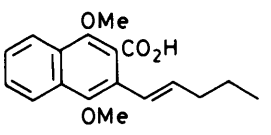
Formation of some 3-Aryl-3,4-dihydroisocoumarins by Thermal Ring Closure of Stilbene-2-carboxylic Acids

Geoffrey C. A. Bellinger, William E. Campbell, Robin G. F. Giles,* and Julius D. Tobias
Department of Organic Chemistry, University of Cape Town, Rondebosch, 7700, South Africa

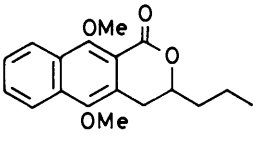
When heated at 200 °C, *cis*- and *trans*-4'- and 2'-methoxystilbene-2-carboxylic acids have been converted into the title compounds in varying yields, as has *trans*-4'-hydroxystilbene-2-carboxylic acid. On the other hand, *trans*-4'-nitrostilbene-2-carboxylic acid affords 3-(4-nitrobenzyl)phthalide. Mass spectrometry provides a simple method of distinguishing between the dihydroisocoumarins and phthalides.

In recent work [1] related to a potential synthesis of the pigment xylindein, we wished to transform the alkenylnaphthoic acid (1) into the δ-lactone (2). This was achieved photochemically, and independent studies [2] showed the photorearrangement to be general. On the other hand, this ring closure did not take place thermally, decarboxylation being preferred,[1] in spite of the report [3] that hydrangea acid (3) and its monomethyl ether (4) gave the natural product hydrangeol (5) and its methyl ether (6) respectively when heated.

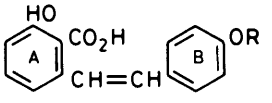
We report here a study designed to determine which structural features lacking in (1) promoted thermal ring closure of the stilbenes (3) and (4), and also to establish support for our suggestion [1] that oxygenation at C-4 in ring B might be a requirement. We have therefore synthesised a variety of stilbene-2-carboxylic acids and heated them.



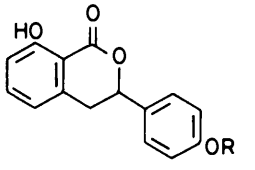
(1)



(2)



(3) R = H
(4) R = Me



(5) R = H
(6) R = Me

Results and Discussion

The geometrically isomeric pairs of acids (7) and (11), (8) and (12), and (9) and (13) were obtained as three mixtures from Wittig reactions of the phosphonium bromide (18)[4] with, respectively, benzaldehyde, 3-methoxybenzaldehyde, and 4-methoxybenzaldehyde, followed by base hydrolysis of the corresponding methyl esters. The *cis*-isomers (7) and (9) were isolated pure from the appropriate mixtures by fractional crystallisation, while the 3'-methoxy-acids were not separated. *trans*-Stilbene-2-carboxylic acid (11) was synthesised by the method of Booth and Turner [5] while the *trans*-4'-methoxy-analogue (12) was obtained by toluenesulphonic acid-catalysed dehydration of the adduct (19)[6] to the benzylidenephthalide (20), followed by hydrogenation to 4'-methoxybenzylphthalide (21). This was ring-opened, by potassium hydroxide in ethanol,[7] to the isomerically pure *trans*-acid (13). *trans*-4'-Hydroxystilbene-2-carboxylic acid (14) was obtained from the hydroxyphenyldihydroisocoumarin (28) (see below) by opening of the δ-lactone ring with potassium t-butoxide in tetrahydrofuran, a reaction which may conceivably proceed *via* the quinone methide (31) through abstraction of the phenolic rather than a methylene proton in (28). However, there is no direct evidence for this, and the same conditions were found to transform the related dihydroisocoumarins (25), (26), and (27) into the *trans*-acids (11), (12), and (13), respectively.

Authentic samples of the dihydroisocoumarins (25)—(28) were synthesised to assist with their identification should they be produced in the thermal reactions described below. Thus, phenyldihydroisocoumarin (25) was obtained by cyclising either *trans*-stilbene-2-carboxylic acid (11), or the *cis*/*trans* mixture of acids (7) and (11) with concentrated sulphuric acid.† Similarly, the isomeric 3- and 4-methoxydihydroisocoumarins (26) and (27) were obtained by cyclisation of the 3'- and 4'-methoxystilbene acids (8) and (12) and (9) and (13). The hydroxydihydroisocoumarin (28) was obtained by boron tribromide demethylation of the ether (27).

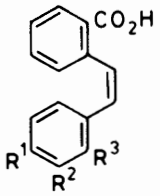
The *cis*-acid (7) and the *trans*-acid (11) were separately heated at 200 °C, but no trace of the phenyldihydroisocoumarin (25) was observed in either case by t.l.c. or ^{1}H n.m.r. spectroscopy; neither did recovered material depress the melting point of authentic starting acid. Similarly, the mixture of 3'-methoxy-acids (8) (75%) and (12) (25%) gave no isocoumarin (26) as judged by t.l.c. and n.m.r. spectroscopy, although the latter method showed that some *cis*-material was converted into the *trans*-isomer [ratio (8) (67%) and (12) (33%) by integration].

Heating of *cis*-4'-methoxystilbene-2-carboxylic acid (9) at the same temperature afforded the 4-methoxyisocoumarin (27) (49%),‡ together with some of the *trans*-acid (13), while heating of the *trans*-acid (13) afforded the same product (27) (67%), together with some of the *cis*-isomer (9). Heating of *trans*-4'-hydroxystilbene-2-carboxylic acid (14) likewise afforded the isocoumarin (28) (54%). The ^{1}H n.m.r. spectra of compounds (25)—(28) showed a characteristic ABX pattern for the protons of the lactone ring as well as a low-field aromatic doublet of doublets for 8-H. For compound (28) these were respectively δ 3.04 (*J* 4 and 17 Hz) and 3.33 (*J* 11 and 17 Hz) (methylene), δ 5.44 (*J* 4 and 11 Hz) (methine), and δ 8.11 (*J* 2 and 7 Hz).

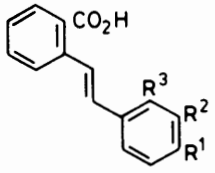
The reactions of the *cis*- and *trans*-2'-methoxystilbene-2-carboxylic acids (10) and (15) might be predicted to parallel

† For cyclisation of the *cis*-compound (7) see ref. 8.

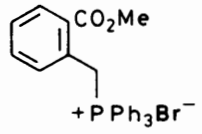
‡ Throughout, yields quoted would be considerably higher if based on unrecovered stilbene acids.



