Intramolecular Coupling of Diaryl Amides by Anodic Oxidation

By **Malcolm Sainsbury** * and **John Wyatt**, School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY

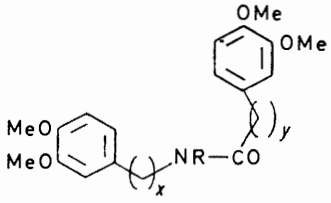
A series of diaryl amides have been converted by electrochemical oxidation into biphenyl derivatives. Limitations to this type of intramolecular coupling reaction, both steric and electronic, are discussed, and some novel dibenzazepine and dibenzazocine structures are described.

PHENOLIC oxidative coupling reactions are frequently key steps in the biosynthesis of natural products, particularly alkaloids.[1] Such reactions can often be replicated in the laboratory by using inorganic oxidants in alkaline media but, although this is an important synthetic route to several structures of pharmacological interest, yields in general are low and the work-up procedure is complicated by the necessity of handling polyhydric phenols in the presence of strong base.

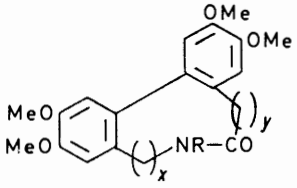
Other methods of aryl–aryl coupling, such as Pschorr or photochemical reactions, are also commonly employed in synthesis but each presents problems either in the inaccessibility of starting materials or in non-selectivity.

Hence there is a requirement for a more convenient technique of aryl–aryl coupling, and it has been claimed that for oxygenated ring systems this is provided by controlled anodic oxidation.[2] Thus electrochemical oxidation of aryl alkyl ethers at low anode potentials (*ca.* 1 V) generates radical cations which then undergo coupling and further oxidation to afford biphenyls. Previously, however, most examples illustrating this method have been directed at specific targets in which the aryl nuclei to be joined are favourably disposed to one another. Here we report a series of experiments designed to test steric requirements for intramolecular cyclization and also to study the effect of substituents.

First we considered amides of type (1) and their oxidative cyclisation to the biphenyl derivatives (2). Four



(1) R = H
(6) R = Me

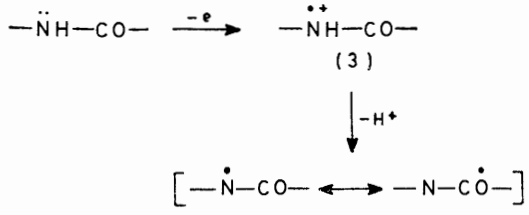


(2) R = H
(7) R = Me

amides were prepared (1; $x = y = 0$; $x = y = 1$; $x = 1$, $y = 2$; $x = 2$, $y = 1$); these were oxidized in acetonitrile solution, containing anhydrous sodium perchlorate as supporting electrolyte, at an anode potential [*vs.* standard calomel electrode (s.c.e.)] corresponding to the midpoint of the first oxidation wave as determined by a combination of polarographic curves (rotating platinum microanode and mercury cathode) and cyclic voltammetry.

We noted that $E_{\frac{1}{2}}$ for this wave is +1.0—1.2 V, which corresponds closely to that at which anisole and many other methoxylated aromatic compounds lose an electron to form the appropriate radical cation,[3] but during preparative electrolyses of each of the above amides at this anode potential an initial high current through the cell rapidly fell almost to zero and resinous material was deposited on the anode surface. Similar results were obtained with a variety of solvent, supporting electrolyte, and electrode systems: pulsing techniques were also unsuccessful.

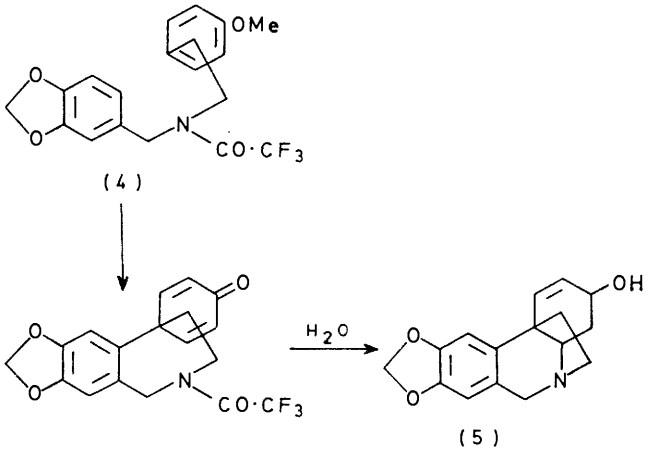
Here the common structural element is a secondary amide function and failure to cyclise, particularly in the cases $x = y = 1$, $x = 1$, $y = 2$, and $x = 2$, $y = 1$, is probably due to a combination of adverse conformational effects [4] and competing electro-oxidation processes at this site. Thus in the last case, for example, an initially formed cation radical (3) might undergo deprotonation to a radical which then subsequently yields resinous products (*N*-phenylbenzamide gives a poorly defined oxidation wave at an anode potential of *ca.* 1.2 V in acetonitrile–sodium perchlorate). Support of this view is



