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Synthesis of Some Benzopyran Derivatives Related to the Seed Germination Stimulant of *Orobanche crenata*. I

3,3a,4,9b-Tetrahydro-2*H*-furo[3,2-*c*][1]benzopyrans

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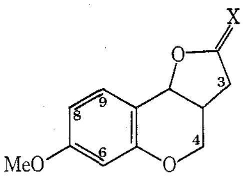
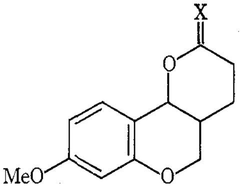
Abstract

The furobenzopyran derivatives (1a) and (1b) have been prepared by a simple route from *m*-methoxyphenol.

In some Mediterranean countries crop yields of broad bean (*Vicia faba* L.) are greatly reduced by parasitism. The germination of seeds of the parasite broomrape (*Orobanche crenata* Forsk.) is triggered by a stimulant exuded from the bean roots. There is evidence, mainly mass spectral, to indicate that the stimulant contains a substituted 3,4-dihydro-2*H*-1-benzopyran (i.e., chroman) moiety (1) or (2).[1]



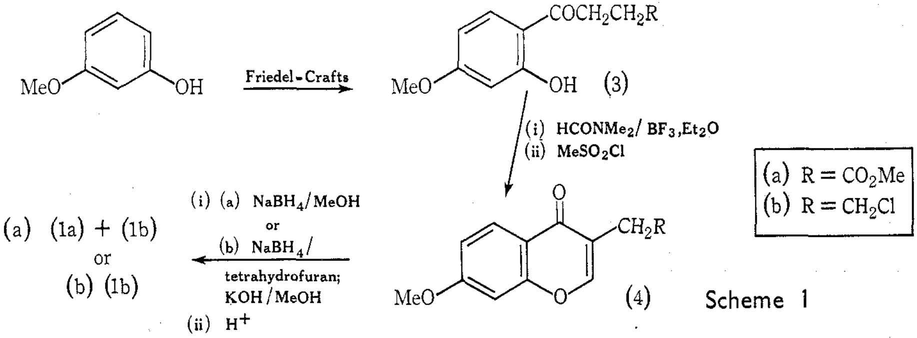
(1)



(2)

(a) $X = O$
(b) $X = H_2$

We have synthesized several compounds of this type to help the structure elucidation work being carried out in Malta. We hope that our work may delineate possible synthetic routes to the active principle itself. We report in this paper a simple synthesis (Scheme 1) of the lactone (1a) and ether (1b). The key reactions, both



Scheme 1

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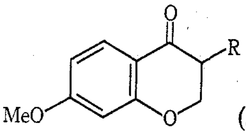
[1] Mallet, A. I., Ph.D. Thesis, University of Malta, 1974.

'one-pot' procedures, are the one-carbon insertion and cyclization (3) → (4),[2] which can be carried out equally well by heating the ketone (3) with dimethylformamide dimethylacetal,[3] and the reduction, followed by cyclization (4) → (1), in which the double bond and the carbonyl group are simultaneously reduced (Scheme 1). In the latter reaction, both the lactone (1a) and the ether (1b) are produced, in combined yield of 89%, from the ester (4a); it is not clear whether reduction of the ester and carbonyl occurs before, or after, formation of the tetrahydrofuran ring.

The coupling constants between the methine protons (H 3a and H 9b) at the pyran–furan ring junction are 5·6 Hz in the lactone (1a) and 5·4 Hz in the ether (1b) which indicates a *cis* configuration in each case. The dihedral angle between these protons in models is about 35° in the *cis* and about 180° in the *trans* configuration.

In preliminary experiments we tried to alkylate 7-methoxy-3,4-dihydro-2*H*-1-benzopyran-4-one (7-methoxychroman-4-one) (5; R = H)[4] using a variety of bases (K, NaH, NaOBu^t, Et$_3$N etc.) and two-carbon alkylating agents (oxiran, 1,2-dibromoethane, ethyl bromoacetate) but in no case was the desired product isolated. We also prepared the 3-formyl derivative (5; R = CHO) in the hope that this might be more amenable to alkylation at C 3 but again without success.



(5)

Experimental

Analyses are by the Australian Microanalytical Service. Melting points are uncorrected. P.m.r. data are of solutions in deuterochloroform and were obtained on a Varian T-60 or, in the case of compounds (1a,b), on a Jeol PFT-100 instrument. Mass spectra were run on a Jeol D-100 instrument.

Methyl 4-(2′-Hydroxy-4′-methoxyphenyl)-4-oxobutanoate (3a)

This was prepared by a modification, by using more aluminium chloride, of Dalal and Nargund's procedure.[5] *m*-Methoxyphenol (23·6 g, 0·19 mol), nitrobenzene (270 ml) and succinic anhydride (19·2 g, 0·19 mol) were mixed under dry nitrogen in a stirred flask and warmed to 33°. Aluminium chloride (55 g) was added in portions during 10 min. The temperature of the mixture was slowly increased to 49° during 2 h and maintained there for a further 1¼ h. The mixture was then cooled in ice and hydrochloric acid (2 M; 400 ml) was added. The nitrobenzene layer was separated and extracted with saturated NaHCO$_3$ solution (3 × 150 ml). Acidification of the extract afforded 4-(2′-hydroxy-4′-methoxyphenyl)-4-oxobutanoic acid (13·4 g, 32%), m.p. 148° (lit.[5] 156°), after recrystallization from aqueous acetone.