(7) $R^1 = R^2 = R^3 = H$
(8) $R^1 = R^3 = H$, $R^2 = OMe$
(9) $R^1 = OMe$, $R^2 = R^3 = H$
(10) $R^1 = R^2 = H$, $R^3 = OMe$



(11) $R^1 = R^2 = R^3 = H$
(12) $R^1 = R^3 = H$, $R^2 = OMe$
(13) $R^1 = OMe$, $R^2 = R^3 = H$
(14) $R^1 = OH$, $R^2 = R^3 = H$
(15) $R^1 = R^2 = H$, $R^3 = OMe$
(16) $R^1 = R^2 = H$, $R^3 = OH$
(17) $R^1 = NO_2$, $R^2 = R^3 = H$



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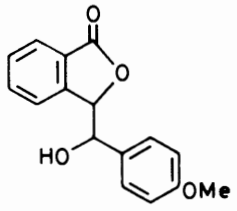

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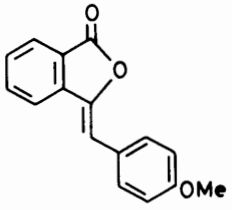

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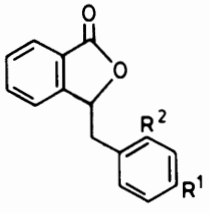
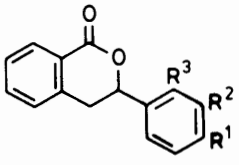
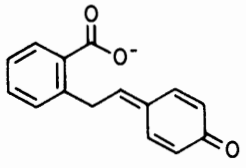


(21) $R^1 = OMe$, $R^2 = H$
(22) $R^1 = R^2 = H$
(23) $R^1 = H$, $R^2 = OMe$
(24) $R^1 = NO_2$, $R^2 = H$



(25) $R^1 = R^2 = R^3 = H$
(26) $R^1 = R^3 = H$, $R^2 = OMe$
(27) $R^1 = OMe$, $R^2 = R^3 = H$
(28) $R^1 = OH$, $R^2 = R^3 = H$
(29) $R^1 = R^2 = H$, $R^3 = OMe$
(30) $R^1 = R^2 = H$, $R^3 = OH$



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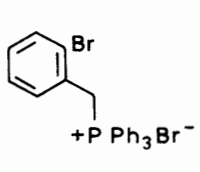

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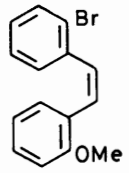

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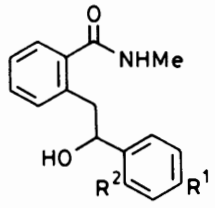


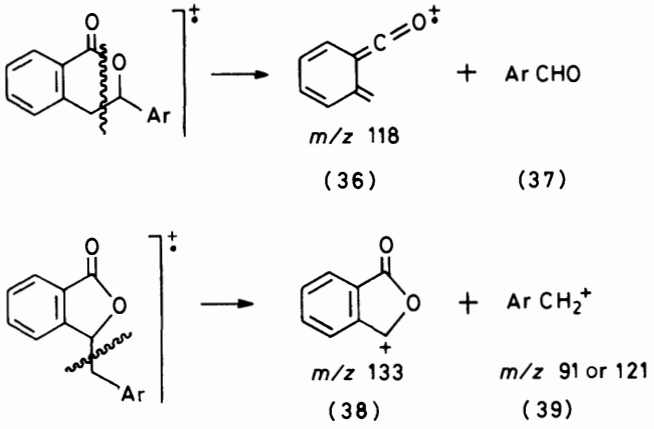
(34) $R^1 = H$, $R^2 = OMe$
(35) $R^1 = OMe$, $R^2 = H$

those of the corresponding 4′-methoxy-compounds, and these were investigated. The *cis*-compound (10) was prepared as follows. Wittig reaction between 2-bromobenzyltriphenylphosphonium bromide (32)[9] and 2-methoxybenzaldehyde afforded a *cis*/*trans* mixture of bromostilbenes from which the *cis*-isomer (33) was fractionally crystallised. Metal–halogen exchange by reaction with butyl-lithium, followed by addition to carbon dioxide, afforded *cis*-2′-methoxystilbene-2-carboxylic acid (10). The corresponding *trans*-acid (15) was derived by potassium t-butoxide-promoted ring opening of the isomeric 2-methoxyphenyldihydroisocoumarin (29) (see below).

Heating of the *cis*-acid (10) afforded a product (37%) whose ^{1}H n.m.r. spectrum showed *inter alia* a two-proton doublet at δ 3.16 (*J* 7.5 Hz) coupled to a symmetrical one-proton triplet at δ 5 94. A one-proton lowfield aromatic doublet of doublets at δ 8.18 was also evident. The non-aromatic region of this spectrum was unlike that of the dihydroisocoumarins (25) to (28) described earlier, being more like that of the benzylphthalides (21) and (22) [the latter having been used in the synthesis of acid (11)[5]]. However, an i.r. carbonyl absorption at 1 728 cm^{-1}, although higher than that (1 718 cm^{-1}) for the corresponding 4-methoxy-compound (27), supported the assignment as a dihydroisocoumarin. In view of the apparently conflicting spectroscopic data, an alternative route to the isocoumarin (29) was devised using the general method of Vaulx *et al.*[10] 2-Methoxybenzaldehyde was treated with the dilithio-salt of *N*-methyl-*o*-toluamide to form the intermediate (34) which was heated to give a product identical with that formed by heating the *cis*-acid (10). In order to exclude the possibility that both thermal reactions were giving rise to 2-methoxybenzylphthalide (23) [the latter reaction by the route (34) ⟶ (29) ⟶ (10) or (15) ⟶ (23)], authentic compound (23) was prepared.[11] This was different from the product of the thermal reaction which was, therefore, assigned the structure of the isocoumarin (29). The uncharacteristic n.m.r. spectrum was ascribed to the molecule adopting a conformation different from that of the related dihydroisocoumarins (25)—(28) to reduce crowding. At −60 °C the ABX pattern for compound (29) changed to give a doublet of doublets at δ 5.96 (*J* 6 and 10 Hz) and a multiplet at δ 3.1—3.3, which is very similar to the spectra observed for compounds (25)—(28). In perdeuteriotoluene this latter pattern was evident at room temperature, but at 100 °C the ABX system appeared as the doublet and triplet observed for compound (29) at room temperature in deuteriochloroform.

It was found that the thermal conversion of the hydroxyamide (34) to the isocoumarin (29) took considerably longer to complete, than did the conversion of the intermediate (35) into the less crowded isocoumarin (27).

A useful distinction between the isomeric aryldihydroiso-



coumarins and benzylphthalides could be made with the aid of mass spectrometry. The isocoumarins in each case gave as the base peak an ion (36), *m/z* 118, the neutral aldehydic fragment (37) not being observed.* On the other hand, the phthalides all afforded the ions (38), *m/z* 133, and (39), the former being the base peak, for the benzylphthalide (22) and the latter predictably constituting the base peak, *m/z* 121, for the methoxybenzyl compounds (21) and (23).

