# A Ready Synthetical Route to the Estrogenic 2,4-Dialkylisoflav-3-enes[1]

By C. E. COOK* and CHARLES E. TWINE, JUN.

(*Chemistry and Life Sciences Laboratory, Research Triangle Institute, Research Triangle Park, North Carolina* 27709)

THE estrogenic activity of isoflav-3-enes has been recorded,[2] but limited by their relative inaccessibility. The 2- and 4-monoalkyl and 2,2,4-trialkyl derivatives are readily obtained,[2-4] but the most active compounds—the 2,4-dialkylisoflav-3-enes, some of which are about as potent as estradiol and diethylstilbestrol—have only been obtained by Grignard reaction with 2-alkylisoflavanones,[2b,c,3a] prepared in turn from 2-alkylisoflavones by a capricious, low-yield hydrogenation[2] or a more reproducible, but lengthy borohydride reduction to isoflavan-4-ols, followed by re-oxidation.[3]

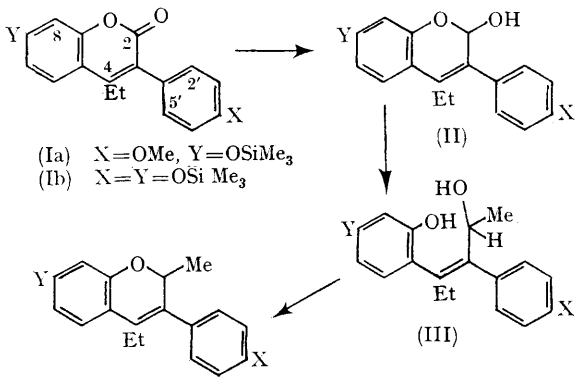
Pursuing the concept that the 4-alkyl-3-arylcoumarins (I) should be useful precursors for isoflav-3-enes,[4a] we have developed a simple, rapid synthesis which converts (I) into 2,4-dialkylisoflav-3-enes (IV) without isolation of any intermediates. The scheme involves reduction of the coumarin (I) with di-isobutylaluminium hydride to intermediate (II) (or a tautomeric form) which without isolation is treated with a Grignard reagent. Acid-catalyzed ring closure of the resulting (III) yields the isoflavene (IV).

4-Ethyl-3-(*p*-methoxyphenyl)-7-trimethylsilyloxycoumarin (72 mmoles) (Ia, prepared from 21·36 g. of the corresponding hydroxycoumarin†) in *ca.* 300 ml. of dry tetrahydrofuran was treated under nitrogen at −60 to −65° with 144 mmoles of di-isobutylaluminium hydride (20% solution in benzene).‡ Excess hydride was destroyed by addition of 72 mmoles of 2-propanol, and the intermediate [presumed to be an aluminium complex of (II)] was treated with excess methyl Grignard reagent. The solution was allowed to warm to room temperature, treated with 1N-HCl (with cooling) and extracted with ether. The ether solution of (III) was stirred for 16 hr. with conc.

† Obtained by reaction of the hydroxycoumarin with hexamethyldisilazane in pyridine (ref. 4a) and used without purification.

‡ Incomplete reaction is obtained with only one molar equivalent of hydride.

HCl. The organic layer was washed with water, sodium hydrogen carbonate solution, and sodium chloride solution, dried, and evaporated. Acetylation of the residue (acetic anhydride–pyridine) and



(Ia) X=OMe, Y=OSiMe$_3$
(Ib) X=Y=OSi Me$_3$

(IVa) X=OMe, Y=OAc
(IVb) X=Y=OAc

crystallization from 95% ethanol yielded 7-acetoxy-4-ethyl-4′-methoxy-2-methylisoflav-3-ene (IVa), m.p. 139—142°, identified by comparison with an authentic sample.[3a] The overall yield from the coumarin (Ia) was 10·5 g. (42%). By a similar process, coumarin (Ib) gave diacetoxyisoflav-3-ene (IVb), m.p. 162—165° (lit.,[2c] 168–169°) in 50% yield. Gas chromatography indicated 95% purity.

Di-isobutylaluminium hydride has been used to reduce lactones to ω-hydroxyaldehydes,[5] but we are not aware of any case in which the resulting mixture has been submitted to a Grignard reaction. Our results indicate that the presence of the aluminium reagents does not interfere with the latter reaction.

We thank Dr. Monroe E. Wall, Director of this laboratory, for his encouragement and support of this work.

(*Received, May 6th*, 1968; *Com.* 558.)

[1] (a) Previous part in this series on "Flavonoids", C. E. Cook and M. E. Wall, *J. Org. Chem.*, in the press. (b) Part of this work was carried out under a contract with the Endocrine Evaluation Branch, General Laboratories and Clinics, National Cancer Institute, National Institutes of Health.

[2] (a) R. B. Bradbury and D. E. White, *J. Chem. Soc.*, **1953**, 871; (b) W. Lawson, *J. Chem. Soc.*, 1954, **4448**; (c) R. A. Micheli, A. N. Booth, A. L. Livingston, and E. M. Bickoff, *J. Medicin. Chem.*, 1962, **5**, 321.

[3] (a) K. H. Dudley, R. C. Corley, H. W. Miller, and Monroe E. Wall, *J. Org. Chem.*, 1967, **32**, 2313; (b) C. A. Amindhan, W. B. Whalley, and M. M. E. Badran, *J. Chem. Soc.*, 1966, 629.

[4] (a) C. E. Cook, Robert C. Corley, and Monroe E. Wall, *J. Org. Chem.*, 1965, **30**, 4114; (b) K. H. Dudley, H. W. Miller, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, 1967, **32**, 2317.

[5] J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, 1963, **46**, 2799.