# Electrochemical Oxidation of Aromatic Ethers. Part 4.[1] Intramolecular Coupling of Diaryl Esters

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A series of methoxylated aryl benzoates have been converted by controlled potential anodic oxidation into inter-molecularly coupled products. In the case of 4-methoxyphenyl benzoate and 4-methoxyphenyl 3-methoxy-benzoate the products are ' *ortho* '-coupled biphenyls and *o*- and *p*-quinones derived from them by further oxidation. In contrast to methoxylated *N*-benzyl-*N*-methylphenylacetamides, which form the corresponding dibenz[*c,e*]-azocin-7-ones on anodic oxidation, the analogous benzyl phenylacetates give ' dimeric ' and ' trimeric ' products. The mechanisms of the reactions are discussed in terms of the stereochemistry and the substitution patterns of the starting esters.

DURING previous work [1] we have shown that the electro-chemical oxidation of secondary amides (1; R = H) leads to electrode filming, but that their tertiary counterparts, *e.g.* (1; R = Me; $x = 1$, $y = 0$ or $x = y = 1$) afford dibenz[*c,e*]azepin-5-ones (2; $x = 1$, $y = 0$) and dibenz-[*c,e*]azocin-7-ones (2; $x = y = 1$), respectively. In these and related reactions [2] no intermolecularly coupled products were isolated, although the yields obtained were often low, and invariably coupling occurred *para* to an existing methoxy-substituent.

(1)　　　　　**(2)**
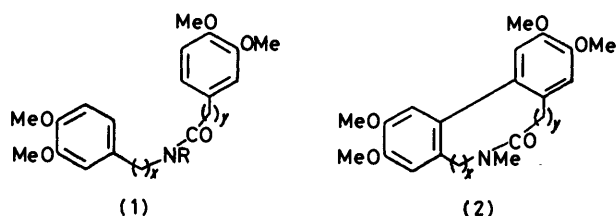
Heterocycles of type (2) are of some pharmaceutical interest, particularly when unsubstituted at nitrogen, but the reason(s) for the filming of the secondary amides required for their production is still unknown. Since lactones are readily converted into lactams, we turned our attention to the anodic oxidation of diaryl esters and

(3)　　　　　**(4)**
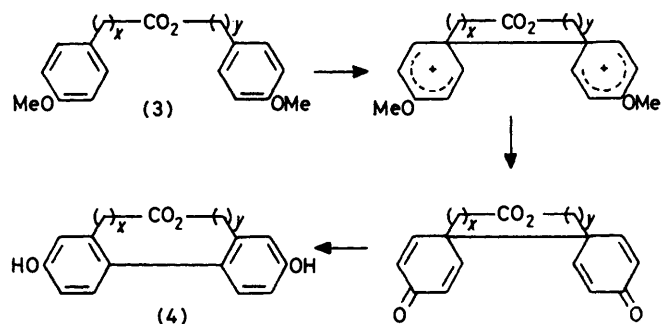
in particular the synthesis of lactones of type (4), which might be expected as the products, through dienone-phenol rearrangements, of the coupling of bis-4-methoxy-aryl esters of general structure (3).

However, the cyclic voltammogram of the ester (3;

$x = y = 1$) showed a stable two-electron redox couple at 1.4 V (*vs.* s.c.e.) and no evidence of chemical products. This suggests that the required mode of coupling is both electronically and stereochemically disfavoured. A pre-parative experiment conducted with this substrate at an anode potential of $+1.4$ V resulted in slow filming of the working electrode, and on work-up mainly starting ma-terial was recovered, together with some polymer.