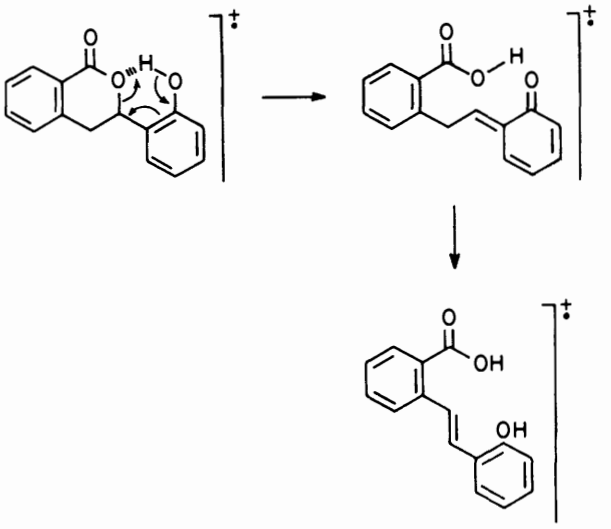
When the *trans* 2′-methoxy-acid (15) was heated, the isocoumarin (29) was again formed (39%), and the n.m.r. spectrum of the recovered acid showed it to contain a little (10%) of the corresponding *cis*-isomer (10). Inspection of the acid recovered from the thermal reaction of the *cis*-acid (10) showed considerable (75%) isomerisation to the *trans*-acid (15) under the conditions used.

It is noteworthy that, while isocoumarins (25)—(28) were obtained smoothly by ring closure of the appropriate acids with concentrated sulphuric acid as described above, similar reaction of *trans*-2′-methoxystilbene-2-carboxylic acid (15) gave a mixture which was not further investigated.

The *trans*-2′-hydroxy-acid (16) was obtained by boron tribromide demethylation of the ether (29) to the phenol (30), followed by butoxide ring opening. The acid (16) was heated to 200 °C for 1 h, but very little, if any, of the dihydroisocoumarin (30) could be detected in the complex reaction mixture.

The ABX pattern in the n.m.r. spectrum of compound (30) was analogous to that of compound (29). The mass spectrum differed from that of all the other dihydroisocoumarins so far described in that, in addition to the peaks at *m/z* 118 and 90 prominent in the other cases, it also showed fragments at *m/z* 222 (73%), 194 (100%), and 165 (35%); this is identical with the major fragmentation pattern of the acid (16). Conversely the acid (16) lacked the intense signals due to fragments at *m/z* 118 and 90 apparent for compound (30). This implies ring opening of compound (30) *via* the *ortho*-quinone methide to the acid (16) on electron impact, as shown in Scheme 1. That the phenolic proton is hydrogen bonded is substantiated by the lowfield singlet at δ 8.75 in the n.m.r. spectrum of (30). Not surprisingly, therefore, the isomer (28) does not show analogous ring opening to the acid (14) in its mass spectrum. Interestingly, the acid (14) gives rise to an intense signal at *m/z* 118 (84%), suggesting the possible formation of the isocoumarin (28) on electron impact.

The fact that stilbene acids were, in general, recovered from the thermal cyclisations raised the possibility that these



Scheme 1.

reactions might be reversible. This was confirmed in the case of the thermal cyclisation of the hydroxyamide (34), in which a minor product (5%) was identified as the *trans*-stilbene (15), which it was inferred arose from ring opening of the dihydroisocoumarin (29). This was confirmed by subjecting compound (29) to identical thermal conditions, when a similar proportion of the *trans*-acid (15) was isolated. In the ring closure of amide (35), considerably more (25%) of the *trans*-acid (13) was recovered. This was, in turn, shown to arise from thermal ring opening of the lactone (27). When this lactone was heated for a much longer period, the *trans*-acid (13) was obtained contaminated with a little of the *cis*-isomer (9), the latter presumably arising through isomerisation of the former.

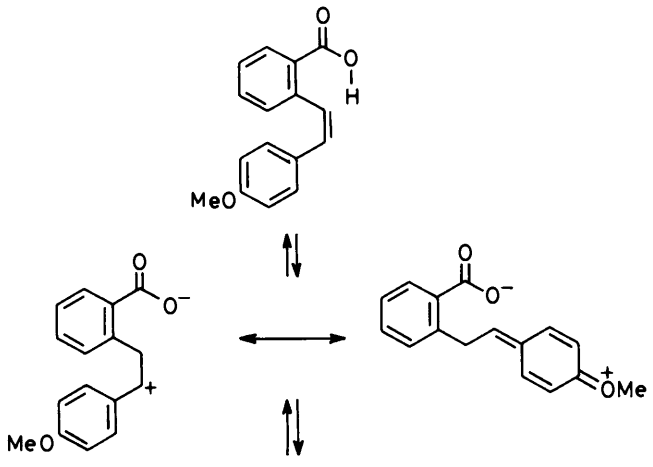
All thermal reactions of stilbene acids so far described had been performed at 200 °C, at which temperature the acids (7), (8), (11), and (12) had not given rise to the appropriate isocoumarins. The question arose as to whether these transformations would take place at a higher temperature. When the *cis*-acid (7) was heated to 300—350 °C, the isocoumarin (25) was isolated (12%), while, under identical conditions, the *trans*-isomer (11) afforded compound (25) in 14% yield.

The mechanism of the cyclisation presumably involves reversible protonation of the double bond carbon *ortho* to the carboxy-group to afford a benzyl carbonium ion, resonance-stabilised, in the case of compounds (9), (10), (13), (14), and (15), by a methoxy- or hydroxy-group. Subsequent reversible ring closure affords the product. The proposal is depicted for the stilbene (9) in Scheme 2. No oxygen-promoted stabilisation is possible for the acids (7), (8), (11), and (12), necessitating a much higher reaction temperature for (7) and (11) [and, presumably, (8) and (12)]. For the hydroxy-acid (14), the quinone methide (31) may be an intermediate.

These findings explain the formation of the dihydroisocoumarins hydrangeol (5) and its methyl ether (6), rather than the isomeric benzyl phthalides,[13] from their respective acid precursors on heating.

