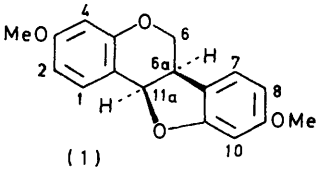
Reactions of 6a,11a-Dihydro-6*H*-benzofuro[3,2-*c*]benzopyran

By **Peter J. M. Gunning, Philip J. Kavanagh, Mary J. Meegan,** and **Dervilla M. X. Donnelly,*** Department of Chemistry, University College, Belfield, Dublin 4, Ireland

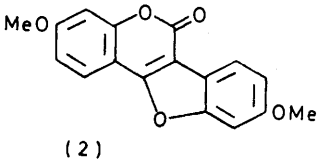
Lead(IV) acetate was found to be a suitable dehydrogenating agent for the preparation of 6*H*-benzofuro[3,2-*c*]-benzopyran from its 6a,11a-dihydro-derivative. The product was also synthesised independently. A scheme for the chemical interconversion of the 6*H*-benzofuro[3,2-*c*]benzopyrans and the related isoflavonoids is suggested.

PREVIOUS workers reported [1,2] that catalytic dehydrogenation of 6a,11a-dihydro-6*H*-benzofuro[3,2-*c*]benzopyran(pterocarpan) gave 6*H*-benzofuro[3,2-*c*]benzopyran or 3-phenylcoumarin, depending on the experimental conditions, and that no reaction occurred when either manganese dioxide or tetrachloro-*o*-benzoquinone was employed. We now report our investigation of the products of reactions of 6a,11a-dihydro-6*H*-benzofuro-[3,2-*c*]benzopyran with 2,3,5,6-tetrachloro-*p*-benzoquinone and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), in dry benzene, *N*-bromosuccinimide (NBS) in carbon tetrachloride, lead(IV) acetate, and *N*-lithioethylenediamine.

2,3,5,6-Tetrachloro-*p*-benzoquinone was ineffective. When 1 equiv. of DDQ was used with 6a,11a-dihydro-3,9-dimethoxy-6*H*-benzofuro[3,2-*c*]benzopyran (1), partial conversion into 3,9-dimethoxy-6*H*-benzofuro[3,2-*c*]benzopyran-6-one (2) occurred. When, however, 3 equiv. of the reagent were employed, a quantitative yield of the coumestone (2) resulted. The mechanism for this reaction is probably similar to that proposed for aldehyde formation from an arylpropene.[3,4]



(1)



(2)

Brink and his associates [5] used DDQ to cyclise (+)-homoedudiol to neorautenol and to dehydrogenate 2′,3′-dihydroneoduleen to neoduleen. The low yields obtained in these reactions may be due to competing oxidations to give the corresponding coumestones.

N-Bromosuccinimide did not react with compound (1) at the benzylic positions, but brought about aromatic bromination to give the 8-bromo-derivative. The n.m.r. spectrum of the product showed signals for the four protons on the heterocycles and a singlet for H-7. Oxidation afforded the corresponding coumestone.

Lead tetra-acetate and compound (1) gave the 6a,11a-dehydrogenation product in yields (30%) adequate for phytochemical studies, but inadequate for extensive biological studies. An alternative route to the pterocarpan ring structure was investigated. By a combination of known reactions,[2,6] 6a,11a-dihydro-8,9-dimethoxy-6*H*-benzofuro[3,2-*c*]benzopyran was oxidised to the corresponding coumestone and reductive fission of the pyran ring with subsequent cyclisation in diethylene glycol afforded 8,9-dimethoxy-6*H*-benzofuro[3,2-*c*]-benzopyran. The previously reported synthesis involves hydrogenolysis of the furan ring.[1,7]

N-Lithioethylenediamine, a reagent known to isomerise olefins and dehydrogenate aromatic systems,[8] abstracts the 6a-proton from the pterocarpan(1). The carbanion then undergoes fission of the pyran ring with subsequent proton shift in the oxyanion to afford 6-methoxy-2-(*p*-methoxyphenyl)-3-methylbenzofuran. Potassamide gives a similar result.[9]

It was realised that a high yield chemical interconversion procedure for members of the 6*H*-benzofuro-[3,2-*c*]benzopyran class would be useful, to facilitate the preparation of standards for use in phytochemical

