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THE SYNTHESIS OF ZINNIOL

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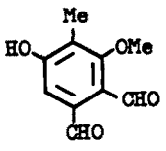
Abstract—Zinniol **10**, 3 - methoxy - 4 -methyl - 5(3 - methyl - 2 - butenyloxy) - 1,2 - benzenedimethanol, a metabolite isolated from the pathogenic fungus *Alternaria zinniae*, has been synthesised.

The pathogenic fungus *Alternaria zinniae* Pape is widely distributed in Canada and the Eastern United States[1] causing leaf and stem blight on zinniae, sunflower and marigold.[2] The tips and margins of infected plants may become chlorotic and then necrotic. Zinnia plants may wilt even though lesions do not ring the stem.

An investigation[3] of filtrates from stationary liquid cultures of *Alternaria zinniae* resulted in the isolation of a major metabolite, $C_{15}H_{22}O_4$, which was named zinniol. On the basis of derivatisation, chemical degradation and spectroscopic evidence the novel pentasubstituted benzene structure **10** was proposed[4] for zinniol which is closely related to quadrilineation (**1**),[5] a metabolite isolated from *Aspergillus quadrilineatus*. We decided to synthesise zinniol for biological evaluation and as a confirmation of structure.



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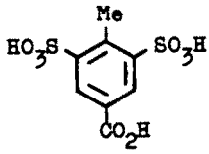

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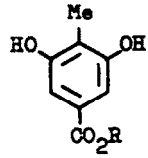
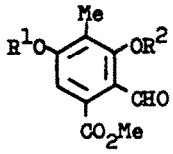
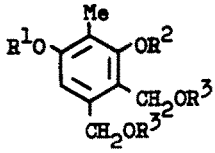


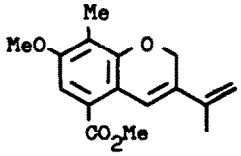
3: R = H
4: R = Me



5: $R^1 = R^2 = H$
6: $R^1 = CH_2CH{:}C(Me)_2$, $R^2 = H$
7: $R^1 = CH_2CH{:}C(Me)_2$, $R^2 = Me$
8: $R^1 = Me$, $R^2 = H$
9: $R^1 = Me$, $R^2 = CH_2CH{:}C(Me)_2$



10: $R^1 = CH_2CH{:}C(Me)_2$, $R^2 = Me$, $R^3 = H$
11: $R^1 = CH_2CH{:}C(Me)_2$, $R^2 = Me$, $R^3 = Ac$
12: $R^1 = Me$, $R^2 = CH_2CH{:}C(Me)_2$, $R^3 = H$
13: $R^1 = Me$, $R^2 = CH_2CH{:}C(Me)_2$, $R^3 = Ac$



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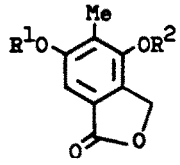
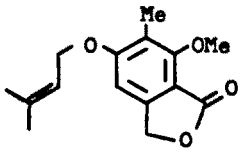


15: $R^1 = Me$, $R^2 = H$
16: $R^1 = Me$, $R^2 = CH_2CH{:}C(Me)_2$
17: $R^1 = CH_2CH{:}C(Me)_2$, $R^2 = H$
18: $R^1 = CH_2CH{:}C(Me)_2$, $R^2 = Me$



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Our synthetic plan was to use a symmetrical starting material such as 3,5 - dihydroxy - 4 - methylbenzoic acid (3), obtainable from *p*-toluic acid by the classical disulphonation and alkali fusion procedure. This particular route to the acid 3 had been explored by Charlesworth and Robinson,[6] who initially isolated *m*-hydroxybenzoic acid which they attributed to monosulphonation, oxidation of the Me group and decarboxylation. However, they improved a procedure described[7] by Asahino and Asano to afford the acid 3 in 42% yield. In our hands the Charlesworth and Robinson procedure had two disadvantages. Firstly, the evaporation of extremely large volumes of aqueous solution required to isolate the dipotassium salt of the disulphonic acid 2, and secondly, *m*-hydroxybenzoic acid was always a major contaminant.

