Tetrahedron Letters No.37, pp. 3999-4002, 1968. Pergamon Press. Printed in Great Britain.

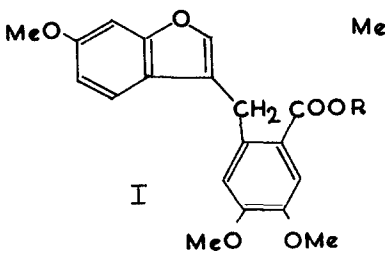
BRAZILIN AND HAEMATOXYLIN. PART IV*. SYNTHESIS OF ψ-TRIMETHYLBRAZILONE

P.M. Chakrabarti

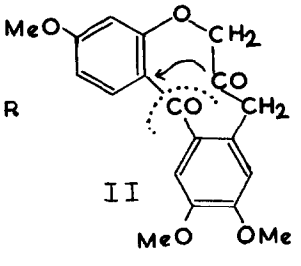
Chemistry Department, The University of Hull
Hull, England.

(Received in UK 10 June 1968; accepted for publication 16 June 1968)

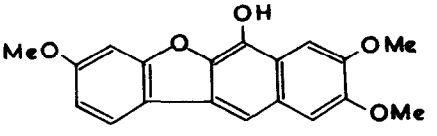
ψ-Trimethylbrazilone (I; R = H)[5,6] has not yet been synthesised. It is isomeric with trimethylbrazilone (II)** and is formed from the latter[7] by treatment with cold concentrated sulphuric acid by an intramolecular rearrangement which may be visualised[9] as involving ring opening along the dotted line followed by ring closure as indicated by the arrow. When treated with dehydrating agents it gives[7] β-anhydrotrimethylbrazilone (III), the structure of which was confirmed by an unequivocal synthesis due to Bentley and Robinson[10]. A synthesis of ψ-trimethylbrazilone now reported appears to be the first synthesis of this compound.



I



II



III

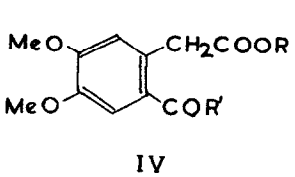
2-Acetyl-4,5-dimethoxyphenylacetic acid (IV; R = H, R' = Me)[2] was oxidised by sodium hypochlorite[4] in almost quantitative yield to give 2-carboxy-4,5-dimethoxyphenylacetic acid[11] (IV; R = H, R' = OH). The dimethyl ester (IV; R = Me, R' = OMe) was converted into the half ester, 2-carbomethoxy-4,5-dimethoxyphenylacetic acid (IV; R = H, R' = OMe), m.p. 176-78° (uncorr.), (Found C, 56.5; H, 5.7. $C_{12}H_{14}O_6$ requires C, 56.68; H, 5.55), by refluxing it for 16 hr. with

---

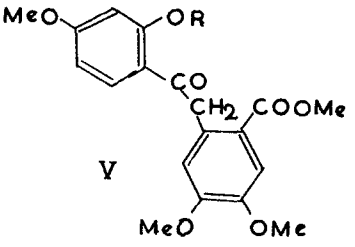
* References (1), (2) and (3) are regarded as Parts I, II and III respectively of this series.

** The large ring diketone structure (II) is now accepted in preference to other structures on the basis of I.R. spectrum of trimethylbrazilone (ref. 8).

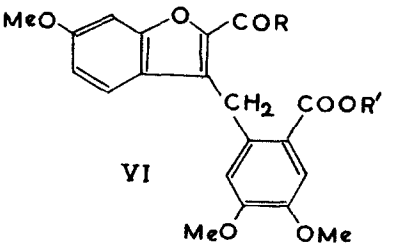
one mol of potassium hydroxide in absolute methanol according to the procedure of Wegscheider and Glogau[12] for the partial hydrolysis of homophthalic esters. The acid chloride prepared from the above half ester underwent the Friedel-Crafts reaction with resorcinol dimethyl ether and $AlCl_3$ in boiling benzene (2 hr.) to furnish 2-carbomethoxy-4,5-dimethoxybenzyl 2'-hydroxy-4'-methoxyphenyl ketone (V; R = H) in 60% yield, m.p. 169-70° (uncorr.) (colourless needles from methanol), deep violet colour with $FeCl_3$ in aqueous-alcoholic solution, (Found C, 63.1; H. 5.7; M from mass spectrum, 360. $C_{19}H_{20}O_7$ requires C, 63.3; H, 5.6; M, 360).