In view of the successful intramolecular cyclisation of the amide (1; R = Me, $x = y = 1$) [1] we examined next 3,4-dimethoxybenzyl 3,4-dimethoxyphenylacetate (5; $x = y = 1$). The cyclic voltammogram of this compound showed only a two-electron redox couple at 1.1 V (*vs.* s.c.e.) and a preparative electro-oxidation at this anode potential gave only resins.† On the other hand the cyclic voltammetric trace of its homologue (5; $x = 1$, $y = 2$) showed, after the initial sweep, additional anodic peaks at 0.7 and $+0.9$ V due to chemical products. Preparative electrolysis as before gave ' dimeric ' and ' trimeric ' substances which are considered to be com-pounds (6; $n = 2$) and (6; $n = 3$), respectively.

(5)　　　　　**(6)**
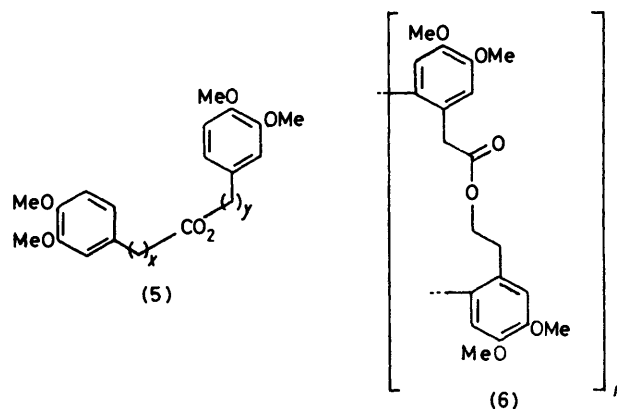
Parker and Ronlán [3] have already commented that the transition states required for the formation of eight- and nine-membered rings *via* electrochemical coupling of diarylalkanes are sterically crowded, and that this leads to the occurrence of inter- rather than intra-molecular reactions. Our results support this conclusion

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† We thank Mr. Robin Maskell for conducting this experiment.

[1] Part 3, M. Sainsbury and J. Wyatt, *J.C.S. Perkin I*, 1976, 661.

[2] S. Tobinaga, *Bio-organic Chem.*, 1975, **4**, 110, and references cited therein.

[3] V. D. Parker and A. Ronlán, *J. Amer. Chem. Soc.*, 1975, **97**, 4714.

and in the case of (5; $x = y = 1$) it seems likely that a number of products are formed, none, however, in sufficient concentration to give rise to recognisable peaks during cyclic voltammetric analysis. Significantly, models show that the greater double bond character of the amide CN function in (1; R = Me, $x = y = 1$) in comparison with that of the corresponding ester CO function in (5; $x = y = 1$) increases the probability of internal coupling from both the standpoints of configuration and conformation.[4]

The initial cyclic voltammogram (Figure, curve 1) of 4-methoxyphenyl 3-methoxybenzoate (7; R = OMe)
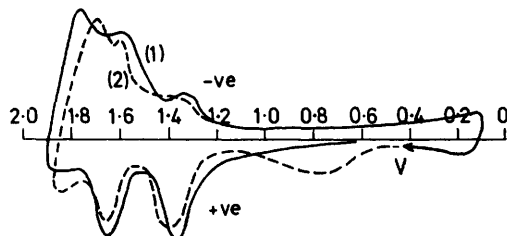

Cyclic voltammograms of 4-methoxyphenyl 3-methoxybenzoate

shows anodic peaks at $+1.35$ and $+1.66$ V, the first being due to the removal of an electron from the relatively activated *para*-disubstituted ring and the second arising from oxidation of the 3-methoxybenzoyl unit. On subsequent complete scans (curve 2) an additional non-reversible peak at $+0.8$ V (*vs.* s.c.e.) was observed. However, if the sweep was terminated at $+1.4$ V this extra peak was eliminated. A preparative experiment stopped after the consumption of the equivalent of 3 F mol^{-1} afforded three products, the biphenyl derivative (8; R = OMe), the substituted 1,4-benzoquinone (10; R = OMe), and 3-methoxybenzoic acid. In this electro-oxidation the current density was 60—100 mA and under these conditions the anode potential, set initially at $+1.4$ V, tended to drift to higher values but was never allowed to exceed $+1.5$ V. Repetition of the experiment at low current density, where the anode potential was more readily maintained at $+1.4$ V, and termination after only the equivalent of 1 F mol^{-1} of current had been consumed, gave the biphenyl in high yield. No other products were isolated. The cyclic voltammogram of this product showed redox couples at 1.35 and 1.45 V on the first scan and a small product peak at 0.8 V on subsequent sweeps.

