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THE REGIO- AND STEREOCHEMISTRY OF THE ALKOXIDE-INDUCED RING-OPENING OF METHOXYMETHYLIDENE-SUBSTITUTED HOMOPHTHALIC ANHYDRIDE

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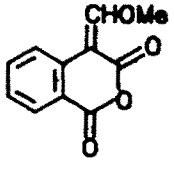
Abstract.- Ring-opening of methoxymethylidene-substituted homophthalic anhydride (1) by methoxide occurs by two modes. Attack at the 1-position ("benzoate" carbonyl) leads to a stable acid-ester. A combination of unambiguous syntheses and ^{1}H- and ^{13}C-n.m.r. spectroscopy has been used to show that this material has the "benzoate ester, acrylic acid" structure (5). This corrects the structure assignment given earlier for this material, which incorrectly concluded "benzoic acid, acrylate ester", (2). Compound (2), resulting from attack at the "acrylate" carbonyl, is a co-product of (5), but is unstable. It recyclises in an alternative fashion to give (dihydro)isocoumarin-type products (15) and (16).

The alpha-substituted beta-alkoxyacrylate substructure, $R'OCH{=}C(R)CO_2R''$, is found in a variety of natural products, including indole alkaloids of several families, the oudemansin[1] and strobilurin[1b,2] fungal metabolites, and a secologanin derivative related to the secoiridoid, xylomollin.[3] Synthetically, it has been used as an acyclic precursor to various heterocycles.[4] Our own interest in this substructure derives from the recent discovery that it confers fungicidal activity on some molecules.[5] A report[6] on the methoxide-induced ring-opening of the homophthalic anhydride derivative (1) to give a methoxyacrylate derivative, assigned structure (2), was therefore of particular relevance to us. However, our subsequent attempts to modify the putative (2) led us to doubt its structural assignment, which was in any case based solely on reasoning by analogy.[6] Furthermore, on the basis of the known instability of the related molecule (3) with respect to ring closure to (4),[7] it seemed unlikely that structure (2) would withstand the highly basic conditions of its preparation.

We therefore set out to determine unambiguously the nature of the alkoxide-induced ring-opened products of (1). The results of these studies are the subject of this paper. By means of a combination of unambiguous syntheses and n.m.r. spectroscopy, we conclude that the acid-ester originally assigned structure (2) is in fact its regioisomer (5), with (E)-stereochemistry. However, the structures of co-products of (5) imply strongly that (2) is indeed also formed, but that it is unstable with respect to ring closure, as expected.



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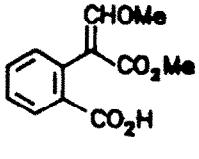

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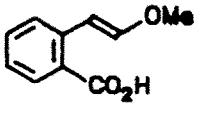

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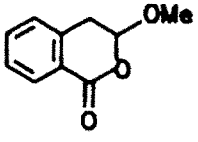

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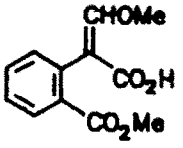
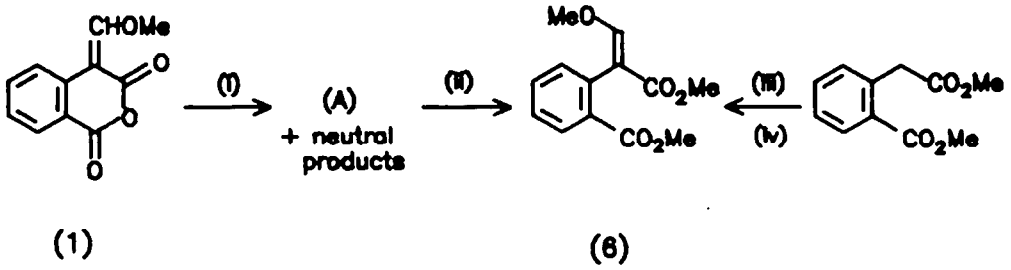


(5)

RESULTS AND DISCUSSION

The Acrylate Ester-Acid from (1).- Repetition of the published procedure led to isolation of a carboxylic acid with the same properties as those reported[6] for structure (2) (Scheme 1). We shall refer to this compound as (A).

Methylation of (A) led to the diester (6) in quantitative yield. The same material was prepared from dimethyl homophthalate via a Claisen condensation with methyl formate followed by O-methylation (Scheme 1), thus defining the skeleton of (A). The (E)-stereochemistry about the double bond follows from that assigned definitively, below, for unsymmetrical diesters.



(1) (6)

