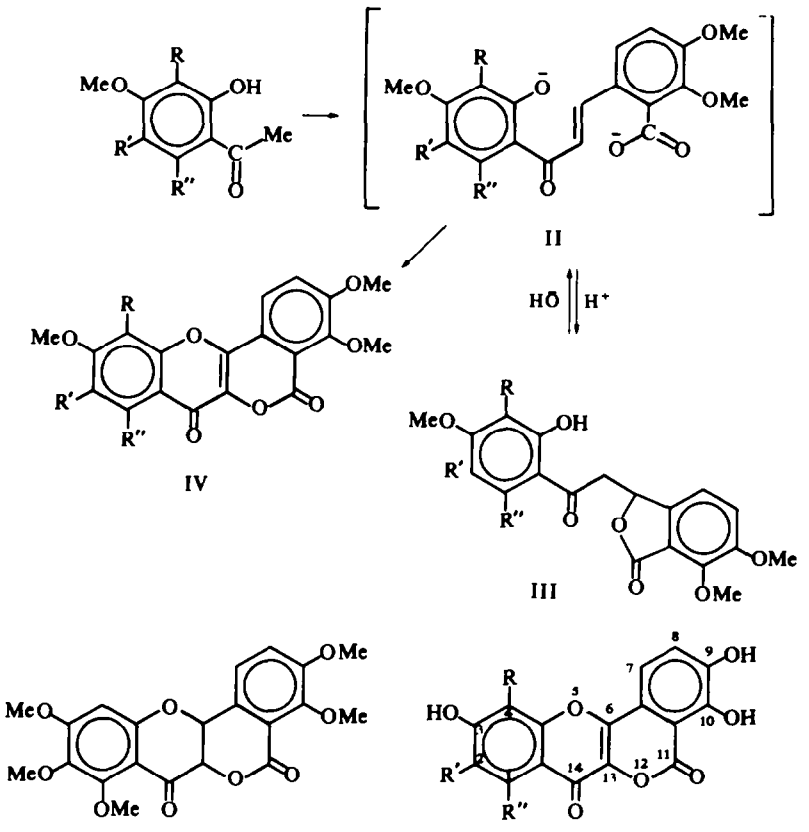
(*Received in the UK* 27 *July* 1967; *accepted for publication* 30 *October* 1967)

**Abstract**—Distemonanthin is a derivative of peltogynan and has 6,13-dehydropeltogynan-11,14-dione system. Its tetramethyl ether (IVa) has been prepared by the condensation of opianic acid with 2-hydroxy-4,5,6-trimethoxyacetophenone followed by oxidation with alkaline $H_2O_2$. Simpler compounds having this system have also been prepared using various *o*-hydroxy acetophenones in the above condensation.

DISTEMONANTHIN, a yellow component of the African wood *Distemonanthus benthamianus* was given the structure of chromono-isocoumarin (VIa)[1] on the basis of degradative studies. Neither it nor any of its derivatives was synthesized earlier. In a recent short communication,[2] a synthesis of its tetramethyl ether (IVa) was outlined and the possible biogenesis discussed. Since the 4-ring system present in distemonanthin was earliest recognized in peltogynol, the parent ring system was named "peltogynan" and consequently distemonanthin obtained the systematic name of 1,3,9,10-tetrahydroxy-2-methoxy-6-13-dehydropeltogynan-11,14-dione (VIa). The full experimental details for the synthesis of IVa and its analogues are described in this paper.

2-Hydroxy-4,5,6-trimethoxyacetophenone (Ia) has been condensed with opianic acid in the presence of alkali. The product has been characterized as a phthalide derivative (IIIa) on the basis of its UV and IR data; obviously the corresponding chalkone (IIa) earlier formed has undergone ready cyclization. However, the phthalide (IIIa) behaves as a chalkone in alkaline medium because it successfully undergoes A.F.O. reaction with alkaline hydrogen peroxide giving a mixture of products. The major product proved to be the desired tetra-O-methyl distemonanthin (IVa) and the minor one its dihydro derivative V. The mechanism of the unusual A.F.O. reaction has already been explained.[2]