Esterification of this acid with methanol/BF$_3$ produced the methyl ester (3a), m.p. 85·5–86° (lit.[4] 85°).

4-Chloro-1-(2′-hydroxy-4′-methoxyphenyl)butan-1-one (3b)

Boron trifluoride etherate (40%; 5 ml) was added to *m*-methoxyphenol (1·5 g) and 4-chlorobutanoic acid (1·5 g) and the mixture heated on a water bath at 90° for 45 min. The mixture was poured into water (50 ml) and extracted with chloroform (3 × 50 ml). The chloroform extracts were dried, evaporated, and eluted through a silica gel column (3 cm diam., 150 g gel) with chloroform, yielding the product (3b) as colourless *needles* (1·2 g, 37%), m.p. 37–39°, after recrystallization from hexane (Found: C, 58·1; H, 5·8; Cl, 15·9. $C_{11}H_{13}ClO_3$ requires C, 57·8; H, 5·7; Cl, 15·5%). ν_{max} 3430 (OH), 1628 cm^{-1} (C=O). λ_{max} (EtOH) 315 nm (ε 7930), 274 (17400), 228 (11500). *m/e* 230

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[2] Bass, R. J., *J. Chem. Soc., Chem. Commun.*, 1976, 78.

[3] Föhlisch, B., *Chem. Ber.*, 1971, **104**, 348.

[4] Graffe, B., Sacquet, M. C., and Maitte, P., *J. Heterocycl. Chem.*, 1975, **12**, 247.

[5] Dalal, G. A., and Nargund, K. S., *J. Indian Chem. Soc.*, 1937, **14**, 406; cf. Chakravarti, D., and Roy, N. K., *J. Indian Chem. Soc.*, 1964, **42**, 607.

(5·5%), 228 (16, M^+), 193 (2), 179 (15), 166 (15), 152 (13), 151 (100). δ 2·19 (quintet, 2H, J 6·6 Hz, CCH_2CCl), 3·08 (t, 2H, J 6·4 Hz, $CH_2C{=}O$), 3·60 (t, 2H, J 6·4 Hz, CH_2Cl), 3·90 (s, 3H, CH_3O), 6·39 (d, 1H, $J_{3',5'}$ 2·4 Hz, H3′), 6·42 (dd, 1H, $J_{5',6'}$ 9·4 Hz, H5′), 7·33 (d, 1H, H6′), 12·77 (s, 1H, OH).

*Methyl (7-Methoxy-4-oxo-4*H*-1-benzopyran-3-yl)acetate (4a)*

The ester (3a) (3·2 g) in dimethylformamide (17 ml) was treated cautiously with boron trifluoride etherate (40%; 10 ml); the mixture was heated at 100° for 18 h, treated with methanesulphonyl chloride[2] (4·6 g) and heated for a further 4 h. The reaction mixture was poured into ice-water (500 ml) and the product extracted with ether. Evaporation of the ether, and recrystallization of the residue from methanol afforded the ester (4a) (1·87 g, 56%), m.p. 128·5–129·5° (lit.[6] 129–130°).

*3-(2′-Chloroethyl)-7-methoxy-4*H*-1-benzopyran-4-one (4b)*

The phenol (3b) (1·1 g) in dimethylformamide (5 ml) was treated cautiously with boron trifluoride etherate (2 ml). A solution of methanesulphonyl chloride (1 ml) in dimethylformamide (2 ml) was then added and the mixture heated on a steam bath for 2 h. The reaction mixture was poured into ice-water and the precipitate collected. This was recrystallized from aqueous ethanol to give the *product* (4b) (0·55 g, 48%), pale yellow needles, m.p. 93·5–95° (Found: C, 60·5; H, 4·7; O, 20·7. $C_{12}H_{11}ClO_3$ requires C, 60·4; H, 4·6; O, 20·1%). ν_{max} 1637 cm^{-1} (C=O). λ_{max} (EtOH) 303 nm (ε 9620), 295 (9900), 247 (16600), 240 (16900). *m/e* 240 (9%), 238 (26, M^+), 204 (17), 203 (100), 189 (8), 176 (9), 151 (5). δ 2·88 (t, 2H, J 7·2 Hz, CH_2Cl), 3·80 (quintet, 2H, J 7·2 Hz, CH_2), 3·90 (s, 3H, CH_3O), 6·92 (d, 1H, $J_{8,6}$ 2·2 Hz, H8), 7·01 (dd, 1H, $J_{6,5}$ 8·4 Hz, H6), 7·77 (s, 1H, O–CH=C), 8·07 (d, 1H, H5).