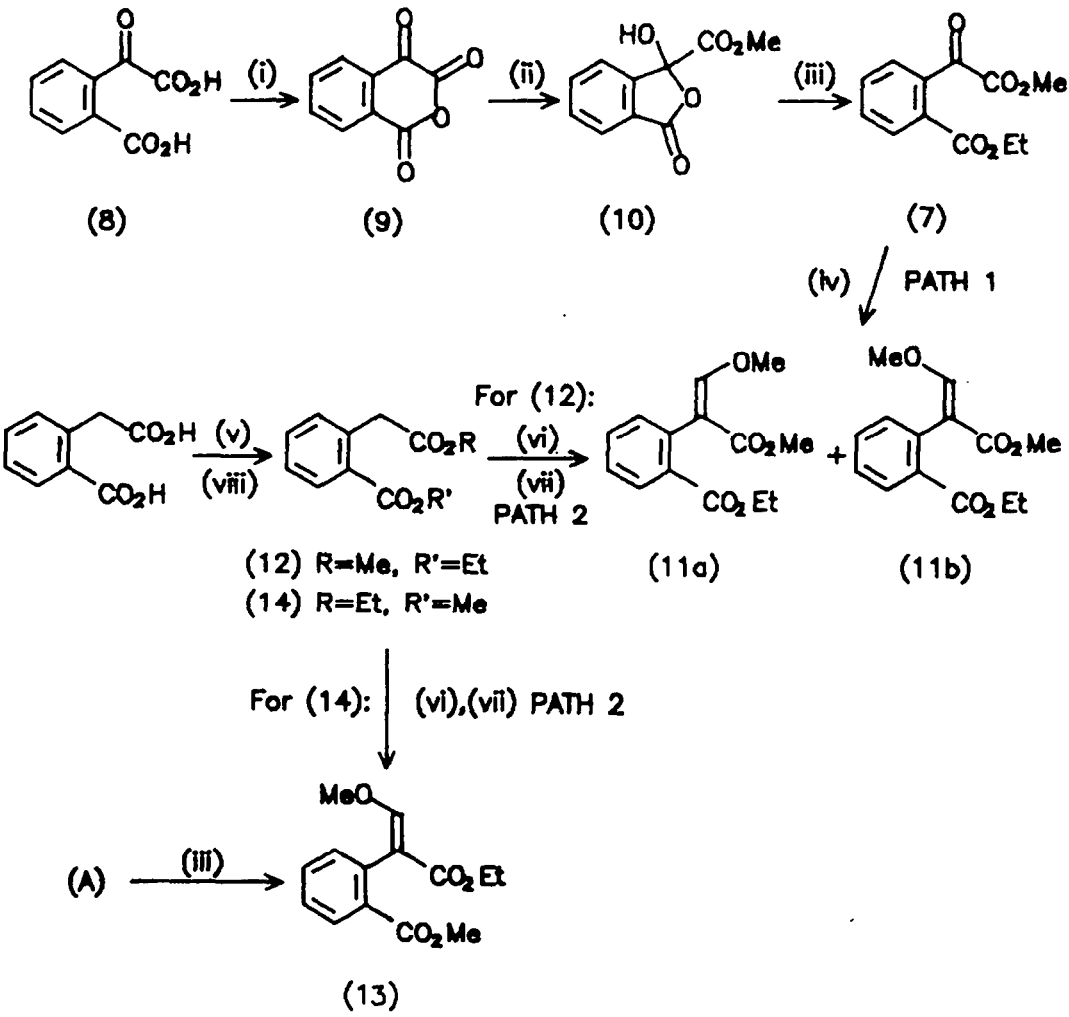
(i) MeO^-, MeOH; (ii) MeI, K_2CO_3, DMF; (iii) NaH, HCO_2Me; (iv) Me_2SO_4, K_2CO_3, DMF.

SCHEME 1

The key observation concerning the structure of (A) came from n.m.r. experiments. The proton-coupled ^{13}C-n.m.r. spectrum of (A) showed that an ester carbonyl resonance at δ 167.24 p.p.m. was coupled to the three protons of a methyl group (J_{CH} ca.4 Hz) and to one other proton (J_{CH} ca.4 Hz). A second carbonyl resonance at δ 172.58 p.p.m., assigned to the carboxylic acid group, was only coupled to a single proton (J_{CH} 3.7 Hz). Low power irradiation of the vinylic proton singlet at δ 7.58 p.p.m. caused collapse of the latter ^{13}C-resonance, but left the former unaffected. Irradiation of aromatic protons did not change the carboxylic acid carbonyl, but caused some peak shape alteration of the ester carbonyl. These results alone are highly indicative that (A) has structure (5), and not (2).

The alternative interpretation is hardly tenable. This would entail the vinylic proton coupling through five bonds to the carboxylic acid carbonyl in (2), but not via three bonds to the ester in (2). Furthermore, an aromatic proton would be coupling via four bonds to the ester carbonyl, but there would be no 3- or more-bond coupling to the carboxylic acid carbonyl. We believe this combination of events to be unlikely. However, we sought conclusive evidence for (5) by means of unambiguous syntheses.

Stereoisomers of the mixed ethyl methyl diesters corresponding to (6) were prepared by two routes (Scheme 2). In the first, the glyoxylate diester (7) was obtained from phthalonic acid (8) via its anhydride (9) by standard reactions. Specifically, it is reported that methanolysis of (9) results in esterification at the glyoxylate carbonyl.[8] This is confirmed by the presence of just two carbonyl-carbon resonances and an acetal-type carbon resonance in the ^{13}C-n.m.r. spectrum, as well as a distinct O-H stretch in the infrared spectrum, indicating that the derived monoester intermediate exists in the phthalide form (10). Ethylation of (10) gives the ring-opened diester (7), which now shows three carbonyl resonances in its ^{13}C-n.m.r. spectrum, and a characteristic infrared spectrum. The methoxymethylidene Wittig reagent gave a 6:1 mixture of two isomers (11a) and (11b) in 84% yield (Path 1, Scheme 2).



(i) Ac_2O; (ii) MeOH; (iii) EtI, K_2CO_3, DMF; (iv) Ph_3PCH_2OMe, t-BuOK; (v) ROH, H^+; (vi) Me_3SiOTf, Et_3N; (vii) $(MeO)_3CH$, $TiCl_4$; (viii) R'I, K_2CO_3, DMF.