[1] S. H. Harper, A. D. Kemp, W. G. E. Underwood, and R. V. M. Campbell, *J. Chem. Soc.* (*C*), **1969**, 1109.
[2] W. J. Bowyer, J. N. Chatterjea, S. P. Dhoubhadel, B. O. Handford, and W. B. Whalley, *J. Chem. Soc.*, **1964**, 4212.
[3] F. E. Lutz and E. F. Kiefer, *Tetrahedron Letters*, 1970, 4851.
[4] J. M. Singh and A. B. Turner, *J.C.S. Perkin I*, 1972, 2294.
[5] A. J. Brink, G. J. H. Rall, and J. P. Engelbrecht, *Phytochemistry*, 1974, 1581.
[6] H. Wanzlick, R. Gritzky, and H. Heidepriem, *Chem. Ber.*, 1963, **96**, 305.
[7] L. Farkas, M. Nogradi, S. Antus, and A. Gottsegan, *Tetrahedron*, 1969, **25**, 1013.
[8] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 567.
[9] C. W. L. Bevan, A. J. Birch, B. Moore, and S. K. Mukerjee, *J. Chem. Soc.*, 1964, 5791.

studies and to achieve partial synthesis of those members of a series more likely to be biologically active from readily available members. A scheme emphasising the central role of 6a,11a-dihydro-6*H*-benzofuro[3,2-*c*]-benzopyran is presented, and includes the reactions described in this paper and the results of a study [10] on the use of DDQ with 7-methoxyisoflavan and 2′-hydroxy-4′,7-dimethoxyisoflavan. Direct oxidation of the isoflavan with DDQ is useful for the conversion of 3-arylcoumarin *via* the isoflavan to the isomeric isoflavone. 2′-Hydroxy-4′,7-dimethoxyisoflavan with DDQ in dry benzene gives a pterocarpan–coumestone mixture.

Subsequent to the completion of these studies a communication [11] on the oxidative conversion of 2′,7-dihydroxyisoflavan appeared in which it is suggested that a quinone methide is an intermediate in pterocarpan formation.

Our attempts to introduce directly a hydroxy-group at position 6a in a 6*H*-benzofuro[3,2-*c*]benzopyran have been unsuccessful to date. The reaction of *m*-chloroperbenzoic acid with the 8,9-dimethoxyderivative gives only the degradation product, 4,5-dimethoxy-*o*-benzoquinone.

In the present work autoxidation of isoflavanones resulted in insertion of a hydroxy-group at the benzylic position. The product has been included in the Scheme though as yet this structural type has not been found in nature.

The recently published [12] new synthesis of pterocarpan offers a route to the compounds shown in the Scheme.

EXPERIMENTAL

M.p.s were measured with a Kofler hot-stage apparatus. N.m.r. spectra (60 MHz) were measured for solutions in $CDCl_3$ (Me_4Si as internal reference). Merck Kieselgel $HF_{254+366}$ was used for t.l.c.

Reaction with 2,3,5,6-*Tetrachloro*-p-*benzoquinone*.—A solution of the pterocarpan (1) (50 mg) in benzene (5 ml) was treated with the quinone (50 mg) in an atmosphere of nitrogen at 78 °C for 10 h. The product mixture contained the starting material (45 mg) and the coumestone (2) (5 mg). The reaction was repeated with xylene as solvent and a similar result obtained.

Reactions with DDQ.—(i) The pterocarpan (1) (208 mg) was dissolved in dry benzene and treated with a solution of DDQ (500 mg) in benzene. The mixture was stirred at room temperature for 12 h and the reduced reagent was filtered off. The combined filtrate and washings were evaporated and the residue (2) crystallised from acetone as plates (160 mg), m.p. 201° (lit.,[2] 201°). The quinol was identified as its diacetate (320 mg), m.p. 187° (lit.,[25] 184°).

(ii) 2′-Hydroxy-4′,7-dimethoxyisoflavan (57 mg) was dissolved in dry benzene (2.5 ml) and treated with a solution of DDQ (45 mg) in benzene. The mixture was stirred at room temperature for 12 h. The filtrate was evaporated and the residue chromatographed (eluant chloroform). The minor band afforded 6a,11a-dihydro-3,9-dimethoxy-6*H*-benzofuro[3,2-*c*]benzopyran, and the major one the coumestone (2).[2]

(iii) The residue (40 mg) from the reaction of 7-methoxyisoflavan and DDQ was subjected to preparative t.l.c. (eluant chloroform). The minor band (10 mg) gave 7-methoxyisoflavan and the major band 7-methoxyisoflavanone (25 mg), as needles (from ethanol), m.p. 91—93° (lit.,[25] 94°).