A preparative electro-oxidation of the biphenyl derivative at an anode potential of $+1.45$ V (utilization of current 2 F mol^{-1} equivalent) gave the benzoquinone (10; R = OMe) and 3-methoxybenzoic acid.

Literature reports[5] suggest that 1,4-benzoquinone is oxidised at $+0.8$ V, and in view of this we considered at first that the anodic peak at 0.8 V in our cyclic voltammograms was due to the 1,4-benzoquinone (10; R = OMe). However, examination of the product showed that it is inert at this potential; similarly very carefully

[4] B. F. Pederson, *Acta Chem. Scand.*, 1967, **21**, 1422.
[5] S. Ikenoya, M. Masui, H. Ohmori, and H. Sayo, *J.C.S. Perkin II*, 1974, 571, and references cited therein.

purified 1,4-benzoquinone, in our hands, shows no oxidation peak at this potential; indeed, no electron loss was observed below $+2.0$ V.

We may now rationalize the formation of the electrolysis products as shown in Scheme 1, but the overall re-
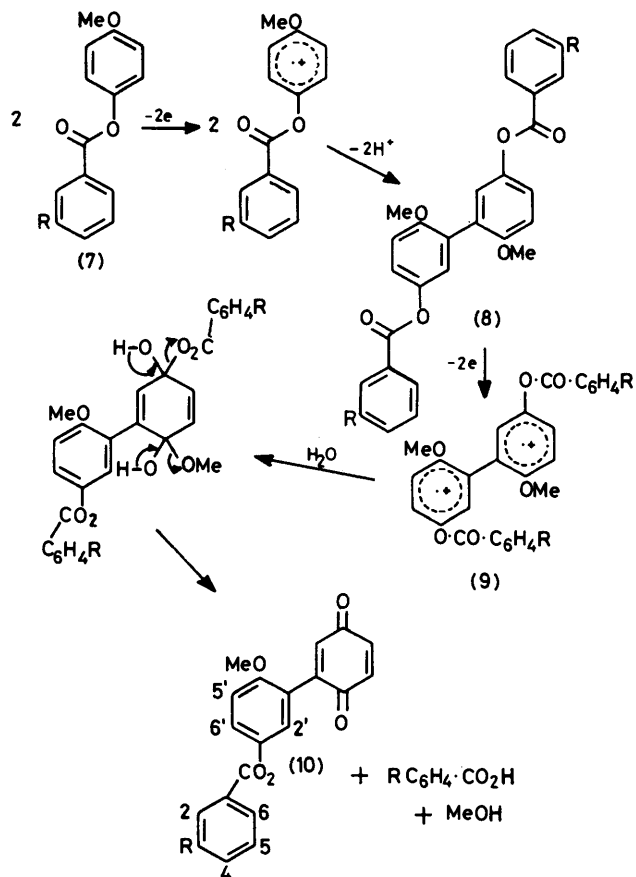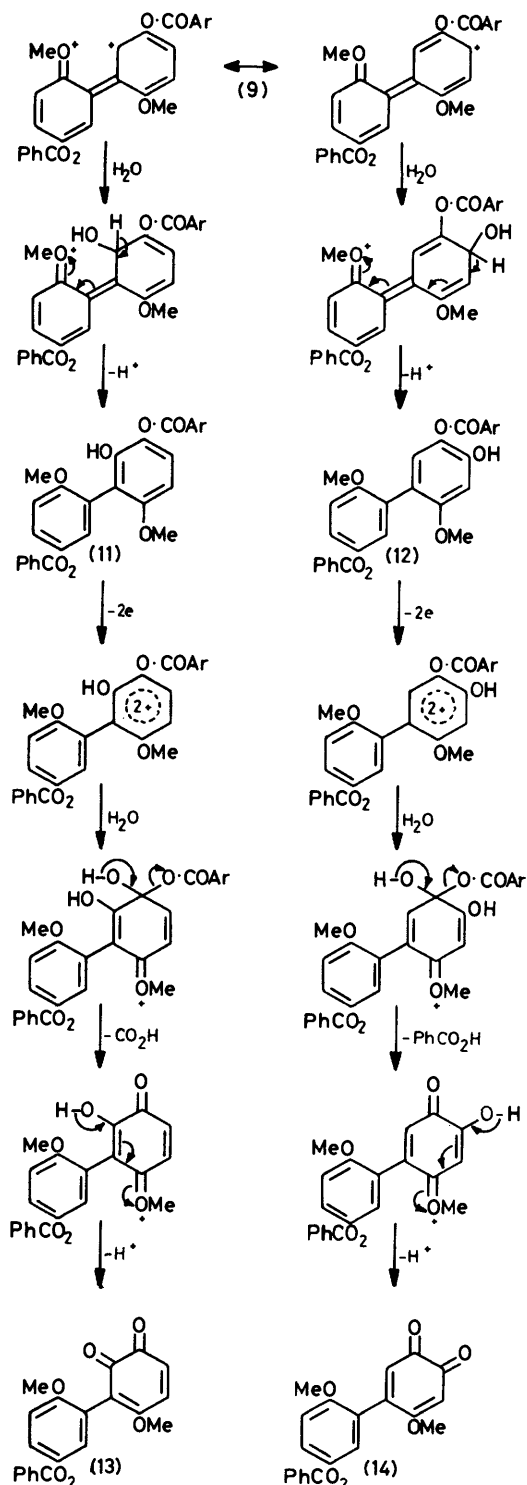

