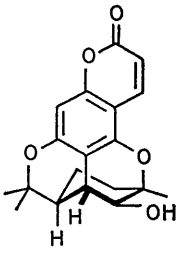
Synthesis and Structure of Eriobrucinol and Isomeric 'Cyclol' Meroterpenes

By LESLIE CROMBIE,* SALLY D. REDSHAW, DAVID A. SLACK, and DONALD A. WHITING*
(*Department of Chemistry, The University of Nottingham, Nottingham* NG7 2RD)

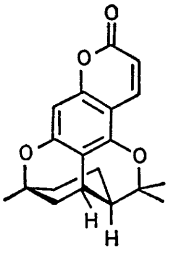
Summary (±)-Eriobrucinol (**3**) and its two regio-isomers (**8**) and (**9**) have been synthesised.

THE Australian shrub *Eriostemon brucei* contains monoterpenylated coumarins which pose problems of regio- and stereo-chemistry in both synthesis and biosynthesis. *X*-Ray analysis[1,2] demonstrated the structure of bruceol (**1**), but deoxybruceol, initially regarded for biogenetic reasons as sharing this skeleton, is now known to have the alternative orientation (**2**).[2] Both occur optically active, but with

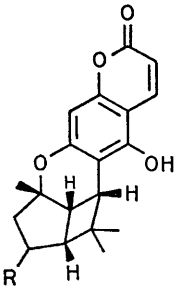
unknown absolute chirality. Eriobrucinol[3] has been assigned the 'cyclol' structure (**3**), *i.e.*, related to (**2**) rather than (**1**), and hydroxyeriobrucinol (**4**) was allocated the same orientation on chemical grounds. Structures for these two cyclols depend on n.m.r. spectral interpretation, and it seemed desirable, following our earlier work on citrans[2,4] and cyclols,[5] to confirm the constitution of eriobrucinol by synthesis of the three possible regioisomers.



(1)



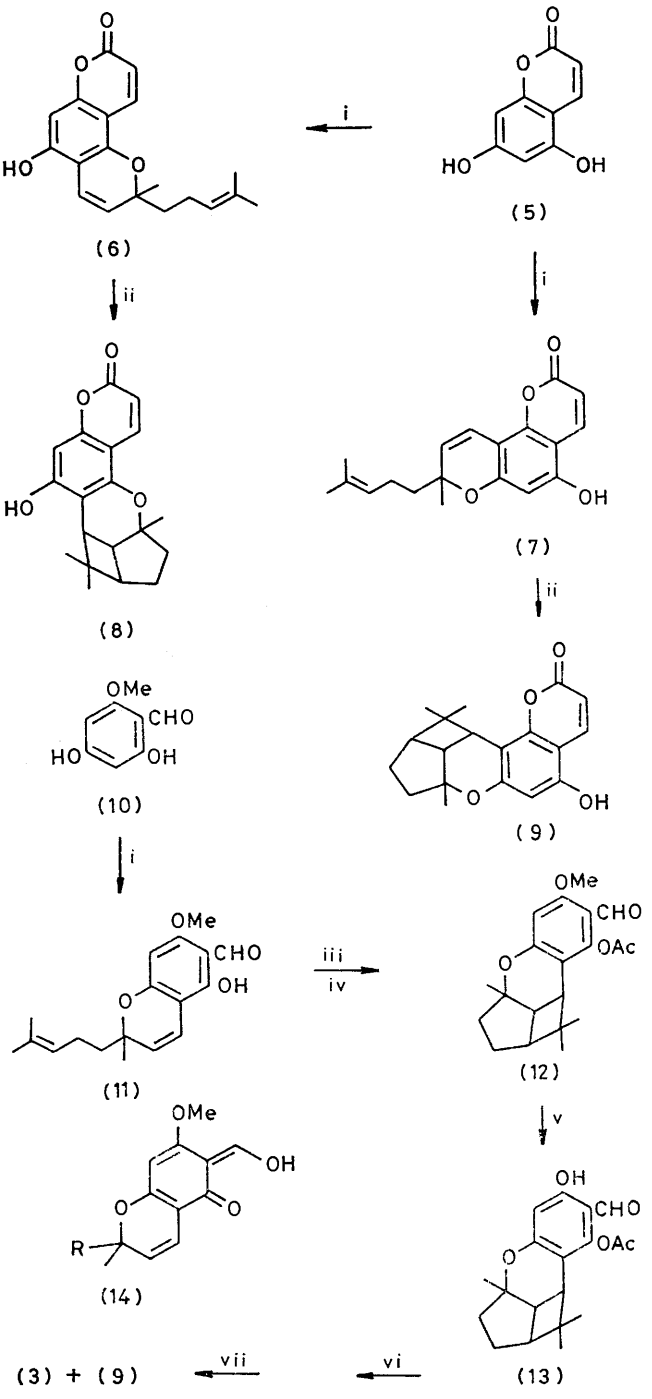
(2)