It might be speculated that electron-withdrawing substituents on the B ring of stilbene-2-acids would yield benzyl phthalides on heating. Accordingly, *trans*-4′-nitrostilbene-2-carboxylic acid (17), obtained by methoxide-promoted ring opening [14] of 4-nitrobenzylphthalide (24), was converted back into the phthalide (24) when heated at 200 °C. Comparison of the thermal product with authentic compound (24) showed them to be identical. The mass spectrum of both samples of

* This type of fragmentation appears to be general for dihydroisocoumarins.[12]

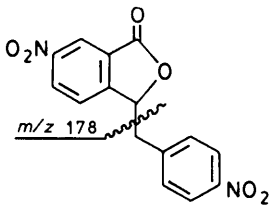


(27)

Scheme 2.

compound (24) gave the ion (38), *m/z* 133, as base peak in conformity with other benzylphthalides mentioned above, although, not surprisingly, no ion of type (39) was observed.

Nitrobenzylphthalide was prepared by a modification of the method of Berti and Marsili.[14] A second product from this reaction proved to be the dinitrobenzylphthalide (40). The assignment was made on the basis of the ^{1}H n.m.r. spectrum, which showed two lowfield aromatic protons, one of which showed *meta*-coupling, and the other both *ortho*- and *meta*-coupling. The pair of two-proton aromatic doublets due to the *para*-nitrobenzyl system was conspicuous. The assignment was confirmed by a mass spectrum, which gave the ion, *m/z* 178, as the base peak.



(40)

Experimental

Unless otherwise stated, n.m.r. spectra were measured for solutions in [^{2}H]chloroform with tetramethylsilane as internal reference, while i.r. spectra were measured for Nujol mulls. Preparative layer chromatography (p.l.c.) was performed on glass plates coated with Merck Kieselgel 60 F 254, while column chromatography refers to dry-packed columns using the same gel (70—230 mesh). Light petroleum refers to the fraction of b.p. 60—80 °C. The phrase 'residue obtained upon work-up' refers to the residue when the organic layer was separated, dried ($MgSO_4$), and the solvent evaporated under reduced pressure. In general, mass spectral fragment ions of less than 30% of the base peak were not recorded.

cis-*Stilbene*-2-*carboxylic Acid* (7).—Lithium methoxide [15 ml (0.015 mol) of a solution containing lithium (0.694 g, 0.1 mol) in dry methanol (100 ml)] was added during 15 min to a solution of 2-methoxycarbonylbenzyltriphenylphosphonium bromide (18) (7.36 g, 0.015 mol) and benzaldehyde (1.91 g, 0.018 mol) in dry methanol (50 ml) at room temperature with stirring under nitrogen. The mixture was then heated under reflux for 2 h. A solution of potassium hydroxide (2.8 g, 0.05 mol) in water (25 ml) was added in one portion and heating continued for a further 2.5 h. The reaction mixture was evaporated to *ca.* 25 ml and washed with diethyl ether (3 × 50 ml). The clear aqueous layer was acidified to pH 2 with concentrated hydrochloric acid and extracted with ethyl acetate (3 × 25 ml). The residue obtained upon work-up was a mixture of *cis*- and *trans*-acids (7) and (11), contaminated with considerable quantities of *o*-toluic acid arising from a side reaction of the phosphonium salt (18) [see synthesis of compound (9) below]. This contaminant was removed by chromatography (eluant 25% ethyl acetate in light petroleum), later fractions affording a mixture of acids (7) and (11). The *product* crystallised preferentially (0.8 g, 14%), m.p. 149—151 °C (after two recrystallisations from 96% ethanol) (lit.,[2] 148—149 °C).

Mixture of cis- *and* trans-3′-*Methoxystilbene*-2-*carboxylic Acids* (8) *and* (12).—By using 3-methoxybenzaldehyde in place of benzaldehyde in the above procedure, chromatography afforded a 3 : 1 mixture of *cis*- and *trans*-acids (8) and (12) (0.25 g, 4%) as colourless needles. The relative proportions of each acid were estimated from the integration of the methoxy-signals (*cis*, δ 3.57 and *trans*, δ 3.84) in the n.m.r. spectrum. The mixture was not separated.

cis-4′-*Methoxystilbene*-2-*carboxylic Acid* (9).—(a) Using 4-methoxybenzaldehyde, chromatography as for compound (7) above yielded a mixture from which the *trans*-isomer crystallised (0.45 g, 7%), m.p. 196 °C (ethanol) (lit.,[2] 196 °C). Recrystallisation of the mother-liquors afforded the *product* (0.2 g, 3%), m.p. 129 °C (ethanol) (lit.,[2] 129—130.5 °C).

(b) 1,5-Diazabicyclo[4.3.0]non-5-ene (1.17 g, 9 mmol) was added in one portion to a solution of the phosphonium salt (13) (4.0 g, 8 mmol) and 4-methoxybenzaldehyde (1.23 g, 9 mmol) in dry acetonitrile (50 ml). The mixture was heated under reflux for 1 h, and then evaporated under reduced pressure. The residual pale yellow oil was dissolved in dichloromethane and washed with 2M-hydrochloric acid. The residue obtained upon work-up was chromatographed (eluant 15% ethyl acetate in light petroleum) to give methyl *o*-toluate (33%) closely followed by the mixture of stilbene esters (0.74 g, 31%) as a colourless solid. Later fractions afforded 4-methoxybenzaldehyde. The esters (0.67 g, 2.5 mmol) in a mixture of water (5 ml), methanol (0.75 ml), and potassium hydroxide (0.27 g, 5 mmol) were heated under reflux for 5 h. The cooled solution was extracted with ethyl acetate, and the residue obtained upon work-up (0.35 g, 55%) was a mixture of the *cis*- and *trans*-acids, containing no *o*-toluic acid. This experiment showed that the *o*-toluic acid formed above is a by-product of the Wittig reaction, and does not arise from a retro-aldol reaction on hydrolysis of the stilbene esters. The *product* could be isolated as in (a) above.

3-(4-*Methoxyphenylmethylene*)*isobenzofuran*-1(3H)-*one* (20).—Crude addition product (14)[6] (2.6 g) and toluene-*p*-sulphonic acid (0.1 g) in dry toluene (100 ml) were heated under reflux for 0.5 h, with azeotropic removal of water. The reaction mixture was evaporated to give a brown-black oil which was dissolved in ethyl acetate (50 ml), and washed with aqueous sodium carbonate (10%; 50 ml). The residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate in light petroleum). The first major yellow fraction gave the *product* as bright yellow needles (2.0 g, 55%), m.p. 147.5—148.5 °C (ethyl acetate–light petroleum) (lit.,[6] 147—147.5 °C).

