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SYNTHESIS OF THE COUMARIN, TODDACULIN

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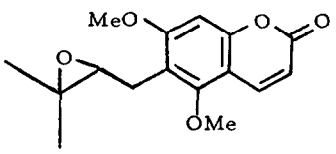
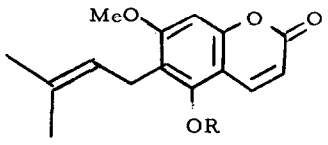
Three biogenetically related compounds, aculeatin[1] (1), the corresponding vicinal diol, toddalolactone[2] (2) and the parent coumarin, toddaculin[3] (3), from which racemic 1 and 2 have been prepared, [3] have been isolated from Toddalia aculeata.

We envisaged a synthesis of toddaculin from 5, 7-dihydroxycoumarin (5) using the ortho Claisen rearrangement of a 1, 1-dimethylallyl ether[4] for insertion of the isoprenyl group at C-6. Since we have found[4, 5] that 1, 1-dimethylallyl ethers of 7-hydroxy-5-alkoxycoumarins rearrange exclusively to C-8, Claisen rearrangement to C-6 required the preparation of the 1, 1-dimethylallyl ether (7) of 5-hydroxy-7-methoxycoumarin (8).

Partial alkylation of 5, 7-diacetoxycoumarin (6) is known[4-6] to give predominantly the 5-monoether. Thus the first step in the conversion of 6 to 8 was necessarily replacement of the 5-OAc by a grouping capable of being removed after hydrolysis and methylation of the 7-OAc. Treatment therefore of 6 with excess 3, 3-dimethylallyl bromide and K_2CO_3 in glyme gave, [5] after saponification, the bis-ether[5] (8%) and two isomeric monoethers (9 and 10). Methylation (MeI, K_2CO_3, acetone) of the mixture of phenols afforded 11 and 12 (71% and 4% respectively from 6) which were conveniently separated by TLC. Hydrolysis of the major isomer (11) with methanolic HCl quantitatively afforded the desired phenol (8). The derived[4] dimethylpropargyl ether (13), on Lindlar hydrogenation, furnished 7 which readily rearranged at 114°. The major pyrolysis product (4) (70%) was a positional isomer of the known[5] 5-hydroxy-7-methoxy-8-(3, 3-dimethylallyl) coumarin, showing that Claisen rearrangement to C-6 had indeed occurred. Methylation of 4 gave toddaculin, m.p. 93-94°, (33% from 8), identical (m.m.p., TLC, NMR) with an authentic sample.[7]

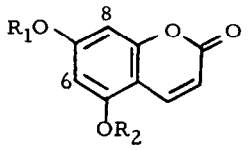


1



3: R = Me

4: R = H



7: R_1 = Me, R_2 = $CMe_2CH{=}CH_2$

8: R_1 = Me, R_2 = H

9: R_1 = H, R_2 = $CH_2CH{=}CMe_2$

10: R_1 = $CH_2CH{=}CMe_2$, R_2 = H

11: R_1 = Me, R_2 = $CH_2CH{=}CMe_2$

12: R_1 = $CH_2CH{=}CMe_2$, R_2 = Me

13: R_1 = Me, R_2 = $CMe_2C{\equiv}CH$

14: R_1 = Ac, R_2 = $CMe_2C{\equiv}CH$

A more direct, though somewhat less efficient, synthesis of the key intermediate (13) (20% from 6) was established by hydrolysis and methylation of the major product (14) isolated from the complex mixture obtained from direct dimethylpropargylation of 5, 7-diacetoxycoumarin.

References

1. P. Dutta, J. Indian Chem. Soc., 19, 425 (1942).
2. E. Spath, B.B. Dey and E. Tyray, Ber., 71, 1825 (1938); 72, 53 (1939).
3. G. Combes, R. Pernet and R. Pierre, Bull. Soc. Chim. France, 1609 (1961).
4. R.D.H. Murray, M.M. Ballantyne and K.P. Mathai, Tetrahedron, 27, 1247 (1971).
5. R.D.H. Murray, T.C. Hogg, M.M. Ballantyne and P.H. McCabe, Tetrahedron Letters, 3317 (1971).
6. V.K. Ahluwalia, T.R. Seshadri and P. Venkateswarlu, Indian J. Chem., 7, 115 (1969).

7. We are grateful to Dr. G. Combes for a sample of natural toddaculin.