SCHEME 1

quirement for the equivalent of 3 F mol^{-1} of (7; R = OMe) remains unaccounted for, since only 2 F are required by this sequence. (It should be noted that although the acetonitrile used in our experiments was previously dried, no effort was made to exclude moisture during the electrolyses and the cells employed were open to the air throughout.)

The biphenyl and 1,4-benzoquinone products are rare examples of electrochemically ' *ortho* '-coupled compounds, and to prove that the 3-methoxybenzoyl unit did not participate in their formation the above experiments were repated with 4-methoxyphenyl benzoate (7; R = H). The cyclic voltammograms of this compound were identical with those of its derivative (7; R = OMe) except that the 1.66 V redox couple of the latter was not observed below 2.0 V. A preparative low current density electro-oxidation at $+1.4$ V anode potential (1 F mol^{-1} equivalent) gave the biphenyl (8; R = H), and an oxidation at $+1.4$ to $+1.5$ V and the consumption of the equivalent of 3 F mol^{-1} of current afforded the 1,4-benzoquinone (10; R = H) and benzoic acid.

Scheme 2

This substrate, like its predecessor (7; R = OMe), showed a product peak at +0.8 V during cyclic voltammetry; such a peak appears in the voltammograms of

other 4-methoxylated benzoates and also in those of monomethoxyphenols, although here it is present as part of a well defined redox couple and is observed in the initial as well as in the subsequent scans.

An additional substance isolated in small yield from the oxidation of (7; R = H) was bright red in colour, and i.r. and u.v. spectra [6] indicated the presence of an *ortho*-quinone unit. [1]H H.m.r. analysis showed it to be a mixture of the two isomers (13) and (14), and the formation of these products can be rationalized as shown in Scheme 2.* The intermediacy of the phenols (11) and (12) and their subsequent oxidation then accounts for the +0.8 V anodic peak in the voltammogram of the starting material and partly for the requirement of the third molecular equivalent of current in the overall electro-oxidation of (7; R = H).

