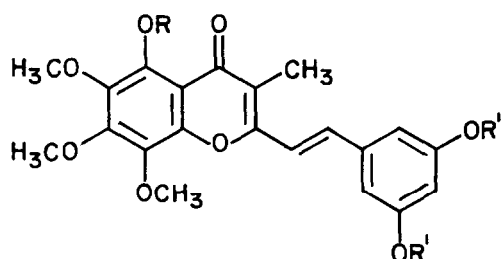


SYNTHESIS OF HORMOTHAMNIONE⁺

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Summary: Synthesis of hormothamnione has been described.

Hormothamnione, the first naturally occurring styrylchromone isolated recently by Gerwick et al.¹ from the marine cyanophyte Hormothamnion enteromorphoides, was shown to be 2-(3',5'-dihydroxy styryl)-3-methyl-5-hydroxy-6,7,8-trimethoxy chromone (I). Its structure was determined on the basis of spectral properties and X-ray analysis of its triacetate derivative. Hormothamnione is an exceptionally potent cytotoxin to cancer cells *in vitro* and appears to be a selective inhibitor of RNA synthesis. As hormothamnione is present in the cyanophyte in small quantities, there is an urgent need for its synthesis for further evaluation of the activity.

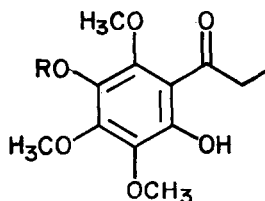


I : R = R' = H

Ia : R = CH₃, R' = -CH₂C₆H₅

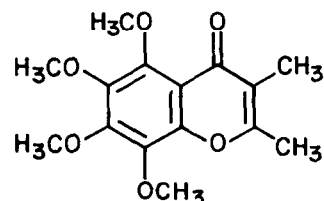
Ib : R = H, R' = -COCH₃

Ic : R = R' = -COCH₃



IIa : R = CH₃

IIb : R = H



III

We now report a synthesis of hormothamnione (I). Our key intermediate, 2-hydroxy-3,4,5,6-tetramethoxy propiophenone (IIa) was prepared in 50% yield by partial methylation of 2,5-dihydroxy-3,4,6-trimethoxypropiophenone (III)² with dimethylsulphate and potassium carbonate in dry benzene. Application of Kostanecki-Robinson reaction³ on IIa with acetic anhydride and sodium acetate at 180°C gave 2,3-dimethyl-5,6,7,8-tetramethoxy chromone (III) in 35% yield; m.p. 98°C. Condensation of the chromone III with 3,5-dibenzoyloxy benzaldehyde⁴ by using sodium ethoxide and ethanol afforded quantitative yield of 2-(3',5'-dibenzoyloxy styryl)-3-methyl-5,6,7,8-tetramethoxy chromone (Ia). The styrylchromone Ia on treatment with borontrichloride⁵ in dichloromethane at -15°C underwent selective demethylation as well as debenzoylation to afford hormothamnione (I) in almost quantitative yield. It was found to

to be identical with natural hormothamnione.⁶ With acetic anhydride and pyridine at room temperature for 24 h, it gave the diacetate derivative (**Id**); m.p. 180°C. (¹H NMR: δ 12.66; S, 1H, exchanges with D₂O). Under similar conditions formation of triacetate (**Ic**) was reported.¹ The compound (**I**) was heated with acetic anhydride and pyridine at 80°C for 6 h to give triacetate **Ic** (85%) as colourless plates^{7,8}.

Acknowledgement: One of the authors (R.A.K.) is thankful to the CSIR, New Delhi for financial support.

References and Notes:

1. W.H. Gerwick, A. Lopez, G.D. VanDuyne, J. Clardy, W. Ortiz and A. Baez, Tetrahedron Lett., 1986, 27, 1979.
2. The propiophenones **Ila** and **Ilb** were prepared, as described by W. Baker, J. Chem. Soc., 1941, 662; by using propionyl chloride instead of acetyl chloride.
3. D.G. Flynn and A. Robertson, J. Chem. Soc., 1936, 215.
4. 3,5-Dibenzyloxymethylbenzoate was reduced (LAH/ether) followed by pyridinium dichromate oxidation to give 3,5-dibenzyloxybenzaldehyde; m.p. 80°C.
5. F.M. Dean, J. Goodchild, L.E. Houghton, J.A. Martin, R.B. Morton, B. Parton, A.W. Price and N. Somvichien, Tetrahedron Lett., 1966, 4153.
6. Synthetic hormothamnione **I**: m.p. 270°C dec. (Lit.¹ m.p. 270°C dec). MS:(M⁺) m/z 400; IR (Nujol): 3400 and 1640 cm⁻¹; UV (MeOH, λ_{max}): 294 and 353; ¹H NMR (90 MHz, CDCl₃ + Acetone-d₆): δ 2.17 (s, 3H), 3.94 (s, 3H), 4.00 (s, 3H), 4.11 (s, 3H), 6.51 (t, 1H), 6.75 (d, 2H), 7.07 (d, J = 16Hz, 1H), 7.6 (d, J = 16Hz, 1H), 8.04 (s, 2H, exchanges with D₂O), 12.7 (s, 1H, exchanges with D₂O).
7. Hormothamnione triacetate **Ic**: m.p. 204°C (Lit.¹ 198-202°C); MS:(M⁺) m/z 526; IR (CHCl₃): 1780 and 1635 cm⁻¹; ¹H NMR (90 MHz, CDCl₃): δ 2.17 (s, 3H), 2.35 (s, 6H), 2.50 (s, 3H), 3.89 (s, 3H), 4.06 (s, 3H), 4.11 (s, 3H), 6.97 (t, 1H), 7.24 (d, 2H), 7.08 (d, J = 16Hz, 1H), 7.58 (d, J = 16Hz, 1H).
8. All the compounds gave satisfactory structural analyses and spectroscopic data.

⁺ NCL Communication No. 4381.

(Received in UK 25 February 1988)