3-(4-*Methoxyphenylmethyl*)*isobenzofuran*-1(3H)-*one* (21).—A solution of the benzylidenephthalide (20) (1.0 g) in glacial acetic acid (250 ml) was hydrogenated at 40 lb in^{-2} in the presence of 10% palladium on charcoal (0.5 g). Filtration followed by evaporation afforded the *product* as colourless spears (0.99 g, 99%), m.p. 83—85 °C (propan-2-ol) (lit.,[14] 84—86 °C), $\nu_{max.}$ 1 759 cm^{-1}; δ 3.11 and 3.29 (1 H each, 2 × dd, *J* 7 and 14 Hz, CH_2), 3.77 (3 H, s, OCH_3), 5.64 (1 H, t, *J* 7 Hz CH), 7.1—7.7 (8 H, m, ArH), and 7.82 (1 H, dd, *J* 2 and 7 Hz, 7-H); *m/z* 254 (M^+, 30%), 133 (41%), 122 (74%), 121 (100%), and 77 (51%).

3,4-*Dihydro*-3-*phenyl*-1H-2-*benzopyran*-1-*one* (25).—This is an adaptation of the methods of Asahina and Asano,[15] and Berti.[8] *trans*-Stilbene-2-carboxylic acid (11) (1 g) was added to ice-cooled concentrated sulphuric acid (10 g) and occasionally swirled for 5 min. The reaction mixture was then poured into crushed ice and extracted with dichloromethane; the extract was washed with water followed by saturated sodium hydrogencarbonate, and then brine. The residue on work-up gave the *product* as colourless rhombohedra (0.95 g, 95%), m.p. 88—90 °C (propan-2-ol), lit.,[8] 88—90 °C), $\nu_{max.}$ 1 720 cm^{-1}; δ 3.08 (1 H, dd, *J* 4 and 17 Hz, equatorial 4-H), 3.35 (1 H, dd, *J* 11 and 17 Hz, axial 4-H), 5.52 (1 H, dd, *J* 4 and 11 Hz, axial 3-H), 7.2—7.7 (8 H, m, ArH), and 8.13 (1 H, dd, *J* 2 and 7 Hz, 8-H); *m/z* 224 (M^+, 5%), 121 (42%), and 118 (100%).

3,4-*Dihydro*-3-(3-*methoxyphenyl*)-1H-2-*benzopyran*-1-*one* (26).—Using the above procedure, a 1 : 1 mixture of the acids (8) and (12) (0.43 g) afforded the *product* (0.1 g, 23%) (yield not optimised) as colourless rhombohedra, m.p. 96—98 °C (propan-2-ol) (lit.,[16] 95 °C), $\nu_{max.}$ 1 713 cm^{-1}; δ 3.10 (1 H, dd, *J* 4 and 17 Hz, equatorial 4-H), 3.16 (1 H, dd, *J* 11 and 17 Hz, axial 4-H), 3.82 (3 H, s, OCH_3), 5.52 (1 H, dd, *J* 4 and 11 Hz, axial 3-H), 6.8—7.7 (7 H, m, ArH), and 8.17 (1 H, dd, *J* 2 and 7 Hz, 8-H); *m/z* 254 (M^+, 72%), 119 (32%), 118 (100%), and 90 (84%).

3,4-*Dihydro*-3-(4-*methoxyphenyl*)-1H-2-*benzopyran*-1-*one* (27).—Using the above procedure, the *trans*-acid (13) (0.5 g) gave rise to the *product* (0.35 g, 70%) as colourless spears, m.p. 109—110 °C (propan-2-ol), (lit.,[2] 109—110 °C), $\nu_{max.}$ 1 718 cm^{-1}, δ 3.06 (1 H, dd, *J* 4 and 17 Hz, equatorial 4-H), 3.16 (1 H, dd, *J* 11 and 17 Hz, axial 4-H), 3.82 (3 H, s, OCH_3), 5.48 (1 H, dd, *J* 4 and 11 Hz, axial 3-H), 6.91 (2 H, d, *J* 9 Hz, 3′- and 5′-H), 7.38 (2 H, d, *J* 9 Hz, 2′- and 6′-H), 7.2—7.65 (3 H, m, 5-, 6-, and 7-H), and 8.14 (1 H, dd, *J* 2 and 7 Hz, 8-H); *m/z* 254 (M^+, 84%), 119 (38%), 118 (100%), and 90 (82%).

3,4-*Dihydro*-3-(4-*hydroxyphenyl*)-1H-2-*benzopyran*-1-*one* (28).—A solution of compound (27) (0.5 g, 2 mmol) in dry dichloromethane (5 ml) was added dropwise during 5 min to a stirred solution of boron tribromide (0.60 ml, 6 mmol) in dichloromethane (10 ml) at −78 °C. The mixture was stirred at that temperature for 1 h and then allowed to warm to room temperature overnight. Water (50 ml) was added to the mixture, and the residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate in light petroleum). The fifth band gave the *product* (0.3 g, 64%) as colourless microneedles, m.p. 149—150 °C (ethyl acetate–light petroleum) (Found: C, 75.2; H, 5.1. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0%); $\nu_{max.}$ 3 400 and 1 690 cm^{-1}; δ 3.04 (1 H, dd, *J* 4 and 17 Hz, equatorial 4-H), 3.33 (1 H, dd, *J* 11 and 17 Hz, axial 4-H), 5.44 (1 H, dd, *J* 4 and 11 Hz, axial 3-H), 6.86 (2 H, d, *J* 9 Hz, 3′- and 5′-H), 7.23 (2 H, d, *J* 9 Hz, 2′- and 6′-H), 6.4—7.8 (1 H, br, OH), 7.2—7.7 (3 H, m, 5-, 6- and 7-H), and 8.11 (1 H, dd, *J* 2 and 7 Hz, 8-H); *m/z* 240 (M^+, 54%), 119 (35%), 118 (100%), and 90 (89%).

trans-4′-*Hydroxystilbene*-2-*carboxylic Acid* (14).—A mixture of compound (28) (0.360 g, 1.5 mmol) and potassium t-butoxide (0.264 g, 2 mmol) were heated together under reflux in dry tetrahydrofuran (20 ml) for 3.5 h, and then evaporated to dryness. The residue was dissolved in water (30 ml) and washed with ethyl acetate. The basic aqueous layer was carefully acidified with concentrated hydrochloric acid, and extracted with ethyl acetate (2 × 30 ml). The residue obtained upon work-up afforded the *product* (0.226 g, 63%), m.p. 163—165 °C (ethyl acetate–hexane) (Found: C, 75.0; H, 5.05. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0%); δ ($(CD_3)_2CO$) 6.88 (2 H, d, *J* 9 Hz, 3′- and 5′-H), 7.08 and 7.98 (1 H each, d, *J* 16 Hz, olefinic CH), 7.46 (2 H, d, *J* 9 Hz, 2′- and 6′-H), 7.2—7.65 (2 H, m, 4- and 5-H), 7.83 br (1 H, d, *J* 7 Hz, 6-H), 7.98 (1 H, dd, *J* 2 and 7 Hz, 3-H), and 6.6—8.4br (1 H, s, OH, D_2O exchangeable); *m/z* 240 (M^+, 100%), 118 (84%), 107 (44%), and 90 (20%).