The yield of the 1,2-benzoquinones (13) and (14) was very low (<8%), and we suppose analogous structures are formed during the electro-oxidation of (7; R = OMe). Certainly, several highly coloured bands were noted during the chromatographic separation of the products, but on work-up these only led to small quantities of complex mixtures which, so far, we have not examined.

EXPERIMENTAL

All preparative electrolyses were conducted with an H-type cell of 200 cm³ capacity, with ' dry ' acetonitrile as solvent and anhydrous sodium perchlorate as supporting electrolyte. The anode was of platinum gauze (area 80 cm²) and the cathode a mercury pool. Current was provided by a Farnell stabilized power supply and the potential of the anode was monitored with a digital voltmeter *via* an agar bridge and a standard calomel electrode (s.c.e.)

Cyclic voltammetry was carried out under the same electrolyte conditions, but using a platinum wire anode and a ' home-made ' waveform generator, the design and circuit diagram of which are due to Dr. J. H. P. Utley, Queen Mary College, London.

U.v. spectra were recorded for solutions in aqueous 95% ethanol; i.r. spectral data refer to Nujol mulls; [1]H n.m.r. spectra were recorded at 100 MHz with tetramethylsilane as internal standard.

Electro-oxidation of 3,4-Dimethoxyphenylethyl 3,4-Dimethoxyphenylacetate (5; x = 1, y = 2).—The title compound (1 g) was added to the anode compartment of the cell, which contained a 10% solution of sodium perchlorate in acetonitrile. The electrolysis was conducted at a controlled anode potential of 1.10 V until the equivalent of 1.9 F mol⁻¹ of substrate had been utilized; then the contents of the anode compartment were separated and diluted with water (200 cm³). Most of the acetonitrile was removed by distillation and the solution was then extracted several times with chloroform. Evaporation of the combined extracts afforded a gum which was chromatographed on silica gel [elution with ethyl acetate–petroleum (b.p. 60—80 °C)] to yield two components, both amorphous solids.

The first, considered to have the dimeric structure (6; n = 2), showed m/e 716 (M⁺); v$_{max.}$ 1 725, 1 600, and 1 585 cm⁻¹; δ (CDCl₃) 2.65 (4 H, t, J 6.5 Hz), 3.34—3.52 (4 H, m),

* Although we have shown certain steps in both Schemes 1 and 2 occurring *via* the simultaneous loss of two electrons, it is most probable that step-wise e.c.e. processes are involved.

[6] See R. A. Morton in ' Biochemistry of Quinones,' Academic Press, London and New York, 1965, ch. 1; E. Adler and G. Anderson, *Annalen*, 1976, 718, 1435.

3.8 (24 H, s, 8 × OCH$_3$), 4.25 (4 H, t, J 6.5 Hz), and 6.50—6.50—6.90 (8 H, m). It could not be crystallised satisfactorily and melted over a 20 °C range. The second product (6; $n = 3$) exhibited m/e ca 1 074 (M^+), and was even more difficult to purify; however, in the ^{1}H n.m.r. spectrum (CDCl$_3$) the ratio of aromatic to aliphatic proton signals was 2 : 9 as required for structure (6; $n = 3$).