Reaction with N-*Bromosuccinimide*.—(−)-6a,11a-Dihydro-3,9-dimethoxy-6*H*-benzofuro[3,2-*c*]benzopyran (200 mg) dissolved in dry carbon tetrachloride (10 ml) was treated with a solution of NBS (125 mg) and benzoyl peroxide (1 mg) in carbon tetrachloride. The mixture was warmed (50 °C) for 10 min and kept at room temperature for 24 h. The filtrate, on evaporation, gave the *8-bromo-derivative* (150 mg), which crystallised from chloroform–ethanol as needles, m.p. 166° (Found: C, 56.0; H, 4.3; Br, 2.4. $C_{17}H_{15}BrO_4$ requires C, 56.2; H, 4.2; Br, 22.0%), τ 2.5 (d, *J* 8.5 Hz, 1-H), 2.54 (s, 7-H), 3.2—3.55 (m, 2-, 4-, and 10-H), 4.4 (m, 11a-H), 5.7 (m, 6*eq*-H), 6.13 and 6.17 (s, 2 × OMe), and 6.4 (m, 6a-H and 6*ax*-H).

Oxidation of the 8-bromo-derivative (50 mg) with DDQ (100 mg) in dry benzene afforded *8-bromo-3,9-dimethoxy-6H-benzofuro*[3,2-c]*benzopyran-6-one* which crystallised from chloroform–light petroleum; m.p. 248° (Found: C, 54.7; H, 2.9; Br, 21.3. $C_{17}H_{11}BrO_5$ requires C, 54.4; H, 2.9; Br, 21.3%), $\nu_{max.}$ ($CHCl_3$) 1 730 cm^{-1}.

Reaction with Lead(IV) *Acetate*.—The pterocarpan (1) (150 mg) was dissolved in dry benzene (15 ml) and lead(IV) acetate (230 mg), which had been quickly washed with light petroleum, was added. The mixture was refluxed for 4 h and filtered. The filtrate was evaporated and the residue subjected to p.l.c. [alumina; diethyl ether–light petroleum (b.p. 40—60 °C)]. Benzene eluted 3,9-dimethoxy-6*H*-benzofuro[3,2-*c*]benzopyran (30 mg), m.p. 107° (from ethanol) (lit.,[2] 110°); τ 2.53 (d, *J* 9 Hz, 1-H), 2.66 (d, *J* 9 Hz, 7-H), 2.77—2.97 (m, 8- and 10-H), 3.32—3.47 (m, 2- and 4-H), 4.39 (s, 6-H), and 6.11 and 6.17 (s, 2 × OMe), $\lambda_{max.}$ (MeOH) 230 (log ε 4.30), 242(4.26), 334(4.54), and 351 nm (4.47). Chloroform eluted the pterocarpan (1) (25 mg) and the coumestone (2) (40 mg).

Reaction with N-*Lithioethylenediamine*.—Freshly cut lithium (1 g) was added over 30 min to dry distilled ethylenediamine (45 ml) in an atmosphere of nitrogen at 90 °C. Stirring was maintained for 1 h. A sample (10 ml) of the reagent was heated to 90 °C and the pterocarpan (1) (500 mg) was added. Heating was continued for 1 h. The flask was cooled to 0 °C and water (25 ml) cautiously added. A benzene extract of this mixture was dried and evaporated. Chromatography (p.l.c.; eluant benzene) afforded 2-(2-hydroxy-4-methoxyphenyl)-6-methoxy-3-methylbenzofuran (200 mg), m.p. 97° (from chloroform–light petroleum) (lit.,[9] 111°), τ 2.42—2.7 (m, 4- and 6′-H), 3.02 (q, *J* 9 and 2 Hz, 5-H), 2.92 (d, *J* 2 Hz, 7-H), 3.33 (q, *J* 9 and 2 Hz 5′-H), 3.30 (d, *J* 2 Hz, 3′-H), 6.13 and 6.15 (2 × OMe), and 7.67 (s, 3-CH_3). The *monoacetate* crystallised from ethanol; m.p. 98° (Found: C, 70.3; H, 5.6. Calc. for $C_{17}H_{18}O_5$: C, 69.9; H, 5.6%), τ 7.8 (s, OAc).