Thermal Reaction of cis-*Stilbene*-2-*carboxylic Acid* (7).—(a) The acid (7) (0.05 g) was heated at 200 °C for 5 h. T.l.c. (eluant 30% ethyl acetate–light petroleum) and n.m.r. spectroscopy showed that no reaction had taken place. The recovered material on admixture with authentic (7) showed no depression of the m.p.

(b) The acid (7) (90 mg) was heated at 300—350 °C for 1 h. The residue was rapidly chromatographed on a short column to remove charred material. The eluant was evaporated and the residue (82 mg) dissolved in ethyl acetate, and washed with aqueous sodium hydrogencarbonate. The aqueous layer on work-up afforded what n.m.r. spectroscopy showed to be a mixture of *cis*- and *trans*-acids (7) (20%) and (11) (80%) (23 mg). The organic layer gave rise to a residue (52 mg) from which the isocoumarin (25) (11 mg, 12%) was separated by p.l.c., identical by t.l.c. and n.m.r. spectroscopy to authentic material.

Thermal Reaction of trans-*Stilbene*-2-*carboxylic Acid* (11).—(a) The acid (11) (0.05 g) was heated at 200 °C for 2 h. No reaction had taken place as for the *cis*-acid above.

(b) The acid (11) (112 mg) was heated at 300—350 °C for 1 h as for the *cis*-acid in (b) above. The basic extract afforded only the *trans*-acid (11) (37 mg) while p.l.c. of the neutral fraction gave isocoumarin (25) (16 mg, 14%).

Thermal Reaction of cis-4′-*Methoxystilbene*-2-*carboxylic Acid* (9).—Compound (9) (0.043 g) was heated at 200 °C for 1 h. P.l.c. of the product (eluant 30% ethyl acetate–light petroleum) afforded the dihydroisocoumarin (27) (0.021 g, 49%) identical with authentic material as evidenced by m.p., t.l.c., and n.m.r. spectroscopy. A band of lower R_F afforded a mixture (0.01 g, 23%) of acids (9) (75%) and (13) (25%) (ratios by integration).

Thermal Reaction of trans-4′-*Methoxystilbene*-2-*carboxylic Acid* (13).—The acid (13) (170 mg) was heated at 200 °C for 5 h. Chromatography (eluant 30% ethyl acetate–light petroleum) gave firstly isocoumarin (27) (114 mg, 67%) identical with material described earlier (m.p., t.l.c. and n.m.r. spectroscopy). Later fractions afforded a mixture (29 mg, 17%) of acids (9) (15%) and (12) (85%).

Thermal Reaction of trans-4′-*hydroxystilbene*-2-*carboxylic Acid* (14).—The acid (14) (0.227 g) was heated at 200 °C for 1 h. The product was chromatographed (eluant 50% ethyl acetate–light petroleum) to afford compound (28) (0.122 g,

54%). This was recrystallised from ethyl acetate–light petroleum to yield the pure dihydroisocoumarin (28) (0.105 g, 46%), identical with authentic material (m.p., t.l.c., and n.m.r. spectroscopy). Later column fractions afforded starting acid (0.081 g, 36%).

cis-2-*Bromo*-2′-*methoxystilbene* (33).—Lithium methoxide (19.25 ml of a 0.019 molar solution in methanol) was added during 10 min to a stirred solution of 2-bromobenzyltriphenylphosphonium bromide (9.00 g, 17.5 mmol) and 2-methoxybenzaldehyde (2.45 g, 18 mmol) in dry methanol (100 ml) under nitrogen at room temperature. The mixture was then heated under reflux for 3 h, evaporated, and chromatographed (eluant 10% ethyl acetate in light petroleum). The first main fraction gave a 3 : 2 mixture of *cis*- and *trans*-2-bromo-2′-methoxystilbene (4.32 g, 85%) (ratios by integration of methoxy singlets), from which the *product* (0.8 g) was crystallised as colourless prisms, m.p. 66—68 °C (propan-2-ol) (Found: C, 62.25; H, 4.65. $C_{15}H_{13}BrO$ requires C, 62.3; H, 4.5%), δ 3.80 (3 H, s, OCH_3), 6.6—7.3 (9 H, m, Ar-H), and 7.4—7.7 (1 H, m, 3-H).

cis-2′-*Methoxystilbene*-2-*carboxylic Acid* (10).—A solution of butyl-lithium (5.5 ml, 9.4 mmol in hexane) was added in one portion to a stirred solution of a 3 : 2 mixture of *cis*- and *trans*-2-bromo-2′-methoxystilbene (6.0 g) in anhydrous ether (50 ml) under nitrogen at room temperature. A deep orange colour developed almost immediately, at which point the reaction mixture was poured directly onto freshly crushed solid carbon dioxide under a current of nitrogen. After all the carbon dioxide had evaporated, hydrochloric acid (50 ml; 2M) was added and the mixture extracted with ethyl acetate (2 × 30 ml). The organic layers were separated and washed with water (2 × 25 ml) followed by saturated aqueous sodium hydrogencarbonate (2 × 30 ml). The combined basic extracts were carefully acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 × 25 ml). The residue obtained upon work-up was the mixture of *cis*- and *trans*-acids (0.6 g) from which the *product* was obtained (140 mg, 2%) as colourless prisms, m.p. 163—165 °C (Found: M^+, 254.093 77. $C_{16}H_{14}O_3$ requires *M*, 254.094 278); δ 3.80 (3 H, s, OCH_3), 6.5—7.4 (9 H, m, Ar-H and *cis* CH=CH), and 7.9—8.2 (1 H, dd, *J* 3 and 6 Hz, 3-H).

2-[2-*Hydroxy*-2-(2-*methoxyphenyl*)]*ethyl*-N-*methylbenzamide* (34).—The general method of Vaulx [10] was employed, using in this case 2-methoxybenzaldehyde. Work-up of the reaction gave the *product* (65%), as colourless prisms, m.p. 188—189 °C (propan-2-ol) (Found: C, 71.55; H, 6.65; N, 4.85. $C_{17}H_{19}NO_3$ requires C, 71.6; H, 6.65; N, 4.9%), δ 2.9—3.2 (2 H, m, CH_2), 2.97 (3 H, d, *J* 5 Hz, NCH_3), 3.90 (3 H, s, OCH_3), 5.03 (1 H, d, *J* 6 Hz, OH, D_2O exchangeable), 5.1—5.4 (1 H, m, CH), 6.4—6.7br (1 H, NH), and 6.8—7.6 (8 H, m, ArH).