We have developed an improved procedure which resolves both problems. Our modification involves isolation of the disulphonic acid 2 as a crystalline material, which is used directly in the alkali fusion reaction. This method affords exclusively 3,5 - dihydroxy - 4 - methylbenzoic acid 3 consistently in 40% yield from *p*-toluic acid.

Treatment of the acid 3 with MeOH-conc H_2SO_4 gave an almost quantitative yield of the corresponding methyl ester 4, which was formylated using a modified Gattermann reaction as described[8] by Birkinshaw and Bracken to yield the salicylaldehyde 5. Selective alkylation of the non-H bonded phenolic group in the salicylaldehyde 5 with one equivalent of 3 - methyl - 2 - butenyl bromide and potassium carbonate in boiling acetone gave the ether 6. Further alkylation of 6 with excess methyl iodide and potassium carbonate in boiling acetone gave the 3-methoxy compound 7. Reduction of 7 with LAH gave the desired product 3 - methoxy - 4 - methyl - 5 - (3 - methyl - 2 - butenyloxy) - 1,2 - benzenedimethanol 10, zinniol.

Alternatively, the salicylaldehyde 6 was reduced with sodium borohydride to afford after hydrolysis the phthalide 17. Methylation of the phenolic group gave the phthalide 18, which was reduced smoothly with LAH to zinniol.

Natural zinniol was isolated[3] as a viscous oil. Similarly, our synthetic material was initially an oil, but on standing for several weeks it crystallised and was then readily recrystallised from cyclohexane. Our synthetic zinniol had identical physical properties (NMR, IR, microanalysis) to those reported[4] for the natural material. Furthermore, synthetic zinniol diacetate (11) had the same physical properties (NMR, IR, UV, and microanalysis) as those described[4] by Starratt for natural zinniol diacetate.

Although chromic acid oxidation[4] of zinniol (10) to a mixture of the phthalides, (18) and (19), established the substitution pattern we decided to synthesise the isomer 12 as additional confirmation of structure. The salicylaldehyde 5 was selectively mono-methylated with one equivalent of methyl tosylate and potassium carbonate in refluxing acetone to give the methyl ether 8, which was then treated with 3 - methyl - 2 - butenyl bromide and potassium carbonate as described previously. A short reaction time (4 hr) in refluxing acetone gave a mixture of starting material 8 and the desired product 9, separated by careful chromatography. An increased reaction time (30 hr) resulted in the formation of a new product the benzopyran 14. The same benzopyran 14 was also formed when dimethylformamide was used as solvent.

In order to avoid this unexpected difficulty and occasional lack of reproducibility the salicylaldehyde 8 was reduced with sodium borohydride and after hydrolysis the phthalide 15 was formed. The phthalide 15 was smoothly alkylated with 3 - methyl - 2 - butenyl bromide and potassium carbonate in boiling acetone to give the alkylated phthalide 16 in good yield. Reduction of the phthalide 16 with LAH gave the desired diol 12, an isomer of zinniol. This diol 12 was isolated as a crystalline solid and was markedly less soluble than zinniol. Similarly, the diol 12 formed a diacetate 13. As expected both the diol 12 and the corresponding diacetate 13 had significantly different physical properties[4] (m.p., NMR, IR) from zinniol (10) and its diacetate 11. Thus the structure proposed by Starratt for zinniol has been confirmed.

EXPERIMENTAL

Column chromatography was carried out on silica gel [Kieselgel 60 (Merck)]. Merck Kieselgel 60 F_{254} (0.25 mm) plates were used for TLC.