IV



V



VI

The compound (V; R = H) with ethyl α-bromoacetate and anhydrous potassium carbonate in dry refluxing acetone for 8 hr. gave the highly viscous ethyl 5-methoxy-2-(2-carbomethoxy-4,5-dimethoxyphenacyl)-phenoxyacetate (V; R = CH_2COOEt) which on short selective hydrolysis with aqueous-methanolic sodium hydroxide afforded the corresponding phenoxyacetic acid (V; R = CH_2COOH). Treatment of (V; R = CH_2COOH) with methanolic sodium methoxide furnished, in about 30% overall yield (based on V; R = H), the 2-carboxy-3-(2-carbomethoxy-4,5-dimethoxybenzyl)-6-methoxybenzofuran (VI; R = OH, R' = Me), m.p. 175-76° (uncorr.) (needles from methanol), (Found C, 63.2; H, 5.1; M from mass spectrum, 400. $C_{21}H_{20}O_8$ requires C,63.0; H, 5.0; M, 400).

The same compound (VI; R = OH, R' = Me) was also prepared, though in a poor overall yield by an alternative route. The compound (V; R = H) was condensed with monochloroacetone in the presence of anhydrous potassium carbonate and a catalytic amount of sodium iodide in refluxing acetone and the crude reaction product (V; R = CH_2COCH_3), without further purification, was cyclised with simultaneous hydrolysis of the ester function by shaking with 10% aqueous

sodium hydroxide at 60° for one hr., to give the 2-acetyl-3-(2-carboxy-4,5-dimethoxybenzyl)-6-methoxybenzofuran (VI; R = Me, R' = H), m.p. 220-22° (softening at 215°), (Found C, 65.8; H, 5.4; M from mass spectrum, 384. $C_{21}H_{20}O_7$ requires C, 65.6; H, 5.2; M, 384). The methyl ester (VI; R = Me, R' = Me) on oxidation with sodium hypochlorite gave the same half ester (VI; R = OH, R'= Me).

Compound (VI; R = OH, R' = Me) was decarboxylated by heating it in freshly distilled quinoline in the presence of copper bronze to give the methyl ester, 3-(2-carbomethoxy-4,5-dimethoxybenzyl)-6-methoxybenzofuran (I, R = Me), m.p. 82°, identical (undepressed mixed m.p. and identical I.R.) with an authentic sample of the methyl ester[5] prepared from ψ-trimethylbrazilone. Hydrolysis of the synthetic methyl ester (I; R = Me) with alcoholic or aqueous potassium hydroxide furnished the corresponding acid, 3-(2-carboxy-4,5-dimethoxybenzyl)-6-methoxybenzofuran, m.p. 171-73°, (Found C, 66.7; H, 5.5. $C_{19}H_{18}O_6$ requires C, 66.7; H, 5.3), identical (undepressed mixed m.p. and identical I.R.) with an authentic sample of ψ-trimethylbrazilone prepared[7] from trimethylbrazilone.

ACKNOWLEDGEMENT: This work was carried out during the tenure of an I.C.I. research fellowship at the University of Hull. My sincere thanks are due to Professor N.B. Chapman and to Dr. K. Clarke for their helpful suggestions.

REFERENCES

1. a) P.M. Chakrabarti, J. Proc. Inst. Chemists (India), 34, 264 (1962).

   b) P.M. Chakrabarti, J. Proc. Inst. Chemists (India), 35, 199 (1963).

2. P.M. Chakrabarti, Tetrahedron Letters, No. 26, 1771 (1963).

3. P.M. Chakrabarti, Tetrahedron Letters, No. 27, 1907 (1963).

4. P.M. Chakrabarti, D.Sc. Thesis, Calcutta University (India) (1964).

5. J. Herzig and J. Pollak, Monatsh., 25, 871 (1904).

6. W.H. Perkin, jun. and R. Robinson, J. Chem. Soc., 385 (1909).

7. J. Herzig and J. Pollak, Ber., 37, 631 (1904).

8. R.E. Richards and M.L. Tomlinson, Nature, 693 (1948).

9. R. Robinson, Bull. Chim. Soc. France, 125 (1958).

10. K.W. Bentley and R. Robinson, J. Chem. Soc., 1353 (1950).

11. W.H. Perkin, jun. and R. Robinson, J. Chem. Soc., 1082 (1907).

12. R. Wegscheider and A. Glogau, Monatsh., 24, 915 (1903).