Synthesis of 8,9-*Dimethoxy*-6H-*benzofuro*[3,2-c]*benzopyran*.—4-Hydroxycoumarin (24 g), pyrocatechol (11 g), and anhydrous sodium acetate (60 g) were dissolved in 1 : 1 acetone–

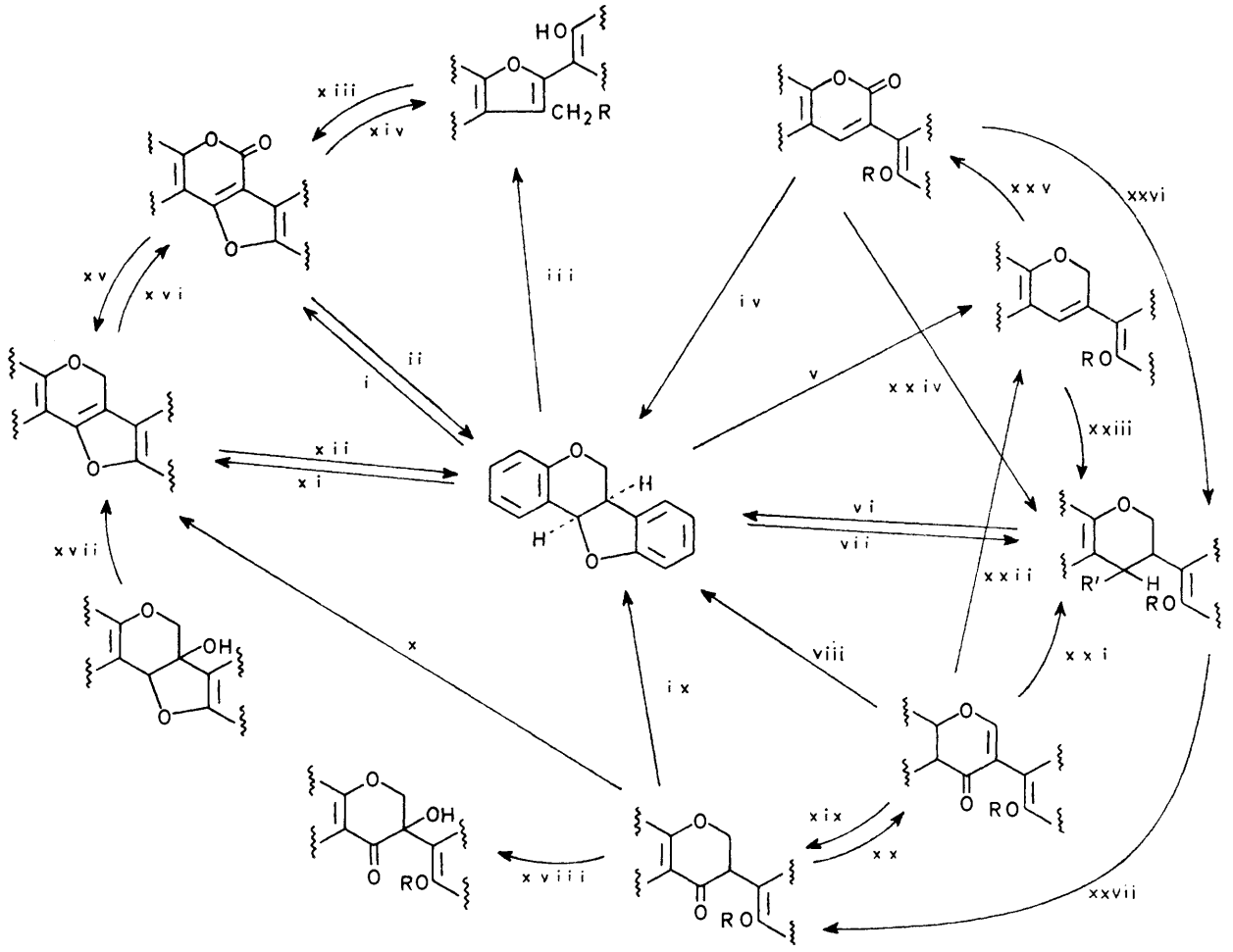
[10] (*a*) D. M. X. Donnelly, P. J. Kavanagh, and P. J. M. Gunning, 'Proceedings of the Fourth Hungarian Bioflavonoid Symposium,' Keszthely, September 1973; (*b*) W. P. Cullen, D. M. X. Donnelly, A. Keenan, and P. J. Keenan, *J.C.S. Perkin I*, 1975, 1671.