M.p's were determined with a Büchi Tottoli apparatus. NMR spectra were determined on a Varian T 60 (internal standard tetramethylsilane). The IR spectra (obtained for Nujol mulls) and mass spectra (determined with an A.E.I. MS902 instrument) were consistent with the structures assigned.

Solvents (B.D.H.) were used as supplied. Light petroleum had b.p. 40–60°.

3,5 - Dihydroxy - 4 - methylbenzoic acid (3)

p-Toluic acid (56 g, 412 mmol) was added in one portion to fuming H_2SO_4 (SO_3 content 50%; 200 ml) and heated at 170° for 8 hr. The mixture was allowed to cool overnight, then poured onto crushed ice (350 g) with stirring. The resulting hot soln was filtered and cooled to give the crystalline 2 which was collected and dried on a porous plate to give a crude moist product (187 g).

The above disulphonic acid (187 g) was added cautiously in portions (5 g) to a stirred melt (140°) of KOH (750 g), NaOH (250 g) and water (80 ml). When addition of the disulphonic acid was complete (½ hr approx) the melt was heated to 250° with continuous stirring and maintained at that temp for 1½ hr. The temp was then raised to 265° for ¾ hr. The melt was allowed to cool to 200° and then poured onto crushed ice (500 g). The resulting soln was carefully acidified with conc HCl (1.7 l). The pale green soln was extracted with ether (3 × 500 ml). The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated to dryness to give the crude acid (27.3 g; 40%), m.p. 246–248°, sufficiently pure for the next stage. However, recrystallisation from water did give a pure sample of 3, m.p. 267° (lit.,[6] 260°) (Found: C, 57.3; H, 5.0. Calc. for $C_9H_8O_4$: C, 57.2; H, 4.8%); NMR δ (DMSO-d_6) 1.95 (3H, s, $ArCH_3$), 6.91 (2H, s, ArH), 9.34 (2H, s, OH), 12.34 (1H, bs, CO_2H).

Methyl 3,5 - dihydroxy - 4 - methylbenzoate (4)

A soln of 3 (6.4 g, 38 mmol) in dry MeOH (100 ml) was treated with conc H_2SO_4 (1.5 ml) and boiled under reflux for 18 hr. The mixture was then evaporated to dryness. The residue was dissolved in ether (100 ml), washed with sat $NaHCO_3$aq (25 ml), water (25 ml), dried over $NaSO_4$ and evaporated to dryness to afford the crude Me ester (6.2 g, 89%) sufficiently pure for the next stage. Recrystallisation from ether/benzene gave a pure sample of 4 m.p. 188–189° (Found: C, 59.1; H, 5.4. $C_9H_{10}O_4$ requires: C, 59.3; H, 5.5%); NMR δ (DMSO-d_6) 2.02 (3H, s, $ArCH_3$), 3.75 (3H, s, CO_2CH_3), 6.87 (2H, s, ArH), 9.45 (2H, s, OH).

Methyl 2 - formyl - 3,5 - dihydroxy - 4 - methylbenzoate (5)

A suspension of zinc cyanide (3.4 g, 29 mmol) and $AlCl_3$ (8.0 g, 60 mmol) in dry ether (90 ml) was stirred and cooled in ice while a soln of 4 (4.4 g, 24 mmol) in dry ether (30 ml) was added in one portion. The mixture was stirred and maintained at 0° while a stream of dry HCl was passed in over a period of 6 hr. The pale brown ppt was filtered off and washed with dry ether (10 ml).

This was immediately dissolved in water (30 ml) and heated at 70° for 1 hr. The product was filtered off, washed with a little water (5 ml) and dried (2.7 g, 53%). Crystallisation from EtOAc gave **5** (2.1 g, 41%) m.p. 168° (Found: C, 57.1; H, 4.7. $C_{10}H_{10}O_5$ requires: C, 57.1; H, 4.8%); NMR δ (DMSO-d_6) 2.03 (3H, s, $ArCH_3$), 3.95 (3H, s, CO_2CH_3), 6.96 (1H, s, ArH), 10.23 (1H, s, CHO), 10.99 (1H, s, OH), 12.68 (1H, s, OH).

