Tetrahedron Letters,Vol.23,No.46,pp 4847-4848,1982　0040-4039/82/464847-02$03.00/0
Printed in Great Britain

SYNTHESIS OF THE COUMARIN, HORTIOLONE

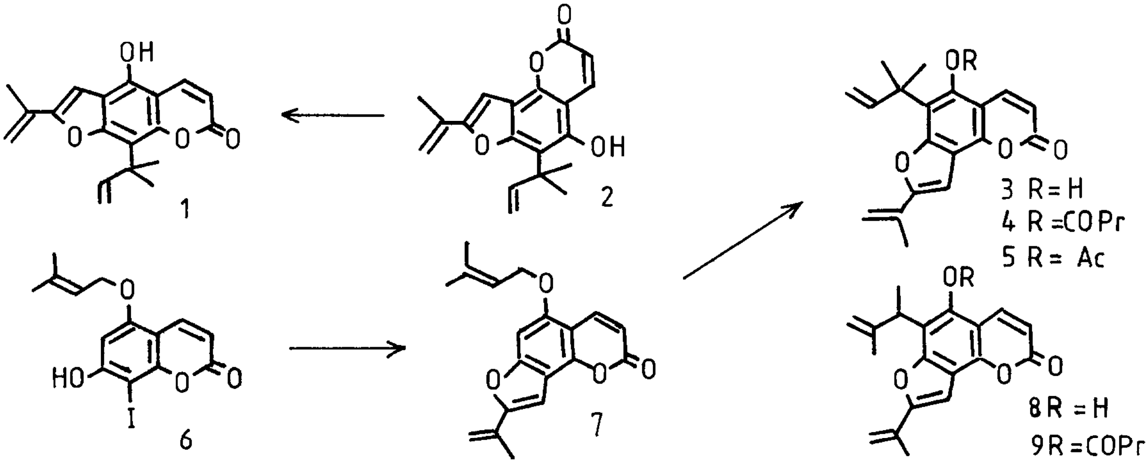
R.D.H. Murray,* Z.D. Jorge and K.W.M. Lawrie
Chemistry Department, University of Glasgow, Glasgow G12 8QQ

Abstract. The structure of the natural coumarin, hortiolone, has been confirmed by a total synthesis in 6 steps from 5,7-diacetoxycoumarin in 48% overall yield.

In 1976 a new 5,7-dioxygenated coumarin, hortiolone, was isolated from *Hortia arborea*.[1] Later it was concluded that it had structure (1) with the phenolic group at C-5 *para* to a 1,1-dimethylallyl substituent at C-8 and the rare isopropenylfuran ring linked to give a linear furanocoumarin nucleus.[2]

From the synthetic viewpoint, we felt that introduction of the 1,1-dimethylallyl group could probably be most efficiently effected by the *ortho* Claisen rearrangement of a prenyl aryl ether, as in other natural coumarin syntheses.[3,4] The phenol (2) was thus deemed to be a suitable intermediate. It was envisaged that hortiolone (1) could be obtained by base-induced opening of the lactone ring of 2 followed by cyclisation of the transient coumarinic acid with the hydroxyl group in 2 which had been liberated during the Claisen rearrangement. The phenol (2), which is more readily seen to be an angular furanocoumarin when redrawn as 3, was obtained as follows.

7-Hydroxy-5-prenyloxycoumarin, readily available from 5,7-diacetoxycoumarin,[5] underwent regiospecific iodination to the 8-iodocoumarin (6, 89%), mp 163-165° when treated with HgO and I_2 in $CHCl_3$.[6] Coupling 6 with the copper(I) acetylide from 2-methylbut-1-en-3-yne[7] in dry pyridine at 80° under argon (12 h) afforded the required isopropenylfuranocoumarin (7, 92%), mp 144-146°.



Thermal rearrangement of a prenyl aryl ether may be conveniently carried out in the presence of butyric anhydride to trap the first formed phenol as its butyrate and thereby prevent the incursion of a second rearrangement leading to the abnormal Claisen rearrangement product.[3,8] The NMR spectrum of the only butyrate obtained when the prenyl ether (7) was heated in butyric anhydride and diethylaniline at 190° disclosed that rearrangement had taken place to the only available benzenoid position but that a 1,2-dimethylallyl group had been introduced. Thus despite the presence of a supposed trapping agent the only product (9) was that from an abnormal Claisen rearrangement.[8]

In order to prevent the obviously rapid rearrangement of the desired phenol (3) to the unwanted phenol (8), the pyrolysis of 7 was repeated in butyric anhydride at 195° but with sodium butyrate replacing the diethylaniline. The butyrate (4) of the normal rearrangement product was now the only product but freeing it from traces of butyric anhydride proved difficult. This problem was circumvented by performing the rearrangement of 7 in refluxing acetic anhydride containing sodium acetate, the acetate (5), mp 149-152° being quantitatively obtained.

Careful hydrolysis of 5 with NaOH (1.5 eq) in MeOH at room temperature for 1 h afforded the corresponding phenol ($3 \equiv 2$), mp 160-164°. When the hydrolysis was repeated using 3 eq base, TLC (EtOAc-petrol, 1:9) indicated quantitative formation of the less polar phenol ($3 \equiv 2$) after 20 min. Base-induced isomerisation of this phenol to the significantly more polar hortiolone (1, 98%), mp 220-223° (lit.[1] 226-227°) was followed by TLC and was complete after 5 h.

Acknowledgements: We are grateful to Professor Delle Monache for a sample of natural hortiolone and the Spanish Ministry of Education and Science and the Science Research Council for financial support.

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(Received in UK 27 August 1982)