SCHEME 2

Isomer (11b) was more efficiently prepared by the second route shown in Scheme 2, starting with diester (12) formed from homophthalic acid, first by esterification with acidic methanol, then alkylation with ethyl iodide. Classical degradation studies had established that monoesterification of homophthalic acid results in the arylacetic acid being esterified first, in preference to the benzoic acid group.[9] The positions of attachment of the two different alkyl groups are thus well defined.[10] The methoxymethylidene group was then introduced by a modification[11] of the Mukaiyama route[12] based on mixed ketene acetals[13] (Path 2, Scheme 2). Under our conditions, in the presence of excess $TiCl_4$, the dimethoxyacetal intermediate eliminated methanol spontaneously to give the beta-methoxyacrylate ester.

The geometries of the isomers of (11) were defined unambiguously by means of several n.m.r. experiments. (a) Irradiation of the vinylic proton of the isomer (11a) resulted in a nuclear Overhauser enhancement for the adjacent aromatic proton. No such nOe was found for isomer (11b). (b) The proton-coupled ^{13}C-n.m.r. spectrum of (11a) showed a coupling of 10.2 Hz between the vinylic proton and the acrylate carbonyl carbon. The corresponding coupling for (11b) was only 3.7 Hz. Literature precedent indicates that $^3J_{CH}$ across a double bond is

invariably greater for the trans-relationship between C and H (in this case, the (Z)-isomer) than for the alternative.[14] (c) Finally, the beta-vinylic proton chemical shifts for the two isomers of beta-monosubstituted acrylate esters are characteristic: that for the (E)-isomer is invariably downfield from that for the (Z)-isomer.[15] The shifts observed for (11a) and (11b) were δ 6.42 and 7.46 p.p.m., respectively. All these data are consistent with (11a) being the (Z)-isomer, and (11b) the (E)-isomer.

The two carbonyl resonances in the proton-coupled ^{13}C-n.m.r. spectrum of (1) showed 3-bond H–C couplings of 3.5 and 4.6 Hz. On the basis of the values observed for the two isomers of (11), (1) therefore has (E)-stereochemistry about the double bond.

Acid (A) was ethylated as before, but the methyl ethyl diester (13) obtained was not the same as either of the two isomers of (11). In particular, the two methyl resonances in its ^{1}H-n.m.r. spectrum were almost the same, whereas those for both isomers of (11) are well split (see Experimental). The chemical shift of the vinylic proton (δ 7.50 p.p.m.) indicates (E)-stereochemistry. Since the alternative regiochemistry of ring-opening of (1) was already suspected, it remained to synthesise the corresponding regioisomeric ethyl methyl diester unambiguously. This was readily effected by the chemistry of Scheme 2, Path 2, to give (13), starting from the known[10] alternative ethyl methyl diester of homophthalic acid (14). Compound (13) was identical in all respects to the ethylation product of (A), thus demonstrating conclusively that (A) does not have the structure (2) previously assigned,[6] but rather is the regioisomeric acid (5) of (E)-stereochemistry.

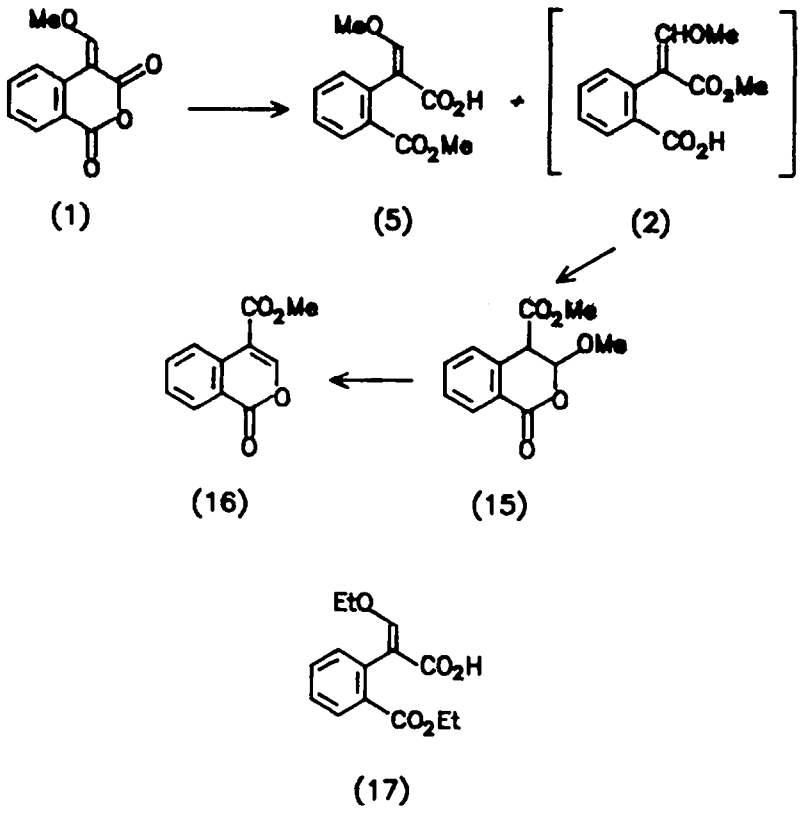
Acrylate Ester-Acid (2).- Since (5) was only ever isolated in about 60% yield, despite disappearance of all starting material (1), we searched for evidence of other products, particularly the acid (2). Three peaks corresponding to non-acidic materials were also observed in the h.p.l.c. trace of the crude reaction mixture. A methanol solution of this mixture readily deposited white crystals of (15a). Flash chromatography of the mother liquors led first to isolation of isocoumarin (16). Its structure assignment follows from its physical properties and comparison with literature data.[6] Later fractions contained a mixture of (15a) and (15b), which could not be separated chromatographically. However, fractional crystallisation of a methanol solution of the mixture (4:1) gave more pure (15a) and eventually led to a fraction enriched in (15b) ((15a)/(15b) = 1:2). However, (15b) could not be obtained pure. The gross constitutions of (15a) and (15b) follow from their spectral and analytical properties: they are isomers of the dihydroisocoumarin (15). In particular, each showed an AB n.m.r. spectral pattern for H-3 and H-4, with the former at a chemical shift typical for an acetal-type proton (δ *ca.* 5.6 p.p.m.). Other spectral data are recorded in the Experimental section. On the basis of proton-coupled ^{13}C-n.m.r. spectra including selective proton-decoupling and heteronuclear 2D-J experiments, we believe the crystalline isomer (15a) has trans-stereochemistry, and the other (15b) is cis. However, a degree of ambiguity remains in these stereochemistry assignments, and so full discussion is postponed until definitive evidence is forthcoming.