Methyl 2 - *formyl* - 3 - *hydroxy* - 4 - *methyl* - 5 - (3 - *methyl* - 2 - *butenyloxy*)*benzoate* (**6**)

A mixture of **5** (4.6 g, 21 mmol), 3 - methyl - 2 - butenyl bromide[9] (3.4 g, 23 mmol) and K_2CO_3 (3.0 g, 22 mmol) in dry acetone (100 ml) was stirred and boiled under reflux for 1½ hr. The mixture was filtered, the residue washed with dry acetone (20 ml) and the filtrate evaporated to give a brown oil. This crude product was dissolved in benzene (10 ml) and percolated through a column of silica gel (50 g) collecting approximately 500 ml of eluent. Evaporation of the solvent afforded a pale yellow crystalline product (4.6 g, 95%). Recrystallisation from light petroleum gave pure **6** (3.9 g, 81%) m.p. 53° (Found: C, 64.6; H, 6.4. $C_{15}H_{18}O_5$ requires: C, 64.7; H, 6.4%); NMR δ ($CDCl_3$) 1.76 (6H, s, $C(CH_3)_2$), 2.11 (3H, s, $ArCH_3$) 3.92 (3H, s, CO_2CH_3), 4.64 (2H, d, J 7 Hz, OCH_2CH), 5.50 (1H, t, J 7 Hz, CH_2CH=C), 7.00 (1H, s, ArH), 10.51 (1H, s, CHO), 12.74 (1H, s, OH).

Methyl 2 - *formyl* - 3 - *methoxy* - 4 - *methyl* - 5 - (3 - *methyl* - 2 - *butenyloxy*)*benzoate* (**7**)

A mixture of **6** (2.3 g, 8.3 mmol), MeI (5.0 g, 35 mmol) and K_2CO_3 (1.7 g, 12 mmol) in dry acetone (50 ml) was stirred and boiled under reflux for 18 hr. It was then filtered and the filtrate evaporated to give a yellow oil, which was percolated through a short column of silica gel (10 g) with benzene as eluant (200 ml). Evaporation of the solvent gave a product that crystallised (2.4 g, 99%). Recrystallisation from light petroleum gave pure **7** (1.9 g, 79%) m.p. 83° (Found: C, 65.6; H, 6.9. $C_{16}H_{20}O_5$ requires: C, 65.7; H, 6.9%): NMR δ ($CDCl_3$) 1.83 (3H, s, CCH_3), 1.81 (3H, s, CCH_3), 2.19 (3H, s, $ArCH_3$), 3.86 ($3H_3$, s, OCH), 3.91 (3H, s, CO_2CH_3), 4.64 (2H, d, J 7 Hz, OCH_2CH), 5.48 (1H, t, J 7 Hz, CH_2CH=C), 6.88 (1H, s, ArH), 10.36 (1H, s, CHO).

4 - *Hydroxy* - 5 - *methyl* - 6 - (3 - *methyl* - 2 - *butenyloxy*)*phthalide* **17**

A soln of **6** (2.2 g, 7.9 mmol) in MeOH (30 ml) was treated with $NaBH_4$ (0.3 g, 7.9 mmol) and stirred at 25° for ½ hr. A soln of 2N-NaOH (15 ml) was then added and the mixture heated at 60° for ½ hr. The MeOH was evaporated and the cooled soln acidified with 2N-HCl. The product was extracted into ether, dried over Na_2SO_4 and evaporated to give an oil that crystallised (1.8 g, 92%). Recrystallisation from isopropanol gave pure **17** (1.3 g, 66%) m.p. 176° (Found: C, 67.9; H, 6.6. $C_{14}H_{16}O_4$ requires: C, 67.7; H, 6.5%); NMR δ (DMSO-d_6) 1.77 (6H, s, $C(CH_3)_2$), 2.15 (3H, s, $ArCH_3$), 4.71 (1H, d, J 7 Hz, OCH_2CH), 5.27 (2H, s, $ArCH_2O$), 5.51 (1H, t, J 7 Hz, CH_2CH=C), 6.92 (1H, s, ArH), 9.74 (1H, bs, OH).