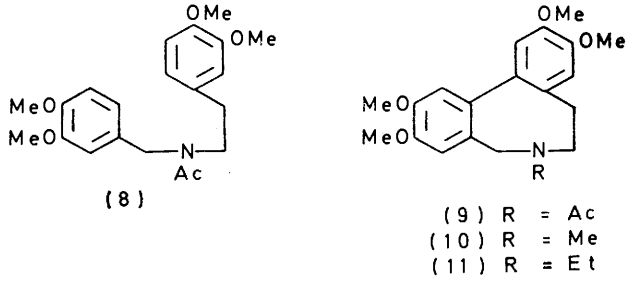
provided by the successful synthesis of (±)-oxocrinine (5)[5] *via* anodic oxidation of the tertiary amide (4); here radical formation by the above mechanism is impossible. Indeed, when the amides (6; $x = y = 1$) and (8) were prepared and oxidized at anode potentials of *ca* 1.1 V the tricyclic structures (7; $x = y = 1$) and (9) were obtained (45 and 60%, respectively). Structural assignments for these products follow from analytical and spectroscopic data (see Experimental section), but additionally, on

[1] Oxidative Coupling of Phenols,' eds. W. I. Taylor and A. R. Battersby, Dekker, New York, 1967; T. Kametani and K. Fukumoto, *Synthesis*, 1972, 657.
[2] A. Ronlán and V. D. Parker, *Chem. Comm.*, 1970, 1567; see also S. Tobinaga, *Bio-organic Chem.*, 1975, **4**, 110, and references cited therein.
[3] M. Sainsbury, *J. Chem. Soc.* (*C*)., 1971, 2888.
[4] B. F. Pederson, *Acta Chem. Scand.*, 1967, **21**, 1422.
[5] E. Kotani, N. Takeuchi, and S. Tobinaga, *J.C.S. Chem. Comm.*, 1973, 550.

reduction with lithium aluminium hydride, the corresponding amines (10) and (11) were obtained, both of which were also fully characterized.

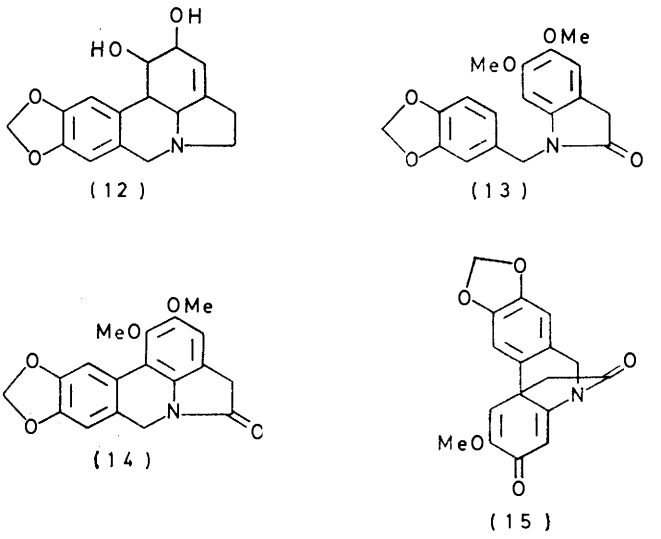


Oxidation of compound (6; $x = 1, y = 0$) on the other hand gave a complex mixture of products from which only 2% of compound (7; $x = 1, y = 0$) was obtained. The related substrate (6; $x = y = 0$) gave only a resinous