[11] M. Cornia and L. Merlini, *J.C.S. Chem. Comm.*, 1975, 429.

[12] H. Horina and N. Inoue, *J.C.S. Chem. Comm.*, 1976, 500.

water (400 ml). To this solution was added with stirring an aqueous solution (250 ml) of potassium iodate (14 g) and

and methylated (dimethyl sulphate–potassium carbonate–acetone). 8,9-Dimethoxy-6*H*-benzofuro[3,2-*c*]benzopyran-



SCHEME Reagents: i, DDQ–C_6H_6;* ii, Na–EtOH;[13] iii, R = H, *N*-lithioethylenediamine;* KNH_2–liq. NH_3;[9] iv, R = H or Ac, B_2H_6–THF–H_2O_2–NaOH;* v, R = H, H^+–EtOH;[9] vi, R = R′ = H, DDQ–C_6H_6;[11] vii, R = R′ = H, H_2;[14] viii, R = H, $NaBH_4$–EtOH;[15] ix, R = H, DDQ–C_6H_6;* x, R = H or Ac, HCl–EtOH;[1,16] xi, $Pb(OAc)_4$–C_6H_6;* xii, H_2;[17] xiii, R = H, SeO_2–AcOH;* xiv, R = OH, $LiAlH_4$;[2] xv, B_2H_6–THF;[18] xvi, DDQ–C_6H_6,* autoxidation;[18] CrO_3–AcOH[2]; xvii, H^+;[19] xviii, R = Me, O_2–NaOH;[10b] xix, H_2;[14] xx, R = Me; DDQ–C_6H_6;* MnO–HOAc–H_2SO_4;[14] reflux SeO_2;[21] xxi, R′ = H, H_2;[14] xxii; R = Me, KBH_4;[22] xxiii, R′ = H, H_2;[23] xxiv, R = Me, R′ = H, $LiAlH_4$–BF_3; $NaBH_4$–BF_3;[24] B_2H_6–THF;* xxv, R = Me, MnO_2–$CHCl_3$;[23] CrO_3–C_5H_5N;[10a] xxvi, R = Me, R′ = OH, B_2H_6–NaOH–H_2O_2;* xxvii, R = Me, R′ = H, CrO_3–H_2SO_4;* if R = Me, R′ = OH, DDQ–C_6H_6;* MnO_2–HOAc–H_2SO_4;[20] reflux SeO_2

* Present work.

sodium acetate (30 g). The mixture was kept at room temperature for 24 h. The precipitate (30 g) was collected

6-one[7] (15 g) was recrystallised from acetone; m.p. 223°, $\nu_{max.}$ ($CHCl_3$) 1 715 cm^{-1}, $\lambda_{max.}$ (MeOH) 214 (log ε 4.56), 243(4.34), 277(3.95), 306(3.95), and 341 nm (4.43).

This product (2 g) was suspended in ether (200 ml), and

[13] N. R. Krishnaswamy and T. R. Seshadri, 'Chemistry of Natural and Synthetic Colouring Matter,' Academic Press, New York and London, 1962, p. 235.

[14] (*a*) A. McGookin, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1940, 787; (*b*) E. Späth and J. Schläger, *Ber.*, 1940, **733**, 1; (*c*) H. Suginome, *Experientia*, 1962, 162; (*d*) E. L. Anderson and G. F. Marrian, *J. Biol. Chem.*, 1934, **127**, 649.

[15] Z. Rappoport, L. K. Dyall, S. Winstein, and W. G. Young, *Tetrahedron Letters*, 1970, 3485.

[16] (*a*) H. Suginome and T. Iwadere, *Bull. Chem. Soc. Japan*, 1966, **39**, 1535; (*b*) M. Nogradi, S. Antus, A. Gottsegan, and L. Farkas, 'Topics in Flavanoid Chemistry and Biochemistry,' Proceedings of the Fourth Hungarian Bioflavonoid Symposium, Keszthely, 1973.