4 - *Methoxy* - 5 - *methyl* - 6 - (3 - *methyl* - 2 - *butenyloxy*)*phthalide* **18**

(a) A soln of **7** (3.1 g, 10.6 mmol) was reduced with $NaBH_4$ (0.3 g, 7.9 mmol) in MeOH (30 ml) as described above, and after crystallisation from light petroleum gave **18** (2.2 g, 79%) m.p. 84° (lit.,[4] 84–85°) (Found: C, 68.8; H, 7.2. Calc. for $C_{15}H_{18}O_4$: C, 68.7; H, 6.9%); NMR δ ($CDCl_3$) 1.78 (6H, bs, $C(CH_3)_2$), 2.21 (3H, s, $ArCH_3$), 3.90 (3H, s, OCH_3), 4.58 (2H, d, J 7 Hz, OCH_2CH), 5.38 (2H, s, $ArCH_2O$). 5.51 (1H, t, J 7 Hz, CH_2CH=C), 7.09 (1H, s, ArH).

(b) A mixture of **17** (1.3 g, 5.2 mmol), methyl tosylate (1.0 g, 5.2 mmol) and K_2CO_3 (0.7 g, 5.2 mmol) in acetone (25 ml) was stirred and boiled under reflux for 18 hr. It was then filtered and the filtrate evaporated to give a white crystalline mass. Recrystallisation from light petroleum gave the product (1.0 g, 73%) m.p. 84° identical with that prepared by method (a).

3 - *Methoxy* - 4 - *methyl* - 5 - (3 - *methyl* - 2 - *butenyloxy*) - 1,2 - *benzenedimethanol*; *Zinniol* **10**

(a) A suspension of LAH (0.6 g, 15 mmol) in dry ether (30 ml) was stirred while a soln of **7** (1.5 g, 5.0 mmol) in dry ether (15 ml) was added dropwise. The mixture was boiled under reflux for 2 hr. The excess reagent was decomposed by successive additions of EtOAc (5 ml) and water (50 ml). The organic layer was separated, washed with water, dried and evaporated to afford an oil (1.3 g, 98%). The product was distilled to afford pure 3 - methoxy - 4 - methyl - 5 - (3 - methyl - 2 - butenyloxy) - 1,2 - benzenedimethanol (1.1 g, 83%) b.p. 200/0.5 mm Hg (Found: C, 67.65; H, 8.4. Calc. for $C_{15}H_{22}O_4$: C, 67.6; H, 8.3%). On standing the zinniol **10** crystallised and was then recrystallised from cyclohexane to give needles m.p. 73° (Found: C, 67.7; H, 8.45. Calc. for $C_{15}H_{22}O_4$: C, 67.6; H, 8.3%); NMR δ ($CDCl_3$) 1.76 (3H, s, CCH_3), 1.81 (3H, s, CCH_3), 2.16 (3H, s, $ArCH_3$), 3.22 (2H, bs, OH, OH), 3.77 (3H, s, OCH_3), 4.55 (2H, d, J 7 Hz, OCH_2CH), 4.69 (2H, s, CH_2OH), 4.76 (2H, s, CH_2OH), 5.52 (1H, t, J 7 Hz, CH_2CH=C), 6.79 (1H, s, ArH).

(b) A soln of **18** (1.3 g, 5.0 mmol) in dry ether (15 ml) was reduced with LAH as described above to give zinniol (1.2 g, 91%) as an oil, which crystallised from cyclohexane to give a product (1.0 g, 77%) identical with that prepared by method (a) above.