2-[2-*Hydroxy*-2-(4-*methoxyphenyl*)]*ethyl*-N-*methylbenzamide* (35).—Prepared as for compound (34), the *product* (69%) formed microneedles, m.p. 153—155 °C (propan-2-ol) (Found: C, 71.5; H, 6.7; N, 4.85. $C_{17}H_{19}NO_3$ requires C, 71.6; H, 6.65; N, 4.9%), δ 2.9—3.2 (2 H, m, CH_2), 2.98 (3 H, d, *J* 5 Hz, NCH_3), 3.90 (3 H, s, OCH_3), 4.85 (1 H, dt, $J_{1,2} = J_{2,OH}$, 5 Hz, $J_{1',2}$ 7 Hz, 2-CH), 5.30 (1 H, d, *J* 5 Hz, OH, D_2O exchangeable), 6.4—6.7 br (1 H, NH), 6.87 (2 H, d, *J* 9 Hz, 3′- and 5′-H), 7.35 (2 H, d, *J* 9 Hz, 2′- and 6′-H), and 7 .1—7.5 (4 H, m, ArH).

3,4-*Dihydro*-3-(4-*methoxyphenyl*)-1H-2-*benzopyran*-1-*one* (27).—Compound (35) (2.50 g, 8.7 mmol) was heated at 190—200 °C for 1.5 h during the passage of dry nitrogen to expel the methylamine. Chromatography (eluant 30% ethyl acetate–light petroleum) afforded the *product* (1.45 g, 65%) which was identical (m.p., t.l.c., and n.m.r. spectroscopy) with material described earlier. Later fractions gave *trans*-acid (13) (0.56 g, 25%), identical by the same criteria with authentic material.

3,4-*Dihydro*-3-(2-*methoxyphenyl*)-1H-2-*benzopyran*-1-*one* (29).—Compound (34) (1 g, 3.5 mmol) was heated at 190—200 °C for 17 h to expel all methylamine which was detected with moist indicator paper. The residue on chromatography (30% ethyl acetate–light petroleum) gave the *product* (0.61 g, 69%) as rhombohedra, m.p. 121—123 °C (Found: C, 75.5; H, 5.45. $C_{16}H_{14}O_3$ requires C, 75.6; H, 5.5%); $\nu_{max.}$ 1 728 cm^{-1}, δ 3.16 (2 H, d, *J* 7.5 Hz, CH_2), 3.84 (3 H, s, OCH_3), 5.94 (1 H, t, *J* 7.5 Hz, CH), 6.92 (1 H, d, *J* 9 Hz, 3′-H), 7.04 (1 H, t, *J* 8 Hz, 5′-H), 7.2—7.7 (5 H, m, ArH), and 8.18 (1 H, d, *J* 2 and 7 Hz, 8-H); *m/z* 254 (M^+, 80%), 119 (40%), 118 (100%), and 90 (78%). Later fractions gave the *trans*-acid (15) (0.045 g, 5%), identical (m.p., t.l.c., and n.m.r.) to material described below.

3,4-*Dihydro*-3-(2-*hydroxyphenyl*)-1H-2-*benzopyran*-1-*one* (30).—Following the procedure for demethylating compound (27) above, compound (29) (0.3 g, 1.2 mmol) was treated with boron tribromide (0.36 ml, 3.6 mmol). The residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate–light petroleum) to give the *product* (0.6 g, 71%) as pale yellow spears, m.p. 178—179 °C (ethyl acetate–light petroleum) (Found: C, 74.85; H, 5.0. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0%), $\nu_{max.}$ 3 490 and 1 705 cm^{-1}; δ 3.24 (2 H, d, *J* 7.5 Hz, CH_2), 5.93 (1 H, t, *J* 7.5 Hz, CH), 6.75—7.7 (7 H, m, ArH), 8.12 (1 H, dd, *J* 2 and 7 Hz, 8-H), and 8.75 (1 H, s, OH); *m/z* 240 (M^+, 95%), 222 (73%), 194 (100%), 165 (35%), 133 (21%), 118 (70%), 107 (37%), and 90 (70%).

trans-2′-*Methoxystilbene*-2-*carboxylic Acid* (15).—The isocoumarin (29) (1 g, 3.9 mmol) and potassium t-butoxide (1.12 g, 10 mmol) were heated under reflux in dry tetrahydrofuran (50 ml) for 3.5 h. Work-up as for compound (14) gave a pale yellow solid (1 g) which was chromatographed (eluant 30% ethyl acetate–light petroleum) to give the product (0.8 g, 80%) as pale yellow needles, m.p. 165—167 °C (aqueous propan-2-ol) (Found: C, 75.25; H, 5.65. $C_{16}H_{14}O_3$ requires C, 75.6; H, 5.5%), δ 3.88 (3 H, s, OCH_3), 6.91 (1 H, d, *J* 9 Hz, 3′-H), 6.98 (1 H, t, *J* 8 Hz, 5′-H), 7.41 and 8.11 (1 H each, d, *J* 16 Hz, *trans*-CH=CH), 7.15—7.90 (5 H, m, Ar-H), and 8.06 (1 H, dd, *J* 2 and 7 Hz, 3-H).

trans-2′-*Hydroxystilbene*-2-*carboxylic Acid* (16).—The isocoumarin (30) (0.15 g, 0.6 mmol) was boiled with potassium t-butoxide (0.112 g, 1 mmol) in dry tetrahydrofuran (25 ml) for 3.5 h. Work-up as for compound (14) gave the *product* (0.10 g, 67%) as colourless microprisms, m.p. 144—146 °C (ethyl acetate–light petroleum) (Found: C, 74.8; H, 5.1. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.0%), δ (CD_3COCD_3) 4.6—6.4br (1 H, OH, D_2O exchangeable), 7.47 and 8.12 (1 H each, d, *J* 17 Hz, CH=CH), 6.75—8.1 [11 H (10 H after D_2O exchange), m, ArH and OH]; *m/z* 240 (M^+, 71%), 222 (62%), 194 (100%), 155 (68%), 133 (18%), and 107 (29%).

3-*Phenylmethylisobenzofuran*-1(3H)-*one* (22).—This compound was prepared by the method of Booth and Turner; [5] $\nu_{max.}$ 1 742 cm^{-1}; δ 3.12 and 3.29 (1 H each, dd, *J* 7 and 14 Hz, CH_2), 6.68 (1 H, t, *J* 7 Hz, CH), 7.0—7.75 (8 H, m, ArH), and 7.84 (1 H, dd, *J* 2 and 7 Hz, 7-H); *m/z* 224 (M^+, 53%), 134 (33%), 133 (100%), 105 (35%), 91 (67%), and 77 (35%).