[17] (*a*) K. Fukui and M. Nakayama, *Tetrahedron Letters*, 1966, 1805; (*b*) N. Adityachaudhury and P. K. Gupta, *Phytochemistry*, 1973, **12**, 425.

[18] D. Ferreira, C. V. de M. Brink, and D. G. Roux, *Phytochemistry*, 1971, **10**, 1141.

[19] D. Perrins and W. Bottomley, *J. Amer. Chem. Soc.*, 1962, **84**, 1919.

[20] A. Robertson and W. B. Whalley, *J. Chem. Soc.*, 1954, 1440.

[21] G. J. H. Rall, J. P. Engelbrecht, and A. J. Brink, *Tetrahedron*, 1970, **26**, 5007.

[22] L. Crombie and D. A. Whiting, *J. Chem. Soc.*, 1963, 1569.

[23] C. A. Anirudhan, W. B. Whalley, and M. N. E. Badran, *J. Chem. Soc.*, 1966, 629.

[24] C. V de M. Brink, W. Nel, G. J. H. Rall, and J. C. Weitz, *J. S. African Chem. Inst.*, 1966, **19**, 24.

[25] K. Wallenfels, G. Bachmann, D. Hofmann, and R. Kern, *Tetrahedron*, 1965, **21**, 2249.

lithium aluminium hydride (0.6 g) in ether was added. The mixture was refluxed for 2 h then treated with ammonium chloride. The residue from evaporation of the ether layer was dissolved in diethylene glycol (20 ml). The solution was refluxed for 20 min, cooled, diluted with water, and extracted with chloroform. The extract, on evaporation, gave 8,9-dimethoxy-6*H*-benzofuro[3,2-*c*]benzopyran (600 mg), which crystallised from ethanol; m.p. 143—145°.

Reduction of 7-Methoxy-3-phenylcoumarin.—(i) The coumarin (1 g) and boron trifluoride–diethyl ether (15 ml) in tetrahydrofuran (50 ml) were added over 1 h to a suspension of sodium borohydride (2 g) in tetrahydrofuran (100 ml). The mixture was stirred for 1 h at 0 °C and refluxed for 2 h. Water was added and the mixture extracted with ether. On evaporation, 7-methoxyisoflavan (350 mg) was obtained, m.p. 100°.

(ii) The coumarin (250 mg) in tetrahydrofuran (30 ml) was treated with diborane solution (1M; 2 ml) at 0—5 °C for 30 min and the mixture was then refluxed for 1.5 h. Sodium hydroxide (3N; 3 ml) and hydrogen peroxide (3 ml) were added. The mixture was diluted, acidified, and extracted with chloroform. The residue (270 mg) from evaporation of the chloroform crystallised from aqueous ethanol as needles of 4-hydroxy-7-methoxyisoflavan (60 mg).[25]

(iii) Diborane gas was passed into a solution of the coumarin (2.2 g) in dry tetrahydrofuran (150 ml) for 2 h. The mixture was kept at room temperature for 12 h, then refluxed for 2 h, and cooled to 25 °C. Chromic acid (3.3 g) in sulphuric acid (96%; 2.5 ml) and water (10 ml) was added and the mixture refluxed for 2 h. The aqueous layer was extracted with ether and the combined ethereal layers were washed and dried. Evaporation gave 7-methoxyisoflavan (215 mg) and 7-methoxyisoflavanone (260 mg).

Reduction of 2',7-Diacetoxy-4'-methoxy-3-phenylcoumarin.—Reduction of the coumarin (1.8 g) as in method (iii) above afforded 6a,11a-dihydro-3-hydroxy-9-methoxy-6*H*-benzofuro[3,2-*c*]benzopyran (420 mg).

Oxidation of a 3-Methyl-2-phenylbenzofuran.—A solution of 2-(2-hydroxy-4-methoxyphenyl)-6-methoxy-3-methylbenzofuran (140 mg) and selenium dioxide (60 mg) in acetic acid was refluxed for 1 h. The mixture was diluted and extracted with ether. The residue from the dried ethereal solution was subjected to preparative t.l.c. (eluant chloroform; double development) to afford the coumestone (2) (25 mg) as needles (from methanol), m.p. 199°.

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