In the exploratory study of simpler models, opianic acid has been condensed with three more ketones viz. gallacetophenone 3,4-dimethyl ether (Ib), 2-hydroxy-3-methyl-4-methoxyacetophenone (Ic) and 4,6-di-O-methyl phloroacetophenone (Id). The products are invariably phthalides (III) which on oxidation with alkaline hydrogen peroxide give mainly the corresponding 6,13-dehydropeltogynan-11,14-diones (IV). In these A.F.O. reactions the amount of hydrogen peroxide used is in excess and hence the main product is only a dehydro derivative. When it is less; some peltogynan-11,14-dione (cf. V) is also formed. Complete demethylation of dehydropeltogynandiones (IVb and c) has been carried out with hydrogen iodide in acetic anhydride medium to give the corresponding phenols (VIb and c). In order to make sure that no reaction other than demethylation takes place with hydrogen iodide the hydroxy compound VIc has been remethylated to yield the parent methyl



II

IV

III

V

VI

For I–IV, a: R = H, R′ = R″ = $OCH_3$
b: R = OMe, R′ = R″ = H
c: R = $CH_3$, R′ = R″ = H
d: R = R′ = H, R″ = $OCH_3$

For VI, a: R = H, R′ = $OCH_3$, R″ = OH
b: R = OH, R′ = R″ = H
c: R = $CH_3$, R′ = R″ = H

ether (IVc). It may be pointed out that methylation under dry conditions does not open the isocoumarin ring. Some of these compounds and methyl ethers could be expected to occur in Nature.

## EXPERIMENTAL

All m.ps reported are uncorrected. Unless otherwise stated, UV spectra were taken in $CHCl_3$ soln and IR in Nujol mull. The figures in brackets in UV spectra represent log ε values. The solvent systems used for qualitative TLC on silica gel were (A) ethyl formate:formic acid:toluene, 4:1:5 and (B) ethyl acetate: benzene:formic acid, 2:4:1.

3-(2-*Hydroxy*-4,5,6-*trimethoxyphenacyl*)-6,7-*dimethoxyphthalide* (IIIa). Compound Ia[3,4] (1 g) was dissolved in EtOH (7·5 ml) and opianic acid (1 g) added. The resulting soln was treated with KOH aq (4 g/8 ml). After standing overnight at room temp, the orange soln was diluted with cold water and acidified. The product (IIIa) crystallized from EtOH as colourless needles (1·7 g), m.p. 180–181°; light brown ferric reaction; $\lambda_{max}$ 287·5 mμ (4·06), $\lambda_{max}$ (0·1N NaOH): 233–244 (infl), 330, 398–406 (infl) mμ (4·14, 4·25 and 3·75); $\nu_{max}$: 1773 (phthalide C=O), 1628 (chelated C=O), 3400 $cm^{-1}$ (broad) (chelated OH). (Found: C, 59·8; H, 5·3; $C_{21}H_{22}O_9$ requires: C, 60·3; H, 5·3%).

*Tetra-O-methyl distemonanthin* (IVa) *and its dihydroderivative* (V). The above phthalide IIIa (1 g) was suspended in MeOH (5 ml) and 10% NaOH aq (20 ml) added when a clear soln resulted. This was cooled in ice and treated with $H_2O_2$ (6 ml, 15%) in several lots. After keeping the soln overnight in the refrigerator, it was diluted with cold water and acidified. The ppt (mother liquor being marked A) was crystallized from glacial AcOH yielding IVa as colourless plates (0·2 g), m.p. 271–272° (lit.[1] 272°); no ferric reaction; $\lambda_{max}$ 260 (infl), 294 (infl), 338, 349 mμ (4·03, 3·85, 4·19, 4·17); $\lambda_{max}$ (0·1N NaOH in 90% EtOH): 258–266 (infl), 310, 386–394 mμ (4·11, 3·67, 4·02); $\nu_{max}$ (Nujol): 1745 (lactone CO), 1655 $cm^{-1}$ (chromone CO). (Found: C, 61·3; H, 4·3; $C_{21}H_{18}O_9$ requires: C, 60·9; H, 4·4%).

The mother liquor (A) was extracted with $CHCl_3$ and the soln evaporated to dryness. The residue was crystallized from boiling glacial AcOH, V separating as colourless needles (0·2 g), m.p. 191–192°; $\lambda_{max}$ 290, 325 mμ (3·74, 4·15); $\lambda_{max}$ (0·1N NaOH in 90% EtOH) 280, 340 mμ (4·05 and 3·68); $\nu_{max}$ 1765 (lactone CO), 1735 $cm^{-1}$ (flavanone CO). (Found: C, 60·9; H, 5·3. $C_{21}H_{20}O_9$ requires: C, 60·6; H, 4·8%).