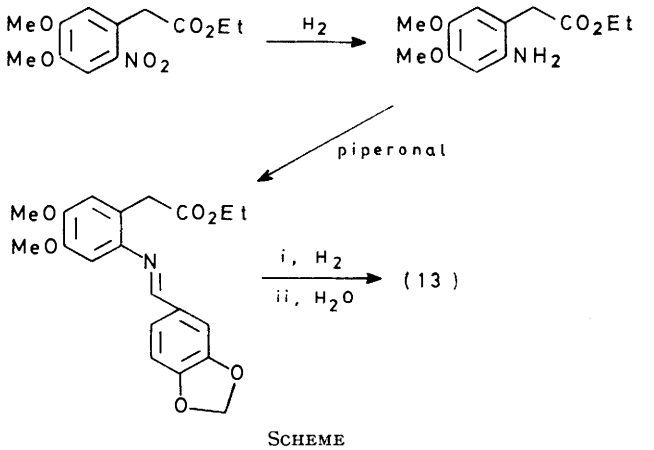


product on electrolysis. In these two examples electronic interactions between one or both the aryl rings and the amide function are possible so it is reasonable to assume that the potentials at which the electrons of the individual rings are ionized are not the same, thus enhancing the possibilities of inter- rather than intramolecular coupling and hence the formation of mixtures. Thus Ronlán and his co-workers [6] have observed that where units of only slightly differing structures are present, both inter- and intra-molecular processes may occur. For example, 3,3',4-trimethoxybibenzyl yields a dimeric structure when oxidized at a low current density, whereas at higher current density both the dimer and an intramolecularly coupled product are formed, indicating that the dimethoxylated ring is more easily ionized to the corresponding radical cation than is its monomethoxylated counterpart.

For some years we [7] have been interested in the synthesis of alkaloids of the lycorine (12) type, and it occurred to us that anodic oxidation of the oxindole derivative (13) followed by *ortho–para*-coupling might afford the lycorine model (14), although we recognized that the *para–para* product (15) was probably the more likely. The starting material was prepared by the route outlined in the Scheme, but despite encouraging preliminary analysis which revealed oxidation waves at anode potentials



$E_{\frac{1}{2}}$ 0.8 and 1.1 V (*vs.* s.c.e.), a preparative electrolysis at the lower potential gave only a tar. This lack of specificity was a disappointment especially since we have already observed [8] that electrolysis of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (16) affords the spirocyclohexadienone (17) in excellent yield. The lactone (16) is, however, not a good model for the present work and we next turned to the 3-benzyloxindole (18).



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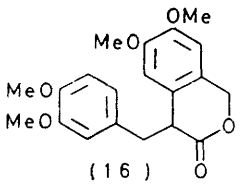
This, like (13), shows two anodic waves, $E_{\frac{1}{2}}$ 0.75 and 1.1 V (*vs.* s.c.e.), and similarly an oxidation attempt at the

[6] A. Ronlán, O. Hammerich, and V. D. Parker, *J. Amer. Chem. Soc.*, 1973, **95**, 7132.

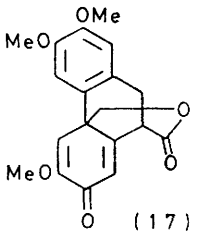
[7] S. F. Dyke, M. Sainsbury, and J. R. Evans, *Tetrahedron*, 1973, **29**, 213.

[8] M. Sainsbury and R. F. Schinazi, *J.C.S. Chem. Comm.*, 1972, 718.

first value resulted only in an intractable gum. However at an anode potential of 1.1 V and a higher current density a 15% yield of the tetracyclic compound (19) was obtained, after work-up. A second electrolysis of (13),

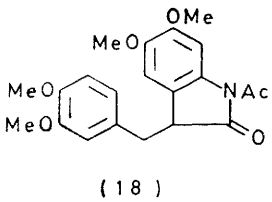


(16)

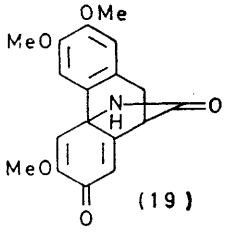


(17)

this time at 1.1 V and at high current density, however, also proved unrewarding and gave only a tar.



(18)



(19)

The dienones (15) and (19), which contain a five-membered ring, are more strained than the spirocyclohexadienone (17), and our results suggest that both inter-

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.