(3) R = H
(4) R = OH

5,7-Dihydroxycoumarin (**5**), on treatment with citral and pyridine at 90 °C, has been shown[2] to afford only the two chromens (**6**) and (**7**); such regiospecificity has been rationalised.[6] Irradiation of (**6**) in acetone–t-butyl alcohol with a 100 W medium-pressure mercury lamp gave the cyclol (**8**) (61%), and similar irradiation of (**7**) afforded (**9**) (18%). In both cases single cyclols were obtained, suggesting that photo-induced chromen isomerisation (*via* a dienone, *cf.* thermal isomerisation[4a]) did not precede the intramolecular 2 + 2 process. Structures (**8**) and (**9**) were not the same as eriobrucinol. Efforts to reach (**3**) from (**9**) through opening of the lactone and re-closure at the second hydroxy-group were unavailing, as were attempts at base isomerisation of (**6**) or (**7**). An alternative route to (**3**), under regio-control, was therefore devised.

2,4-Dihydroxy-6-methoxybenzaldehyde[7] (**10**) [from formylation of monomethylphloroglucinol, τ −2·30 and 0·36 (chelated and free OH's) in confirmation of orientation] was treated with citral and pyridine at 90 °C for 72 h to provide a single chromen (**11**). The structure of the latter can be predicted with confidence[6] and was confirmed by the presence of a chelated OH (τ −2·72) and the observation of a nuclear Overhauser enhancement (12%) between the OMe and adjacent aromatic H. This chromen was unaffected by irradiation, and neither heat nor boron trifluoride[8] induced 2 + 2 cycloaddition. However the acetate of (**11**) on irradiation yielded the desired cyclol (**12**) (78%), m.p. 141—141·5 °C.† Demethylation of (**12**) with magnesium iodide–diethyl ether was accomplished (62%) without deacetylation, to give (**13**). Elaboration of the *ortho*-hydroxy-aldehyde unit to a coumarin without *O*-deacetylation was then investigated. The reagents 1,1-dimethoxy-1-dimethylaminoethane[9] and 1,1-bismorpholinoethene,[9a] although used successfully in connection with the citran (**2**),[2] both led to complex reactions



i, citral–pyridine, 90 °C; ii, *hν*, Me_2CO–Bu^tOH; iii, Ac_2O, pyridine; iv, *hν*–Me_2CO; v, MgI_2–Et_2O; vi, Ac_2O, KOAc, 160 °C; vii, MeOH–HCl.

and studies with model 2,6-dihydroxybenzaldehydes and their acetates confirmed their unsuitability. However, resort to the classical Perkin reaction provided the acetates

† The striking photochemical difference between (**11**) and its acetate may involve energy dissipation *via* formation of (**14**) in the former case.

of the desired coumarin (**3**), m.p. 151·5—152 °C (30%), and its isomer (**9**) (29%). Deacetylation finally gave (±)-eriobrucinol (**3**), having spectroscopic properties identical with a natural specimen kindly provided by Professor Jeffries. This synthesis confirms the orientation and structure of the natural cyclol.‡

(*Received*, 18*th April* 1979; *Com.* 405.)

‡ Prof. Jefferies has kindly informed us that the structures of eriobrucinol and hydroxyeriobrucinol have lately been confirmed in his laboratory by *X*-ray analysis; he has also found (±)-deoxybruceol in *E. brucei*.

[1] A. M. Duffield, P. R. Jefferies, F. N. Maslen, and A. I. M. Rae, *Tetrahedron*, 1963, **19**, 593.
[2] M. J. Begley, L. Crombie, D. A. Slack, and D. A. Whiting, *J.C.S. Perkin I*, 1977, 2402.
[3] P. R. Jefferies and G. K. Worth, *Tetrahedron*, 1973, **29**, 903.
[4] (a) M. J. Begley, L. Crombie, R. W. King, D. A. Slack, and D. A. Whiting, *J.C.S. Perkin I*, 1977, 2393; (b) D. G. Clarke, L. Crombie, and D. A. Whiting, *J.C.S. Chem. Comm.*, 1973, 582; (c) W. M. Bandaranayake, L. Crombie, and D. A. Whiting, *J. Chem. Soc.* (*C*), 1971, 804.
[5] W. M. Bandaranayake, M. J. Begley, B. O. Brown, D. G. Clarke, L. Crombie, and D. A. Whiting, *J.C.S. Perkin I*, 1974, 998.
[6] D. G. Clarke, L. Crombie, and D. A. Whiting, *J.C.S. Perkin I*, 1974, 1007.
[7] D. D. Pratt and R. Robinson, *J. Chem. Soc.*, 1924, 188; P. Karrer and A. Block, *Helv. Chim. Acta*, 1927, **10**, 374.
[8] L. Crombie and R. J. Ponsford, *J. Chem. Soc.* (*C*), 1971, 796.
[9] (a) D. H. R. Barton, G. Hewitt, and P. G. Sammes, *J. Chem. Soc.* (*C*), 1969, 16; (b) E. Effenberger and R. Maier, *Annalen* 1969, **729**, 246.