3-(2-*Hydroxy*-3,4-*dimethoxyphenacyl*) 6,7-*dimethoxyphthalide* (IIIb). A soln of Ib (2 g) in EtOH (18 ml) was treated with opianic acid (2·1 g), followed by KOH aq (9 g/18 ml). After 24 hr the product was crystallized from EtOH yielding IIIb as colourless plates (2·3 g), m.p. 171–172°; light brown ferric reaction; $\lambda_{max}$ 292 mμ (4·32); $\lambda_{max}$ (0·1N NaOH): 337 and 405–410 mμ (infl) (4·21, 3·92); $\nu_{max}$ 1770 (phthalide C=O), 1635 $cm^{-1}$ (chelated C=O). (Found: C, 62·2; H, 5·6; $C_{20}H_{20}O_8$ requires: C, 61·9; H, 5·2%).

3,4,9,10-*Tetramethoxy*-6,13-*dehydropeltogynan*-11,14-*dione* (IVb). The above phthalide IIIb (2 g) was suspended in MeOH (10 ml) and oxidized using 10% NaOH aq (40 ml) and 15% $H_2O_2$ (20 ml) at 15–20°. The product was crystallized from glacial AcOH yielding IVb as colourless silky needles (1·0 g), m.p. 312–314°, TLC using solvent system A showed a single spot; $\lambda_{max}$ 248, 317 (infl), 333 and 353 mμ (4·31, 4·10, 4·13 and 4·20); $\lambda_{max}$ (0·1N NaOH in 90% EtOH): 264, 305 (infl), 380–386 mμ (4·09, 3·50 and 3·90); $\nu_{max}$ 1740 (lactone C=O), 1668 $cm^{-1}$ (chromone C=O). (Found: C, 62·8; H, 4·3%; $C_{20}H_{16}O_8$ requires: C, 62·5; H, 4·2%).

3,4,9,10-*Tetrahydroxy*-6,13-*dehydropeltogynan*-11,14-*dione* (VIb). Compound IVb (0·2 g) was suspended in $Ac_2O$ (4 ml) and treated with HI (8 ml). The resulting mixture was refluxed for 3 hr and then poured over ice-cold $Na_2SO_3$ aq and the solid filtered off. It was crystallized from pyridine–MeOH yielding VIb (0·1 g) as light yellow needles, m.p. above 310°; yellowish green ferric reaction; $\nu_{max}$ 3425 (OH), 1685 (shoulder), 1680 and 1640 $cm^{-1}$ (C=O). (Found: C, 58·6; H, 2·9; $C_{16}H_8O_8$ requires: C, 58·6; H, 2·5%).

The tetra-acetate prepared by the $Ac_2O$–pyridine method crystallized from glacial AcOH, m.p. above 310°; TLC using solvent system A showed a single spot; $\lambda_{max}$ 255, 272, 320, 342 mμ (4·34, 4·03, 4·16, 4·19); $\nu_{max}$ 1785, 1755, 1665 (C=O bands). (Found: C, 58·4; H, 3·6. $C_{24}H_{16}O_{12}$ requires: C, 58·1; H, 3·3%).

3-(2-*Hydroxy*-3-*methyl*-4-*methoxyphenacyl*) 6,7-*dimethoxyphthalide* (IIIc). Compound Ic (1·8 g) was condensed with opianic acid (2·1 g) using EtOH (18 ml) and KOH (9 g/18 ml). The product was crystallized from EtOH yielding IIIc as colourless plates (2·2 g), m.p. 160–161°; light brown ferric reaction; $\lambda_{max}$ 290 mμ (4·17); $\lambda_{max}$ (0·1N NaOH): 335, 400–405 mμ (infl) (4·08, 3·76); $\nu_{max}$ 1765 (phthalide C=O), 1640 $cm^{-1}$ (chelated C=O). (Found: C, 64·0; H, 4·9; $C_{20}H_{20}O_7$ requires: C, 64·5; H, 5·4%).