6-*Acetyl*-5,6,7,8-*tetrahydro*-2,3,10,11-*tetramethoxydibenz*-[c,e]*azocine* (9).—*N*-Acetyl-*N*-veratryl-3,4-dimethoxyphenethylamine (8) (2 g) and anhydrous sodium carbonate (1 g) were 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 1.15 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 cm^3). Most of the acetonitrile was removed by distillation and the solution was extracted several times with chloroform. Evaporation of the extracts afforded a gum which was chromatographed on neutral alumina (elution with chloroform–petroleum) to yield the *azocine* (1.2 g) as prisms, m.p. 190° (from ethanol–ether); $\lambda_{max.}$ 215, 259, and 283 nm; $\nu_{max.}$ 1 665sh, 1 630, and 1 600 cm^{-1}, δ ($CDCl_3$) 2.18 (3 H, s, Ac), 3.1 (1 H, d, J 14 Hz) and 5.3 (1 H, d, J 14 Hz) (5-H_2), 2.22—3.40 (4 H, m, 7- and 8-H_2) 3.95 (12 H, s, 4 × OMe), and 6.88 (1 H, s), 6.9 (1 H, s), 6.95 (1 H, s), and 7.6 (1 H s) (aromatic): *m/e* 343 (M^+) (Found: C, 67.9; H, 6.7; N, 3.7. $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.8; N, 3.8%).

6-*Ethyl*-5,6,7,8-*tetrahydro*-2,3,10,11-*tetramethoxydibenz*-[c,e]*azocine* (11).—The product (9) (0.5 g) was dissolved in tetrahydrofuran (50 cm^3) and an excess of lithium aluminium hydride was added. The mixture was then heated under reflux for 3 h, the excess of reagent was destroyed with ethyl acetate, water was added, and the mixture was extracted with chloroform. The extracts were evaporated

248, and 282 nm; $\nu_{max.}$ 1 618, 1 600, and 1 583 cm^{-1}, *m/e* 343 (M^+, 100%), 314 (60), 165 (20), and 150 (20) (Found: C, 66.5; H, 6.2; N, 4.2. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.2; N, 4.1%).

Ethyl 2-Amino-4,5-dimethoxyphenylacetate.—This compound, prepared from ethyl 2-nitro-4,5-dimethoxyphenylacetate [10] by hydrogenation in methanol over 10% palladium–carbon at 100 lb in^{-2}, had m.p. 59°, $\lambda_{max.}$ 239 and 301 nm; $\nu_{max.}$ 3 400, 3 200, 1 710, and 1 610 cm^{-1}, *m/e* 239 (M^+), 207, and 193. [In our hands it is stable although Walker [10] states that on warming decomposition occurred and he was unable to isolate it.]

Ethyl 4,5-Dimethoxy-2-(3,4-methylenedioxybenzylideneamino)phenylacetate.—The preceding product (6 g) and piperonal (4.15 g) were heated in xylene solution (150 cm^3) in a Dean-Stark apparatus for 6 h. The solvent was removed and the residue was triturated with ether and crystallized from ethanol as prisms (8 g, 80%), m.p. 94—95°; $\lambda_{max.}$ 285 and 352 nm; $\nu_{max.}$ 1 730, 1 720, 1 680, 1 620, 1 600, and 1 580 cm^{-1}, δ ($CDCl_3$) 1.7 (3 H, t *J* 8 Hz), 3.82 (2 H, s), *ca.* 4.0 (12 H, m), 4.18 (2 H q, *J* 8 Hz), 6.7—7.7 (5 H, m), and 8.40 (1 H, s), *m/e* 387 (M^+), 372, and 314.

Ethyl 4,5-Dimethoxy-2-(3,4-methylenedioxybenzylamino)-phenylacetate.—The foregoing compound in ethanol was hydrogenated over Adams catalyst at 40 lb in^{-2} during 5 h to give the title compound as *prisms* (89%), m.p. 89—90° (from diethyl ether); $\lambda_{max.}$ 250, 284, and 302 nm; $\nu_{max.}$ 3 400, 1 725, 1 610, and 1 590 cm^{-1}, *m/e* 389 (M^+).

5,6-Dimethoxy-1-(3,4-methylenedioxybenzyl)indolin-2-one (13).—The foregoing amine (5 g) was passed, in chloroform solution, through a column packed with basic alumina (Merck). Removal of the solvent afforded the *oxindole* (13), in almost quantitative yield; it crystallized from ethanol as needles, m.p. 102—103°; $\lambda_{max.}$ 277 and 301 nm; $\nu_{max.}$ 1 705, 1 619, 1 601, and 1 584 cm^{-1}; δ ($CDCl_3$) 3.48 (2 H, s), 3.70 (3 H, s), 3.75 (9 H, m), 4.72 (2 H, s), 6.30 (1 H, s), 6.71 (1 H, s), and 6.74 (3 H, m), *m/e* 343 (M^+), 192, and 151 (Found: C, 66.4; H, 6.2; N, 4.0. $C_{19}H_{21}NO_5$ requires C, 66.5; H, 6.2; N, 4.1%).