2,2'-Dimethoxy-5,5'-bis-(3-methoxybenzoyloxy)biphenyl (8; R = OMe).—4-Methoxyphenyl 3-methoxybenzoate (1 g) was oxidised in the usual way at an anode potential of +1.4 V, the cell current being maintained at ca. 50 mA (1F mol^{-1} current utilization). Column chromatography on silica gel [elution with 20% ethyl acetate in petroleum (b.p. 60—80 °C)] gave the *diester* (8; R = OMe) as a crystalline solid, which was recrystallized from ethyl acetate; yield 0.64 g (65%); m.p. 113—114 °C; m/e 514 (M^+); λ$_{max.}$ 224 (ε 31 400), 241 (28 400), and 292 nm (15 500); ν$_{max.}$ 1 732, 1 601, and 1 590 cm^{-1}; δ (CDCl$_3$) 3.72 (6 H, s, 2 × OCH$_3$), 3.82 (6 H, s, 2 × OCH$_3$), 6.90br (2 H, d, J 9 Hz), 6.95—7.28 (6 H, m), 7.38 (2 H, t, J 7 Hz), 7.69br (2 H, t, J 2 Hz), and 7.72br (2 H, dt, J 7 and 2 Hz). The signals at δ 7.38, 7.69, and 7.72 arise from the 5-, 6-, and 2-protons, respectively, of the 3-methoxybenzoyl fragments ($J_{2.4} = J_{2.6} = 2$ Hz; $J_{4.5} = J_{5.6} = 7$ Hz), and the doublet at 6.90 from the 3- and 3'-protons of the biphenyl nucleus (Found: C, 70.0; H, 5.1. C$_{30}$H$_{26}$O$_8$ requires C, 70.0; H, 5.1%).

3-(1,4-Benzoquinon-2-yl)-4-methoxyphenyl 3-Methoxybenzoate (10; R = OMe).—A repetition of the above experiment, but allowing 3 F mol^{-1} equivalent of current to be utilized, gave on work-up a red oil. G.l.c. analysis (10% OV1 on Chromosorb W, AW/DCMS, at 237 °C) showed two peaks, that of lower retention being due to 3-methoxybenzoic acid (identified by direct comparison and g.l.c.–mass spectrometric studies with an authentic sample). The oil was chromatographed on silica gel [elution with ethyl acetate–petroleum (b.p. 60—80 °C) mixtures]. Initial fractions contained 3-methoxybenzoic acid (identification confirmed by mixed m.p. *etc.*) and subsequent ones a red oil. After some weeks, the oil slowly crystallised to afford the *quinone* (10; R = OMe) as yellow prisms (from methanol) (0.32 g, 45%). On some occasions red crystals of the same material were obtained. Both forms have m.p. 82—84 °C; m/e 364 (M^+); λ$_{max.}$ 241 (ε 19 400), and 283 nm (8 200); ν$_{max.}$ 1 735, 1 655, 1 610, and 1 600 cm^{-1}; δ (CDCl$_3$) 3.77 (3 H, s, OCH$_3$), 3.82 (3 H, s, OCH$_3$), 6.70—6.80 (3 H, m, 1,4-benzoquinonyl group), 6.88 (1 H, d, $J_{5'.6'}$ 9 Hz, H-5'), 6.94 (1 H, d, $J_{2'.6'}$ 2.5 Hz, H-2'), 7.04 (1 H, dt, $J_{4.5}$ 7.5, $J_{2.4} = J_{4.6} = 17$ Hz, H-4), 7.15 (1 H, dd, $J_{5'.6'}$ 9, $J_{2'.6'}$ 2.5 Hz, H-6'), 7.3 (1 H, t, $J_{4.5} = J_{5.6} = 7.5$ Hz, H-5), 7.59 (1 H, t, $J_{2.4} = J_{2.6} = 1.7$ Hz, H-2), and 7.67 (1 H, dt, $J_{5.6}$ 7.5, $J_{2.6} = J_{4.6} = 1.7$ Hz, H-6) (Found: C, 69.2; H, 4.4. C$_{21}$H$_{16}$O$_6$ requires C, 69.2; H, 4.4%).

5,5'-Benzoyloxy-2,2'-dimethoxybiphenyl (8; R = H).—Oxidation of 4-methoxyphenyl benzoate (7; R = H) as for its derivative (7; R = OMe) at an anode potential of +1.4

V and an equivalent current utilization of 1 F mol^{-1} gave the *diester* (8; R = H) as a solid (70%), m.p. 161—163 °C (from ethyl acetate); m/e 454 (M^+); λ$_{max.}$ 241 (ε 17 400) and 273 nm (9 800); ν$_{max.}$ 1 730, 1 598, and 1 579 cm^{-1}; δ (CDCl$_3$) 3.80 (6 H, s, 2 × OCH$_3$), 6.9 (2 H, d, J 9 Hz), 7.1—7.3 (4 H, m), 7.38—7.6 (6 H, m), and 8.08 (4 H, dt, J 7 and 2 Hz) (Found: C, 74.0; H, 4.75. C$_{28}$H$_{22}$O$_6$ requires C, 74.0; H, 4.9%).