3 - *Methoxy* - 4 - *methyl* - 5 - (3 - *methyl* - 2 - *butenyloxy*) - 1,2 - *benzenedimethanol diacetate*; *Zinniol diacetate* **11**

A soln of **10** (0.36 g, 1.2 mmol) in dry pyridine (1 ml) was treated with Ac_2O (1 ml) and stirred at 25° for 2 hr. The mixture was quenched with water (10 ml), the crude product collected by filtration and dried *in vacuo* over P_2O_5. Recrystallisation from light petroleum gave pure **11** (0.23 g, 50%) m.p. 62–63° (lit.,[4] 65–66°); NMR δ ($CDCl_3$) 1.77 (6H, bs, $C(CH_3)_2$), 2.05 (3H, s, $OCOCH_3$), 2.06 (3H, s, $OCOCH_3$), 2.16 (3H, s, $ArCH_3$), 3.74 (3H, s, OCH_3), 4.55 (2H, d, J 7 Hz, OCH_2CH), 5.16 (2H, s, CH_2OAc), 5.22 (2H, s, CH_2OAc), 5.50 (1H, bt, J 7 Hz, CH_2CH=C), 6.72 (1H, s, ArH).

Methyl 2 - *formyl* - 3 - *hydroxy* - 5 - *methoxy* - 4 - *methylbenzoate* **8**

A mixture of **5** (1.25 g, 6.0 mmol), methyl tosylate (1.15 g, 6.2 mmol) and K_2CO_3 (0.85 g, 6.2 mmol) in dry acetone (30 ml) was stirred and boiled under reflux for 5 hr. The mixture was filtered and the filtrate evaporated to give an oil (1.6 g). The crude product was dissolved in benzene (5 ml) and percolated through a short column of silica gel (12 g) eluting with benzene. Evaporation of the appropriate fractions gave a pale yellow solid (1.15 g, 86%) which crystallised. Recrystallisation from n-hexane gave pure **8** (1.0 g, 75%) m.p. 84° (Found: C, 58.7; H, 5.3. $C_{11}H_{12}O_5$ requires; C, 58.9; H, 5.4%): NMR δ ($CDCl_3$) 2.12 (3H, s, $ArCH_3$), 3.96 (3H, s, CO_2CH_3), 7.03 (1H, s, ArH), 10.50 (1H, s, CHO), 12.69 (1H, s, OH).

Methyl 2 - *formyl* - 5 - *methoxy* - 4 - *methyl* - 3 - (3 - *methyl* - 2 - *butenyloxy*)*benzoate* **9**

A mixture of **8** (0.35 g, 1.6 mmol), 3 - methyl - 2 - butenylbromide (0.3 g, 2.0 mmol) and K_2CO_3 (0.3 g, 2.2 mmol) in dry acetone (20 ml) was stirred and boiled under reflux for 4 hr. It was then filtered and the filtrate evaporated to give a yellow oil that contained **8** and **9**. Careful chromatography over silica gel (30 g) separated the two components as crystalline solids. Recrystallisation of the product from light petroleum gave **9** (0.13 g, 28%) m.p. 52° (Found: C, 65.7; H, 6.9. $C_{16}H_{20}O_5$ requires: C, 65.7; H, 6.9%); NMR δ ($CDCl_3$) 1.63 (3H, s, CCH_3), 1.80 (3H, s, CCH_3), 2.20 (3H, s, $ArCH_3$), 3.96 (6H, s, OCH_3 and CO_2CH_3), 4.45 (2H, d, J 7 Hz, OCH_2CH), 5.57 (1H, t, J 7 Hz, CH_2CH=C), 6.88 (1H, s, ArH) 10.27 (1H, s, CHO).