A control experiment showed that the dihydroisocoumarins (15) lose methanol to give isocoumarin (16) under the conditions of the initial anhydride ring-opening. The structures of the isomers of (15) lead us to propose that they result from base-induced ring-closure of the elusive acid-ester (2).

The important conclusion to emanate from the isolation of (15) and (16) is that the alternative regioisomer (2) from methoxide-induced ring-opening of (1) is indeed formed, but as expected is unstable under the strongly basic conditions.

The analytical yield of (5) is 62%, (15a) 15.2%, (15b) 3.0%, and (16) 4.4%. We have been unable to account for the remaining 15% of (1), but suspect that highly polar species are formed. The relative propensity for alkoxide attack of (1) at the acrylate carbonyl compared with the benzoate carbonyl is therefore about 3:1.

Competing reversible Michael attack of methoxide at the methoxymethylidene group of (1) cannot be ruled out, since reaction of (1) with ethanolic ethoxide gave (17), where the



(17)

methoxide group already present in (1) is also substituted. Alternatively, methoxide and ethoxide could be exchanging after ring-opening.

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We are grateful for the interest shown in this work and comments by Drs J.M.Clough and C.R.A.Godfrey (ICI Agrochemicals). The latter developed the modification to the Mukaiyama route to beta-methoxyacrylate esters (Scheme 2). K.Beautement prepared (6) by Scheme 1.

EXPERIMENTAL

Starting materials were commercially available, or came from the ICI specimen collection. Solvents were distilled before use and stored over molecular sieves (4A). Organic extracts were dried over magnesium sulphate unless stated otherwise, prior to evaporation under reduced pressure. Flash chromatography was carried out over Merck 60H silica, using a gradient of diethyl ether in hexane, unless otherwise stated. M.p.s were determined in capillaries in a Buchi melting point apparatus, and are uncorrected. Ir spectra were recorded as films or nujol mulls on a Perkin-Elmer 883 Infrared Spectrophotometer. ^{1}H-N.m.r. spectra were recorded at 60MHz on a Perkin-Elmer R24A spectrometer, or at 250MHz on a Bruker WM250 instrument, in deuterochloroform unless otherwise stated, and were referenced to tetramethylsilane. ^{13}C-N.m.r. spectra were recorded on a Bruker WM250 instrument at 62.9MHz. Reported multiplicities in ^{13}C-n.m.r. spectra (s, d, etc.) refer to one-bond couplings only. Electron impact mass spectra were recorded on a AEI MS9 instrument. Chemical ionisation spectra were recorded on a Finnigan MAT 8200. In general, fragmentation patterns were unexceptional and full data are not reported here. Microanalyses were determined in-house. Purity of samples was also checked by t.l.c. on Kodak Chromagram silica sheets, and reversed phase h.p.l.c. on a Hewlett-Packard 1084B Liquid Chromatograph, using a Hichrom ODS Hypersil stationary phase eluted with solutions of acetonitrile in distilled water.

(E)-4-Methoxymethylene-3,4-dihydro-1H-2-benzopyran-1,3-dione (1).- This was prepared by the procedure of Wolfbeis[6] by refluxing together homophthalic acid (22g), acetic anhydride (60g), and trimethyl orthoformate (16g). Recrystallisation from hot chlorobenzene gave the product anhydride (1) (15.65g, 62.8%) as white needles, m.p. 185-186°C (lit.[6] 182°C) (Found: C, 64.4; H, 4.0%; M^+ 204. Calc. for $C_{11}H_8O_4$: C, 64.7; H, 3.9%; M 204); ν_{max} (nujol) 3123w, 1758, 1730, 1707, and 1605 cm^{-1}; δ_H (250MHz, d_6-DMSO, 313K) 4.30 (3H, s, OCH_3); 7.47 (1H, t, ArH), 7.77 (1H, t, ArH), 8.08 (1H, d, ArH), 8.17 (1H, s, =CH), 8.20 (1H, d, ArH) p.p.m. δ_C (d_6-DMSO, 313K) 168.80 (d, =CH), 162.15 (s, $^3J_{CH}$ 3.5 Hz), 161.07 (s, $^3J_{CH}$ 4.6 Hz), 135.28 (d, Ar), 133.50 (s, Ar), 129.75 (d, Ar), 127.23 (d, Ar), 125.48 (d, Ar), 118.95 (s, Ar), 99.81 (s, =COCO), 65.07 (q, OCH_3) p.p.m. The value of the coupling constant to the vinylic proton indicates a cis-relationship between this proton and the carbonyl group (cf. Discussion).).