*3,3a,4,9b-Tetrahydro-2*H*-furo[3,2-*c*][1]benzopyran-2-one (1a) and 3,3a,4,9b-Tetrahydro-2*H*-furo[3,2-*c*][1]benzopyran (1b)*

The ester (4a) (0·48 g) and sodium borohydride (0·5 g) were mixed, cooled in ice, and methanol (5 ml) was added cautiously. The mixture was then heated under reflux for 18 h; the initially colourless solution rapidly became yellow. The mixture was cooled, acidified with dilute hydrochloric acid and extracted with chloroform. The extract was washed, dried and evaporated, and the residual oil chromatographed on 2-mm silica gel preparative t.l.c. plates with hexane/acetone (1 : 1) as eluent. Under these conditions the R_F values of (1a) and (1b) are about 0·33 and 0·46 respectively, and both compounds could be readily extracted from the appropriate band of the plates.

The *lactone* (1a) formed colourless crystals (38%), m.p. 88–88·5°, after recrystallization from chloroform–hexane (Found: C, 65·1; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·4; H, 5·5%). ν_{max} 3012, 2978, 2966, 2940, 2919, 2841, 1784 and 1763 (C=O), 1619, 1591, 1584, 1507, 1474, 1441, 1397, 1267, 1206, 1162, 1039, 1032, 955, 950, 909, 887, 846, 814, 691 cm^{-1}. λ_{max} (EtOH) 284 nm (ε 2610), 278 (2640), 228 (6710), 214 (6780). *m/e* 220 (100%), 176 (49), 175 (83), 162 (11), 161 (80), 151 (15). δ 2·33–2·87 (m, 2H, $CH_2C{=}O$), 2·97 (m, 1H, $CHCC{=}O$), 3·68–4·27 (m, 2H, CH_2OAr), 3·78 (s, 3H, CH_3O), 5·43 (d, 1H, J 5·6 Hz, CHAr), 6·42 (d, 1H, $J_{6,8}$ 2·8 Hz, H6), 6·59 (dd, 1H, $J_{8,9}$ 8·5 Hz, H8), 7·29 (d, 1H, H9).

The cyclic *ether* (1b) was obtained (51%) after microdistillation (100°/0·1 mm) as a pale yellow oil (Found: C, 69·5; H, 6·8. $C_{12}H_{14}O_3$ requires C, 69·8; H, 6·8%). ν_{max} 3007, 2969, 2943, 2876, 2843, 1620, 1584, 1503, 1464, 1386, 1269, 1200, 1161, 1069, 894, 833, 799 cm^{-1}. λ_{max} (EtOH) 284 nm (ε 2620), 278 (2520), 226 (6770), 214 (6630). *m/e* 206 (100%), 205 (68), 176 (34), 175 (78), 162 (15), 161 (73), 151 (35). δ 1·39–2·74 (m, 3H, $CHCH_2CO$), 3·37–4·19 (m, 4H, CH_2O), 3·78 (s, 3H, CH_3O), 4·57 (d, 1H, J 5·4 Hz, CHAr), 6·44 (1H, $J_{6,8}$ 2·8 Hz, H6), 6·57 (dd, 1H, $J_{8,9}$ 7·4 Hz, H8), 7·31 (d, 1H, H9). This ether (1b) could also be obtained from the chloro compound (4b) by a two-step procedure: reduction by sodium borohydride in tetrahydrofuran followed by cyclization with 5% methanolic potassium hydroxide.

*3-Formyl-7-methoxy-3,4-dihydro-2*H*-1-benzopyran-4-one (5; $R = CHO$)*

7-Methoxy-3,4-dihydro-2*H*-1-benzopyran-4-one[4] (6·02 g) dissolved in dry benzene (60 ml) was added slowly to a stirred and ice-cooled mixture of sodium methoxide (5·9 g), ethyl formate (14·3 ml)

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[6] Chatterjea, J. N., Shaw, S. C., and Singh, J. N., *J. Indian Chem. Soc.*, 1974, **51**, 281.

and benzene (40 ml). Stirring was continued for 3 h, then the mixture was acidified with sulphuric acid (2 M; 75 ml) and the benzene layer exhaustively extracted with sodium carbonate solution (0·5 M; 10 × 30 ml). The basic extracts were quickly acidified and the precipitated *product* (5; R = CHO) was washed with water, dried, and recrystallized from ether yielding crystals (5·22 g, 75%), m.p. 100–101° (Found: C, 63·8; H, 4·8. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). This compound decomposes slowly both in the solid state and in solution; the main product appears to be 7-methoxy-3-(7′-methoxy-4′-oxo-3′,4′-dihydro-2′*H*-1-benzopyran-3′-ylmethyl)-4*H*-1-benzopyran-4-one, m.p. 174° (lit.[7] 175°).

Acknowledgments

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[7] Kasturi, T. R., Damodaran, K. M., Subrahmanyam, G., Brown, P., and Pettit, G. R., *Chem. Commun.*, 1968, 794.