3,9,10-*Trimethoxy*-4-*methyl*-6,13-*dehydropeltogynan*-11,14-*dione* (IVc). The above IIIc (2 g) was oxidized with alkaline $H_2O_2$ at 15–20°. The product was crystallized from glacial AcOH yielding IVc as colourless silky needles (1 g), m.p. 314–315°; TLC using solvent system A showed a single spot; $\lambda_{max}$ 246, 315 (infl), 332, 353 mμ (4·49, 4·33, 4·35, 4·40); $\lambda_{max}$ (0·1N 90% ethanolic NaOH) 265, 300–305 (infl), 383–387 mμ (4·15, 3·68, 4·06); $\nu_{max}$ 1745 (lactone C=O), 1670 $cm^{-1}$ (chromone C=O). (Found: C, 64·7; H, 4·5. $C_{20}H_{16}O_7$ requires: C, 65·2; H, 4·4%).

3,9,10-*Trihydroxy*-4-*methyl*-6,13-*dehydropeltogynan*-11,14-*dione* (VIc). The above IVc (0·2 g) was demethylated using $Ac_2O$ and HI. The product was crystallized from pyridine–MeOH yielding VIc (0·1 g) as yellow needles, m.p. above 310°; yellowish green ferric reaction, $\nu_{max}$ 3580 (—OH), 1710 (shoulder), 1705, 1652 and 1640 $cm^{-1}$ (C=O). (Found: C, 62·2; H, 3·6; $C_{17}H_{10}O_7$ requires: C, 62·6; H, 3·1%). This product on remethylation with $Me_2SO_4$ by the $K_2CO_3$–acetone method gave *only* IVc, identified by mixed m.p. and TLC using solvent system A.

The triacetate crystallized from glacial AcOH as a colourless compound, m.p. above 310°; TLC using solvent system A showed a single spot; $\lambda_{max}$ 254, 270, 322, 340 mμ (4·43, 4·09, 4·31, 4·25); $\nu_{max}$ 1770, 1745, 1640 $cm^{-1}$ (C=O). (Found: C, 61·0; H, 3·9; $C_{23}H_{16}O_{10}$ requires: C, 61·1; H, 3·6%).

3-(2-*Hydroxy*-4,6-*dimethoxyphenacyl*) 6,7-*dimethoxyphthalide* (IIId). Compound Id (2 g) was condensed with opianic acid (2·1 g) using EtOH (18 ml) and KOH aq (9 g/18 ml). The product was crystallized from EtOH yielding IIId as colourless needles (2 g), m.p. 174–176°, light brown ferric reaction; TLC using solvent systems A and B showed a single spot; $\lambda_{max}$ 291 mμ (4·27); $\lambda_{max}$ (0·1N NaOH): 325–332, 402 (infl)

mμ (4·33, 3·51), $\nu_{max}$ (KBr): 1775 (phthalide C=O), 1630 $cm^{-1}$ (chelated C=O). (Found: C, 62·0; H, 5·4; $C_{20}H_{20}O_8$ requires: C, 61·9; H, 5·2%).

1,3,9,10-*Tetramethoxy*-6,13-*dehydropeltogynan*-11,14-*dione* (IVd). The above IIId (1 g) was oxidized with alkaline $H_2O_2$ at 15–20°. The product showed two spots on TLC using systems A and B. Hence it was fractionally crystallized from EtOH. The sparingly soluble fraction on recrystallization from glacial AcOH gave colourless needles of pure IVd (0·2 g), m.p. above 310°; TLC using solvent systems A and B showed single spots; $\lambda_{max}$ 257, 307–320 (infl); 332–337; 352 mμ (4·42, 4·25, 4·32, 4·38); $\lambda_{max}$ (0·1N NaOH in 90% EtOH): 252–260, 299 (infl), 380–382 mμ (4·54, 4·20, 4·38); $\nu_{max}$ (KBr) 1750 (lactone C=O), 1670 $cm^{-1}$ (chromone C=O). (Found: C, 62·0; H, 4·5. $C_{20}H_{16}O_8$ requires: C, 62·5; H, 4·2%).

## REFERENCES

[1] F. E. King, T. J. King and P. J. Stokes, *J. Chem. Soc.* 4595 (1954).
[2] A. C. Jain, P. D. Sarpal and T. R. Seshadri, *Tetrahedron Letters* **36**, 4381 (1966).
[3] V. D. N. Sastri and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **23A**, 262 (1946).
[4] W. J. Horton and M. G. Stout, *J. Org. Chem.* **27**, 830 (1962).