Reaction between (1) and sodium methoxide in methanol.- This was carried out by the procedure described by Wolfbeis,[6] by treating the homophthalic anhydride derivative (1) (10g) under N_2 with methanolic sodium methoxide. The product (E)-3-methoxy-2-(2'-methoxycarbonylphenyl)-propenoic acid (5) was recrystallised from methanol (6.84g, 59.1%) m.p. 147°C (lit.[6] 149°C) (Found: C, 60.7; H, 5.2%; M^+ 236. Calc. for $C_{12}H_{12}O_5$: C, 61.0; H, 5.1%; M 236. ν_{max} (nujol) 2400-3300b, 1719, 1685, 1655, 1639 cm^{-1}. δ_H (250MHz) 3.85 (6H, s, 2 x OCH_3), 7.2-7.5 (3H, m, ArH), 7.58 (1H, s, =CH), 7.95 (1H, m, ArH), 7.58 (1H, s, =CH), 7.95 (1H, m, ArH), 11.05 (1H, s, exch., CO_2H) p.p.m. δ_C 172.58, 167.24, 159.51, 133.22, 132.08, 131.35, 130.51, 130.12, 127.40, 111.70, 61.73, 51.56 p.p.m.). A parallel reaction was worked up differently. The crude reaction product was dissolved in dichloromethane, extracted with aqueous sodium carbonate and water, and the organic phase dried. The neutral product obtained contained three components (h.p.l.c.). This was taken into warm methanol, and after cooling in a freezer, white crystalline 3-methoxy-4-methoxydihydroisocoumarin (15a) was deposited (0.48g) m.p. 95°C (Found: C, 61.0; H, 4.9%; M^+ 236. $C_{12}H_{12}O_5$ requires: C, 61.0; H, 5.1%; M 236. ν_{max} (nujol) 1730, 1706 cm^{-1}. δ_H (250MHz) 3.55 (3H, s, $CHOCH_3$), 3.72 (3H, s, CO_2CH_3), 4.10 (1H, d, J 2.7 Hz, $CHCO_2Me$), 5.73 (1H, d, J 2.4 Hz, CHOMe), 7.35 (1H, bd, ArH), 7.46 (1H, dt, ArH), 7.61 (1H, dt, ArH), 8.12 (1H, bd, ArH) p.p.m. δ_C 168.72 (s, CO_2Me), 162.63 (s, ArC=O), 134.20 (d, Ar), 133.92 (s, ArCH), 130.03 (d, Ar), 128.86 (d, Ar), 128.73 (d, Ar), 124.46 (s, ArC=O), 102.05 (d, CHOMe), 57.01 (q, $CHOCH_3$), 52.94 (q, CO_2CH_3), 48.74 (d, $CHCO_2Me$) p.p.m.). The mother liquors were concentrated and flash chromatographed (hexane/ether/methanol gradients). The first component obtained was the white crystalline 4-methoxycarbonylisocoumarin (16) (40mg) m.p. 93-95°C (lit.[6] 97°C) (Found: C, 64.4; H, 4.1%; M^+ 204. Calc. for $C_{11}H_8O_4$: C, 64.7; H, 3.95%; M 204. ν_{max} (nujol) 3124w, 1741, 1717, 1619 cm^{-1}. δ_H (60MHz) 3.88 (3H, s, OCH_3), 7.1-8.8 (4H, m, ArH), 8.18 (1H, s, =CH)). Later fractions contained a mixture of (15a) and its isomer. Repeated fractional crystallisation deposited more pure (15a), and an oily residue containing (15b) and (15a) in a ratio of 2:1. (For (15b): ν_{max} (film) 1736, 1605 cm^{-1}. δ_H (250MHz) 3.60 (3H, s, $CHOCH_3$), 3.75 (3H, s, CO_2CH_3), 4.26 (1H, d, J 3.69 Hz, $CHCO_2Me$), 5.58 (1H, d, J 3.69 Hz, CHOMe), 7.3-7.65 (3H, m, ArH), 8.12 (1H, bd, ArH) p.p.m. δ_C 167.93 (s, CO_2Me), 163.27 (s, ArC=O), 134.16 (d, Ar), 133.68 (s, ArCH), 130.36 (d, Ar), 128.81 (d, Ar), 128.18 (d, Ar), 124.88 (s, ArC=O), 101.39 (d, CHOMe), 57.41 (q, $CHOCH_3$), 52.70 (q, CO_2CH_3), 47.96 (d, $CHCO_2Me$) p.p.m.). Quantitative h.p.l.c. analysis using methyl benzoate as an internal standard gave yields for the products: (5) 62%; (15a) 15.2%; (15b) 3.0%; (16) 4.4%.