Methyl 3 - (1 - *methylvinyl*) - 7 - *methoxy* - 8 - *methyl* - 2*H* - *benzopyran* - 5 - *carboxylate* **14**

(a) A mixture of **8** (0.26 g, 1.2 mmol), 3 - methyl - 2 - butenyl bromide (0.23 g, 1.2 mmol) and K_2CO_3 (0.23 g, 1.7 mmol) in acetone (15 ml) was boiled under reflux for 30 hr. It was then filtered and the filtrate evaporated to give a yellow oil (0.31 g, 92%). This product was chromatographed over silica gel (10 g) to give as the first component eluted **14** (0.09 g, 29%). Crystallisation from n-hexane gave a pure sample m.p. 88° (Found: C, 6.97; H, 6.4. $C_{16}H_{18}O_4$ requires: C, 70.1; H, 6.6%); NMR δ ($CHCl_3$) 2.06 (3H, s, CCH_3), 2.11 (3H, s, $ArCH_3$), 3.84 (3H, s, OCH_3), 3.91 (3H, s,

CO_2CH_3), 4.92 (3H, s, OCH_2 and C=CH), 5.06 (1H, bs, C=CH), 7.06 (1H, s, ArH), 7.46 (1H, bs, ArCH=C).

(b) A mixture of **8** (1.0 g, 4.5 mmol), 3 - methyl - 2 - butenyl bromide (0.95 g, 6.4 mmol) and K_2CO_3 (0.85 g, 6.2 mmol) in dry DMF (10 ml) was stirred and heated at 100° for 2 hr. The dark brown soln was poured in water (50 ml) and extracted with benzene (3 × 20 ml). The combined extracts were washed with water (2 × 50 ml), dried over Na_2SO_4 and evaporated to afford a brown oil (1.4 g). Chromatography over silica gel (30 g) gave a pure sample of **14**, identical in all respects with that prepared by method (a) above.

4 - Hydroxy - 6 - methoxy - 5 - methylphthalide **15**

A soln of **8** (1.1 g, 5.0 mmol) in MeOH (15 ml) was treated with $NaBH_4$ (0.15 g, 4.0 mmol) and stirred at 25° for ½ hr. A soln of 2N-NaOH (8 ml) was added and the mixture heated at 60° for 15 min. The MeOH was evaporated *in vacuo* and the resulting soln cooled then acidified with 2N-HCl. The ppt was collected and dried over P_2O_5 at 75° *in vacuo* to give needles (0.9 g, 95%). Recrystallisation from MeOH gave **15** (0.82 g, 86%) m.p. 234° (Found: C, 61.7; H, 5.2. $C_{10}H_{10}O_4$ requires; C, 61.85; H, 5.2%); NMR δ (DMSO-d_6) 2.07 (3H, s, $ArCH_3$), 3.83 (3H, s, OCH_3) 5.17 (2H, s, OCH_2Ar), 6.83 (1H, s, ArH), 9.68 (1H, bs, OH).

6 - Methoxy - 5 - methyl - 4 - (3 - methyl - 2 - butenyloxy) - phthalide **16**

A mixture of **15** (0.5 g, 2.6 mmol), 3 - methyl - 2 - butenyl bromide (0.4 g, 2.7 mmol) and K_2CO_3 (0.4 g, 2.9 mmol) in dry acetone (100 ml) was stirred and boiled under reflux for 15 hr. The mixture was then filtered and the filtrate evaporated to afford a pale brown oil (0.63 g, 93%). This product was percolated through a short column of silica gel (10 g) eluting with benzene. Evaporation of the eluent and crystallisation from n-hexane gave **16** (0.55 g, 82%) m.p. 86° (Found: C, 68.6; H, 7.0. $C_{15}H_{18}O_4$ requires; C, 68.7; H, 6.9%); NMR δ ($CDCl_3$) 1.68 (3h, s, CCH_3), 1.80 (3H, s, CCH_3), 2.22 (3H, s, $ArCH_3$), 3.88 (3H, s, OCH_3), 4.48 (2H, d, J 7 Hz, OCH_2CH), 5.30 (2H, s, OCH_2Ar), 5.47 (1H, t, J 7 Hz, CH_2CH=C), 7.07 (1H, s, ArH).