3-(2-*Methoxyphenylmethyl*)*isobenzofuran*-1(3H)-*one* (23).—3-(2-Methoxyphenylmethylene)isobenzofuran-1(3H)-one [11] (0.5 g) was hydrogenated using the method described for the synthesis of the 4-methoxy-analogue (21). The solution was filtered, and the solvent evaporated off. Chromatography (30% ethyl acetate–light petroleum) afforded the *product* (0.45 g, 89%), m.p. 64—66 °C (propan-2-ol) (lit.,[11] 76—77 °C), $\nu_{max.}$ 1 762 cm^{-1}; δ 3.09 and 3.30 (1 H each, 2 × dd, *J* 7 and 14 Hz, CH_2), 3.82 (3 H, s, OCH_3), 5.76 (1 H, t, *J* 7 Hz, CH), 6.87 (1 H, d, *J* 7 Hz, 3′-H), 6.95—7.7 (6 H, m, ArH), and 7.86 (1 H, dd, *J* 2 and 7 Hz, 7-H); *m/z* 254 (M^+, 18%), 133 (33%), 121 (100%), and 91 (72%).

Thermal Reaction of cis-2′-*Methoxystilbene*-2-*carboxylic Acid* (10).—The acid (0.6 g) was heated at 200 °C for 1.5 h and then dissolved in ether (50 ml). The solution was extracted with saturated aqueous sodium hydrogencarbonate (2 × 30 ml), and the extract carefully acidified with hydrochloric acid; this was then extracted with ether (2 × 20 ml). The residue obtained upon work-up of the extract was chromatographed (30% ethyl acetate–light petroleum) to afford compound (29) (0.22 g, 37%) identical with authentic material (m.p., t.l.c., and n.m.r. spectroscopy). The basic aqueous layer afforded a mixture (0.13 g, 22%) of the *cis*- and *trans*-acids (10) and (15) (ratio 1 : 3 by n.m.r. spectroscopy).

Thermal Reaction of trans-2′-*methoxystilbene*-2-*carboxylic Acid* (15).—The acid (15) (173 mg) was heated at 200 °C for 5 h. Following the previous procedure, the neutral fraction afforded a residue (87 mg) which was chromatographed as above to afford compound (29) (68 mg, 39%). The basic aqueous layer gave a mixture (62 mg, 36%) of the *cis*- and *trans*-acids (10) and (15) (ratio 1 : 10).

Thermal Reaction of 3,4-*Dihydro*-3-(4-*methoxyphenyl*)-1H-2-*benzopyran*-1-*one* (27).—(a) Compound (27) (340 mg) was heated at 200 °C for 17 h. Chromatography (eluant 30% ethyl acetate–light petroleum) gave first unchanged compound (27) (198 mg, 58%) followed by a mixture (54 mg, 16%) of the *cis*- and *trans*-acids (10) and (15) (1 : 10 by integration). (b) On being heated for 1.5 h, the *cis*-acid could not be detected.

Thermal Reaction of 3,4-*Dihydro*-3-(2-*methoxyphenyl*)-1H-2-*benzopyran*-1-*one* (29).—Compound (29) (192 mg) was heated at 200 °C for 17 h. Chromatography (eluant as above) gave first unchanged lactone (169 mg, 88%) followed by *trans*-acid (10 mg, 5%).

3-(4-*Nitrophenylmethyl*)*isobenzofuran*-1(3H)-*one* (24) and 3-(4-*Nitrophenylmethyl*)-6-*nitroisobenzofuran*-1(3H)-*one* (40).—Prepared by a modification of the method of Berti and Marsili [14] for compound (24). 3-Benzylphthalide (0.25 g) was added in one portion to a mixture of sodium nitrate (0.1 g) and concentrated sulphuric acid (2.5 ml) at room temperature. The mixture immediately became yellow and an exothermic reaction ensued. The mixture darkened during 5 min, after which it was poured onto crushed ice–water, and then filtered. T.l.c. indicated a number of products. Column chromatography yielded 3-(4-*nitrophenylmethyl*)*isobenzofuran*-1(3H)-*one* (24) as the major component (63 mg, 25%), m.p. 166—168 °C (lit.,[14] 162—164 °C), $\nu_{max.}$ 1 749 cm^{-1}; δ 3.24 (1 H, dd, *J* 7 and 14 Hz, CH_2), 3.49 (1 H, dd, *J* 5 and 14 Hz, CH_2), 5.77 (1 H, dd, *J* 5 and 7 Hz, CH), 7.39 (2 H, d, *J* 9 Hz, 2- and 6-H). 8.12 (2 H, d, *J* 9 Hz, 3- and 5-H), and 7.2—8.2 (4 H, m, ArH); *m/z* 269 (7%), 133 (100%), 105 (31%), and 77 (30%). Later fractions afforded 3-(4-*nitrophenylmethyl*)-6-*nitroisobenzofuran*-1(3H)-*one* (40) (17 mg, 5%), m.p. 157—158 °C (propan-2-ol) (Found: C, 57.0; H, 2.95; N, 8.8. $C_{15}H_{10}N_2O_6$ requires C, 57.3; H, 3.2; N, 8.9%), $\nu_{max.}$ 1 759 cm^{-1}; δ 3.30 (1 H, dd, *J* 7 and 14 Hz, CH_2) 3.52 (1 H, dd, *J* 5 and 14 Hz, CH_2), 5.89 (1 H, dd, *J* 5 and 7 Hz, CH), 7.40 (2 H, d, *J* 9 Hz, 2′- and 6′-H), 7.58 (1 H, d, *J* 9 Hz, 4-H), 8.16 (2 H, d, *J* 9 Hz, 3′- and 5′-H) 8.57 (1 H, dd, *J* 2 and 9 Hz, 5-H), and 8.67 (1 H, d, *J* 2 Hz, 7-H); *m/z* 314 (4%), 178 (100%), and 133 (32%).

trans-4′-*Nitrostilbene*-2-*carboxylic Acid* (17).—This compound had the following n.m.r. spectral properties: δ 7.02 and 8.30 (1 H each, d, *J* 16 Hz, olefinic H), 7.67 (2 H, d, *J* 9 Hz, 2′- and 6′-H), 8.21 (2 H, d, *J* 9 Hz, 3′- and 5′-H), and 7.3—8.15 (4 H, m, Ar-H).

Thermal Reaction of trans-4′-*Nitrostilbene*-2-*carboxylic Acid* (17).—The acid (17) (50 mg) was heated at 200 °C for 1.5 h. The product was dissolved in methylene chloride and extracted with saturated aqueous sodium hydrogencarbonate. The organic layer was worked up and chromatographed (eluant 20% ethyl acetate–light petroleum) to afford compound (24) (15 mg, 30%) identical with authentic material (m.p., t.l.c., i.r., n.m.r., and mass spectroscopy). The basic solution yielded acid (17) (14 mg, 28%).

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