Methyl (E)-3-methoxy-2-(2'-methoxycarbonylphenyl)propenoate (6).- (E)-3-Methoxy-2-(2'-methoxycarbonylphenyl)propenoic acid (5) (1.08g) was stirred at room temperature in DMF (15ml) with methyl iodide (1ml, excess) and potassium carbonate (0.7g). After about 2h the solution was diluted with water and extracted into ether. The organic phase was washed twice with water, dried ($MgSO_4$) and stripped to give the product as a colourless oil (0.98g, 85.2%) (Found: C, 62.4; H, 5.7%; M^+ 250. $C_{13}H_{14}O_5$ requires: C, 62.4; H 5.6%; M 250. ν_{max} (film) 1709b, 1637 cm^{-1}. δ_H (60MHz) 3.62, 3.74, 3.76 (each 3H, s, OMe), 7.1-7.6 (3H, m, ArH), 7.48 (1H, s, =CH), 7.95 (1H, m, ArH) p.p.m.). The material was identical in all respects to a sample prepared from dimethyl homophthalate by condensation with methyl formate promoted by sodium hydride, followed by methylation in DMF with dimethyl sulphate and potassium carbonate.

3-Hydroxy-3-(methoxycarbonyl)phthalide (10).- Phthalonic acid (8) (1g) was warmed briefly with acetic anhydride (2ml) on a steam bath. The solution was immediately cooled on ice, and the pale yellow phthalonic anhydride (9) was filtered rapidly at the pump. This was dissolved immediately and without washing in excess dry methanol. After about 1h, excess methanol was stripped, and the residue was distributed between water and chloroform, separated and the aqueous layer re-extracted with chloroform. The combined organic phase was dried (Na_2SO_4) and stripped to give a colourless oil which slowly crystallised (1.11g). A small sample was recrystallised from toluene/hexane: m.p. 71-71.5°C (lit.[16] 94°C from benzene) (Found: C, 57.6; H, 3.8%; calc. for $C_{10}H_8O_5$: C, 57.7; H, 3.9%. ν_{max} (film) 3480b, 1775, 1745 cm^{-1}. δ_H (60MHz) 3.72 (3H, s, OCH_3), 6.12 (1H, s, exch.), 7.4-8.0 (4H, m, ArH) p.p.m. δ_C 168.63, 167.65, 144.77, 134.89, 131.48, 127.04, 125.78, 122.77, 99.69, 54.43 p.p.m. This spectrum can only be assigned to the phthalide structure given. Ring-opened versions would require 3 C=O peaks; only 2 are observed. MS: EI m/z 149 (no M^+); CI/NH_3 m/z 191 (M-OH), 209 (M+H), 226 ($M+NH_4$), 417(2M+H).

Methyl 2-ethoxycarbonylphenylglyoxylate (7).- Phthalide derivative (10) (0.5g) was stirred in DMF (5ml) containing excess ethyl iodide and potassium carbonate. After 1h, water was added and the mixture extracted with ether, washed with water, dried and stripped to give a colourless oil (0.26g, 45.3%). (Found: C, 57.8; H, 4.0%; M^+ 236. $C_{12}H_{12}O_5$ requires: C, 57.7; H, 3.9%; M 236. δ_H (60MHz) 1.33 (3H, t, J 7Hz, CH_2CH_3), 3.81 (3H, s, OMe), 4.32 (2H, q, J 7Hz, OCH_2), 7.1-7.7 (3H, m, ArH), 8.0 (1H, m, ArH) p.p.m. δ_C 187.04 (s, $COCO_2Me$), 166.4 (s, CO_2Et), 161.3 (s, CO_2Me), 138.7, 130.2 (each s, Ar), 132.9, 131.4, 129.5, 129.0 (each s, ArH), 62.2 (t, OCH_2), 53.0 (q, OCH_3), 14.1 (q, OCH_2CH_3) p.p.m.).