3-(1,4-Benzoquinon-2-yl)-4-methoxyphenyl Benzoate (10; R = H).—This compound together with benzoic acid was obtained from the anodic oxidation of 4-methoxyphenyl benzoate at +1.4 V after the equivalent of 3 F mol^{-1} of current had been consumed. It was isolated as a yellow *oil* which did not crystallize; m/e 334 (M^+); λ$_{max.}$ 241 (ε 23 000) and 280 nm (7 770); ν$_{max.}$ 1 735, 1 650, 1 605, and 1 595 cm^{-1}; δ (CDCl$_3$) 3.80 (3 H, s, OCH$_3$), 6.8—6.9 (3 H, m), 7.0 (1 H, d, $J_{5'.6'}$ 9 Hz, H-5'), 7.10 (1 H, d, $J_{2'.6'}$ 2.5 Hz, H-2'), 7.30 (1 H, dd, $J_{5'.6'}$ 9, $J_{2'.6'}$ 2.5 Hz, H-6'), 7.5—7.65 (3 H, m), and 8.20br (2 H, dt, J 7 and 2 Hz, H-2 and -6) (Found: C, 71.8; H, 4.2. C$_{20}$H$_{14}$O$_5$ requires C, 71.85; H, 4.2%).

3-(4-Methoxy-1,2-benzoquinonyl)-4-methoxyphenyl Benzoate (13) *and* 4-(3-Methoxy-1,2-benzoquinonyl)-4-methoxyphenyl *Benzoate* (14).—These compounds were obtained in late fractions [20% ethyl acetate in petroleum (b.p. 60—80 °C)] from the chromatographic separation in the previous experiment. T.l.c. suggested the presence of a single compound, and the material crystallized as bright red prisms, m.p. 142—144 °C; m/e 364 (M^+), 258 (13%), 104 (50%), and 76 (100%); λ$_{max.}$ 235 (ε 14 500), 270sh (10 000), 320sh (3 100), and 360sh nm (1 270); ν$_{max.}$ 1 730, 1 680, 1 669sh, 1 644, 1 630, 1 610sh, and 1 596 cm^{-1}. The ^{1}H n.m.r. spectrum (CDCl$_3$) shows a typical pattern for the (3-substituted 4-methoxyphenyl) benzoate unit, but the signals are slightly more broad than usual: δ [numbering system as for structure (10)] 3.88 (3 H, s, OCH$_3$), 7.0 (1 H, d, $J_{5'.6'}^{i}$ 9 Hz, H-5'), 7.09 (1 H, d, J 3 Hz, H-2'), 7.29 (1 H, dd, $J_{5'.6'}$ 9, $J_{2'.6'}$ 3 Hz, H-6'), 7.5—7.65 (3 H, m), and 8.20br (2 H, dt, J 7 and 2 Hz, H-2 and -6'). In addition, an extra 3 H singlet at δ 3.80 was observed (OMe) and a doublet (J 3.75 Hz) at δ 5.98 coupled to a similar signal at δ 6.80. Another pair of coupled signals, now simply broadened singlets (J 1.0 Hz) occurred at δ 6.02 and 6.82. These signals are due to the protons of the 1,2-benzoquinonyl units present in (13) and (14), respectively. Integrated intensities suggest that these compounds exist in the mixture in the ratio 3 : 1. Despite a number of attempts the mixture could not be completely separated; the components crystallized together (Found: C, 68.9; H, 4.1. Calc. for C$_{21}$H$_{16}$O$_6$: C, 69.2; H, 4.4%).