*4-(3,4-Dimethoxybenzylidene)-6,7-dimethoxyisochroman-3-one.**—6,7-Dimethoxyisochroman-3-one (15 g) [11] and veratraldehyde (11.3 g) were treated with pyrrolidine (6.9 g) in portions and the mixture was then heated at 100 °C under nitrogen. After cooling, the solid yellow product was collected, washed with 5% acetic acid in ethanol, and recrystallized from ethanol to give *needles* (19.3 g, 75%), m.p. 176—177°; $\lambda_{max.}$ 213 (ε 16 600), 250 (10 900), and 370 nm (12 100) (Found: C, 67.3; H, 5.7. $C_{20}H_{20}O_6$ requires C, 67.4; H, 5.7%).

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (16).—The foregoing product (2.03 g) in glacial acetic acid (250 cm^3) was hydrogenated over Adams catalyst (0.3 g) at 60 lb in^{-2} until the solution became colourless (*ca.* 15 h). The catalyst and solvent were removed, and the residue crystallized from ethanol, as plates (1.96 g, 96.6%), m.p. 104—105°; $\lambda_{max.}$ 213 (ε 19 550) and 285 nm (6 340); $\nu_{max.}$ 1 750 cm^{-1}; δ ($CDCl_3$) 3.17 (2 H, d, *J* 8 Hz, 4-CH_2), 3.69, 3.75, and 3.84 (13 H, br, s, 4 × OMe and 4-H), 4.8 (2 H, q, *J* 14 Hz 1-H_2), and 6.42—6.8 (5 H, m, aromatic) (Found: C, 67.3; H, 6.3. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.2%).

Electrochemical Oxidation of Compound (16).—The isochroman-3-one was oxidized in the normal way at an anode potential of 1.22 V to give, after work-up, *9,10-dihydro-3,6,7-trimethoxy-4α,10-methanoxymethanophenanthrene-2,11-dione* (17) as needles, m.p. 256—257° (from ethanol); yield 70—80%; $\lambda_{max.}$ 265 (ε 6 650), 290 (4 180), and 360 (nm (4 750); δ ($CDCl_3$) 3.17br (3 H, s), 3.77 (3 H, s), 3.93 (6 H, s), 4.1 (2 H, q *J* 14 Hz), 5.98 (1 H, s), 6.53 (1 H, s), 6.78 (1 H, s), and 6.97 (1 H, s) (Found: C, 66.5; H, 5.4. $C_{19}H_{18}O_6$ requires C, 66.6; H, 5.3%).

Electrolysis of 1-Acetyl-5,6-dimethoxy-3-veratrylindolin-2-one (18).—*Compound* (18), m.p. 102—104° (Found: C, 65.4; H, 6.0; N, 3.6. $C_{21}H_{23}NO_6$ requires C, 65.4; H, 6.0; N, 3.6%), was prepared from 5,6-dimethoxy-3-veratrylideneindolin-2-one [10] by hydrogenation and treatment of the product with acetic anhydride, and was electrolysed at an anode potential of 1.10 V. A high current density was employed and it became necessary to cool the cell with an ice–water bath. *9,10-Dihydro-3,6,7-trimethoxy-4α,10-iminomethanophenanthrene-2,11-dione* (19) was obtained after chromatography; yield 15%, m.p. 286—288° (from ethanol); $\nu_{max.}$ 3 310, 1 740, 1 650, 1 635, and 1 610 cm^{-1}; δ [10% $(CD_3)_2SO$ in $CDCl_3$] 3.40br (3 H, s, CH_2·CH), 3.65, 3.8, and 3.9 (each H, s, (OMe), and 5.8, 5.95, 6.50, and 6.87 (each 1 H, s, olefinic or aromatic); *m/e* 327 (M^+) (Found: C, 65.9; H, 5.1; N, 4.4. $C_{18}H_{17}NO_5$ requires C, 66.0; H, 5.2; N, 4.3%).

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[10] G. N. Walker, *J. Amer. Chem. Soc.*, 1955, **77**, 3844.
[11] T. S. Stevens, *J. Chem. Soc.*, 1927, 178; J. Finkelstein, U.S.P. 3,480,634 (*Chem. Abs.*, 1970, **72**, 43,486s).