Methyl 3-methoxy-2-(2'-ethoxycarbonylphenyl)propenoate (11) (a) Path 1 (Scheme 2).- Methoxymethyltriphenylphosphonium chloride (1.24g, 3eqvt) was stirred under N_2 in ether (20ml). Potassium t-butoxide (0.36g, 2.7eqvt) was added, and the yellow-orange solution was stirred vigorously for 0.5h at room temperature. The glyoxylate (7) (0.26g) was then added in ether (5ml). After 1.5h at room temperature, saturated aqueous sodium acetate solution was added, the layers were separated, and the organic phase washed twice with water. The aqueous washings were back-extracted with ether, the combined organics were dried and stripped to give an orange oil. Treatment with hexane/ether caused precipitation of triphenylphosphine oxide. The organic solution was flash chromatographed through silica using a slow hexane/ether gradient. The first material isolated was the (E)-isomer (11a) as a colourless oil (34 mg; 11.7%) (Found: $C_{\underline{}}$ 63.9; H, 6.0%; M^+ 264. $C_{14}H_{16}O_5$ requires: C, 63.6; H, 6.1%; M 264. ν_{max} (film) 1711, 1636 cm^{-1}. δ_H (250MHz) 1.33 (3H, t, J 7 Hz, $CH_2\underline{CH_3}$), 3.67 (3H, s, $CO_2\underline{CH_3}$), 3.81 (3H, s, $=CHOCH_3$), 4.28 (2H, q, J 7 Hz, CO_2CH_2), 7.25-7.55 (3H, m, ArH), 7.51 (1H, s, =CH), 7.99 (1H, dd, 3-ArH) p.p.m. Irradiation at δ 3.81 p.p.m. led to signal enhancement at δ 7.51 p.p.m. No other nOes were observed. δ_C 167.85 (s, $\underline{CO_2}Me$, $^3J_{CH}$ 3.7 Hz), 167.09 (s, $\underline{CO_2}Et$), 158.05 (d, =CH), 133.77 (s, 1-Ar), 132.20 (d, Ar), 131.52 (d, Ar), 130.77 (s, 2-Ar), 130.29 (d, Ar), 127.50 (d, Ar), 112.41 (s, $=\underline{C}CO_2$), 61.78 (q, $=CHO\underline{CH_3}$), 60.82 (t, $CO_2\underline{CH_2}$), 51.42 (q, $CO_2\underline{CH_3}$), 14.16 (q, $CH_2\underline{CH_3}$) p.p.m.). Later fractions eluted the (Z)-isomer (11b) as white crystals (0.21g; 72.2%) m.p. 118-119°C (Found: C, 63.9; H, 6.0%; M^+ 264. $C_{14}H_{16}O_5$ requires: C, 63.6; H, 6.1%; M 264. ν_{max} (nujol) 1705, 1618 cm^{-1}. δ_H (250 MHz) 1.34 (3H, t, J 7 Hz, $OCH_2\underline{CH_3}$), 3.66 (3H, s, $CO_2\underline{CH_3}$), 3.93 (3H, s, $=COCH_3$), 4.31 (2H, q, J 7 Hz, $OCH_2\underline{CH_3}$), 6.59 (1H, s, =CH), 7.21 (1H, bd, 6-ArH), 7.38 (1H, bt, ArH), 7.49 (1H, bt, ArH), 7.97 (1H, bd, 3-ArH) p.p.m. Irradiation of the peak at d 6.59 p.p.m. led to enhancement of the signal at δ 7.21 p.p.m. Irradiation at δ 3.95 p.p.m. led to signal enhancement at δ 6.59 p.p.m. δ_C 167.35 (s, $\underline{CO_2}Et$), 165.36 (s, $\underline{CO_2}Me$, $^3J_{CH}$ 10.2 Hz), 157.73 (d, =CHOMe), 136.63 (s, 1-Ar), 131.82 (d, 2 x Ar), 131.71 (s, 2-Ar), 130.39 (d, Ar), 127.57 (d, Ar), 112.45 (s, $=\underline{C}CO_2$), 62.51 (q, $=CHO\underline{CH_2}$), 61.00 (t, $CO_2\underline{CH_2}$), 51.12 (q, $CO_2\underline{CH_3}$), 14.23 (q, $CH_2\underline{CH_3}$) p.p.m.). Path 2 (Scheme 2).- Trimethylsilyl triflate (2.22g, 1.93ml) was added slowly to a solution of triethylamine (1.01g, 1.39ml) in ether (10ml) under nitrogen, contained in a dropping funnel at room temperature, with swirling. After about 15mins, the clear solution was added to methyl 2-ethoxycarbonylphenylacetate (12) (1.8g) in ether (10ml) at 0°C, and stirred at room temeprature for about 1h. A 2-phase mixture resulted, containing the mixed ketene silyl methyl acetal. A separate flask purged with N_2 and cooled to -70°C was charged with trimethyl orthoformate (1.1g, 1.14ml) in methylene chloride (15ml). To this was slowly added $TiCl_4$ (1.9g, 1.1ml) in methylene chloride (5ml) with stirring. A pale cream precipitate developed. The ketene silyl acetal solution was transferred to the dropping funnel with the aid of dichloromethane (5ml) and added slowly to the $TiCl_4/(MeO)_3CH$ mixture at -70°C. When the addition was complete, the temperature was allowed to rise spontaneously to room temperature, and stirring was continued for about 1h, after which time a brownish solution had developed. The solution was poured into excess aqueous sodium carbonate solution, with stirring. The white precipitate was removed by filtration, and the filtrates separated. The organic layer was washed three times with water, while the aqueous layer was back-extracted with ether, and the combined organic phase dried and stripped. The crude pale brown oil was separated by flash chromatography on silica. Early fractions contained recovered starting material (0.98g, 54.4%). The (E)-isomer of (11) produced was obtained as a colourless oil (0.72g, 33.6%), followed by a small amount of the (Z)-isomer (0.02g, 0.9%). In each case, the spectroscopic and chromatographic properties were exactly as those reported for the materials prepared by Path 1 (above). Subsequent experiments on related systems showed that the yield of product could be increased if the silylation was carried out in dichloromethane instead of ether.

Methyl 2-carboxyphenylacetate.- Homophthalic acid (50g) was refluxed in methanol (200ml) containing concentrated sulphuric acid (15 drops) for 1.5h. Methanol was removed on the rotary evaporator, water was added to the resulting yellow oil and the phases separated. The organic phase solidified to an off-white mass which was taken into dilute aqueous sodium bicarbonate solution, and extracted twice with diethyl ether. The aqueous phase was then acidified to pH 4. The precipitate was filtered off, washed copiously with water, and dried to give off-white powder (44.4g, 82.4%), m.p.95-96°C (lit.[17] 96-97°C)) (Found: C, 61.6; H 5.2%; M^+, 194. Calc. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.2%; M 194. ν_{max} (nujol) 2400-3300, 1723, and 1677 cm^{-1}; δ_H (60MHz) 3.63 (3H, s, CH_3), 3.99 (2H, s, CH_2), 7.05-7.6(3H, m, ArH), 8.08 (1H, dd, 3-ArH), ca.10.8 (1H, s, exch., CO_2H) p.p.m.).