5 - Methoxy - 4 - methyl - 3 - (3 - methyl - 2 - butenyloxy) - 1,2 - benzenedimethanol **12**

A suspension of LAH (0.4 g, 10 mmol) in dry ether (20 ml) was stirred while a soln of **16** (1.5 g, 5.7 mmol) in dry ether (25 ml) was added dropwise. The mixture was refluxed for 1½ hr. The excess reagent was decomposed with EtOAc (5 ml) followed by water (40 ml). The organic layer was separated, washed with water, dried over Na_2SO_4 and evaporated to afford a crystalline solid (1.4 g, 92%). Recrystallisation from diethyl ether gave pure **12** (1.3 g, 86%) m.p. 95° (Found: C, 67.7; H, 8.4. $C_{15}H_{22}O_4$ requires; C, 67.6; H, 8.3%); NMR δ ($CDCl_3$) 1.68 (3H, s, CCH_3). 1.78 (3H, s, CCH_3), 2.16 (3H, s, $ArCH_3$), 3.39 (2H, bs, OH, OH), 3.82 (3H, s, OCH_3), 4.33 (2H, d, J 7 Hz, OCH_2CH), 4.64 (2H, s, CH_2OH), 4.74 (2H, s, CH_2OH), 5.59 (1H, t, J 7 Hz, CH_2CH=C), 6.66 (1H, s, ArH).

5 - Methoxy - 4 - methyl - 3 - (3 - methyl - 2 - butenyloxy) - 1,2 - benzenedimethanol diacetate **13**

A soln of **12** (0.2 g, 7.9 mmol) in dry pyridine (1 ml) was treated with Ac_2O (1 ml) and stirred at 25° for 3 hr. The mixture was then quenched with water (20 ml), the crude product collected, washed with water and dried over P_2O_5. Crystallisation from light petroleum gave pure **13** (0.14 g, 51%) m.p. 73° (Found: C, 65.2; H, 7.4. $C_{19}H_{26}O_6$ requires; C, 65.1; H, 7.5%); NMR δ ($CDCl_3$) 1.69 (3H, s, CCH_3), 1.79 (3H, s, CCH_3), 2.04 (3H, s, $OCOCH_3$), 2.08 (3H, s, $OCOCH_3$), 2.17 (3H, s, $ArCH_3$), 3.82 (3H, s, OCH_3), 4.30 (2H, d, J 7 Hz, OCH_2CH), 5.14 (2H, s, CH_2O), 5.21 (2H, s, CH_2O), 5.53 (1H, t, J 7 Hz, CH_2CH=C), 6.68 (1H, s, ArH).

REFERENCES

[1]A. W. Dimock and J. H. Osborn, *Phytopathology* **33**, 372 (1943).
[2]W. C. McDonald and J. W. Martens, *Ibid.* **53**, 93 (1963).
[3]G. A. White and A. N. Starratt, *Can. J. Botany* **45**, 2087 (1967).
[4]A. N. Starratt, *Can. J. Chem.* **46**, 767 (1968).
[5]J. H. Birkinshaw, P. Chaplen and R. Lahazoliver, *Biochem.* **67**, 155 (1952).
[6]E. H. Charlesworth and R. Robinson, *J. Chem. Soc.* 1531 (1934).
[7]Y. Asahina and J. Asano, *Ber. Dtsch. Chem. Ges.* **66**, 687 (1933).
[8]J. H. Birkinshaw and A. Bracken, *J. Chem. Soc.* 368 (1942).
[9]H. L. Simon, Ad. Kaufmann and H. Schinz, *Helv. Chim. Acta* **29**, 1133 (1946).