Methyl 2-ethoxycarbonylphenylacetate (12).- Monomethyl homophthalate (1.94g) was stirred in dimethyl formamide (15ml) with anhydrous potassium carbonate (1.5g) and ethyl iodide (1.5g) at room temperature for 1h. Ether and water were added, and the two phases separated. The organic layer was washed with water, dried, and the solvent removed to give the product as a colourless oil (1.83g, 82.4%) (Found: C, 64.6; H,6.3%; M^+ 222. Calc. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35%; M 222. ν_{max} (film) 1731, 1710 cm^{-1}. δ_H (60MHz) 1.31 (3H, t, J 7 Hz, $OCH_2\underline{CH_3}$), 3.61 (3H, s, OMe), 3.97 (2H, s, CH_2), 4.28 (2H, q, J 7 Hz, OCH_2CH_3), 7.1-7.5 (3H, m, ArH), 8.0 (1H, m, ArH) p.p.m.).

Ethyl 2-carboxyphenylacetate.- This was prepared as the methyl ester above. The crude white product was recrystallised as fine needles from hot water (17.35g, 66.7%) m.p. 107-108°C (lit.[9] 107-108°C) (Found; C, 63.0; H, 5.8%, M^+ 208. Calc. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.8%; M 208. ν_{max} (nujol) 2400-3200b, 1731, 1679 cm^{-1} δ_H (60MHz) 1.21 (3H, tr, J 7 Hz, $OCH_2\underline{CH_3}$), 3.98 (2H, s, CH_2), 4.11 (2H, q, J 7 Hz, OCH_2CH_3), 7.1-7.6 (3H, m, ArH), 8.10 (1H, m, ArH) p.p.m.).

Ethyl 2-methoxycarbonylphenylacetate (14).- This was prepared in the same way as the regioisomeric homophthalate diester (12), above, by alkylation of the homophthalate half (methyl) ester by means of ethyl iodide in dimethyl formamide containing potassium carbonate. The crude brown oil which was obtained solidified on stirring. This was purified by flash chromatography to give fine white needles (1.77g, 84.6%) m.p. 49°C (lit.[10] 48-49°C) (Found: C, 64.7; H, 6.3%; M^+ 222. Calc. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35%; M 222. ν_{max} (nujol) 1729, 1714 cm^{-1}. δ_H (60MHz) 1.22 (3H, tr, J 7 Hz, OCH_2CH_3), 3.81 (3H, s, OMe), 3.94 (2H, s, CH_2), 4.09 (2H, q, J 7 Hz, OCH_2CH_3), 7.1-7.6 (3H, m, ArH), 7.95 (1H, m, ArH) p.p.m.).

Ethyl (E)-3-methoxy-2-(2'-methoxycarbonylphenyl)propenoate (13).- (a) From arylacrylic acid (5).- The acid (5) (0.504g) was dissolved in dimethyl formamide (15ml) and stirred with diethyl sulphate (0.39g) and potassium carbonate (0.35g) and the reaction stood overnight. It was poured into aqueous potassium carbonate, and extracted with ether. The organic layer was washed twice with water, dried and stripped. The crude product was flash chromatographed to give pure product as an oil (0.37g, 65.0%) (Found: C, 63.3; H, 6.3%; M^+ 264. $C_{14}H_{16}O_5$ requires: C, 63.6; H, 6.1%; M 264. ν_{max} (film) 1710, 1640 cm^{-1}. δ_H (60MHz) 1.15 (3H, t, J 7 Hz, OCH_2CH_3), 3.68 (3H, s, OMe), 3.72 (3H, s, OMe), 4.08 (2H, q, J 7 Hz, OCH_2CH_3), 7.1-7.5 (3H, m, ArH), 7.46 (1H, s, =CH), 7.95 (1H, m, ArH) p.p.m.). (b) From ethyl 2-(methoxycarbonyl)phenylacetate (14).- The homophthalate diester (14) was treated firstly with trimethylsilyltriflate/triethylamine, then $TiCl_4$/trimethyl orthoformate in dichloromethane, as in the preparation of (11) by Path 2, above. Purification of the product by flash chromatography gave material identical to that prepared by method (a).

(E)-3-Ethoxy-2-(2'-ethoxycarbonylphenyl)propenoic acid (17).- 4-Methoxymethylidene homophthalic anhydride (1) (0.51g) was treated with ethanolic sodium ethoxide (from ca. 0.06g Na). A bright yellow colour resulted which faded on stirring at room temperature 1.5h. The mixture was acidified to pH 6 with acetic acid and stripped to give a yellow-white solid. This was taken into saturated sodium bicarbonate solution and extracted with ether and dichloromethane. After acidification, the aqueous layer was extracted with ether and chloroform, the organic layer washed, dried and stripped. Recrystallisation from methanol gave white crystals of the product (0.53g, 84.1%) m.p. 165-166° (Found: C, 63.5; H, 6.5%; M^+ 264. $C_{14}H_{16}O_5$ requires, C, 63.6; H, 6.1%; M 264. ν_{max} (nujol) 2400-3400b, 1702, 1669 cm^{-1}. δ_H (60MHz, d_6-DMSO) 1.16 (6H, m, 2 x OCH_2CH_3), 3.98 (2H, q, J 7 Hz, OCH_2CH_3), 4.10 (2H, q, J 7 Hz, OCH_2CH_3), 7.05-7.8 (4H, m, ArH), 7.50 (1H, s, =CH) p.p.m.).

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