Synthesis of *meta,meta*-Bridged Biaryls ([7.0]-Metacyclophanes) *via* Aryl-Aryl Coupling: Factors affecting the Cyclisation

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Two bis(iodoaryl)heptanoids (28) and (33), the iodoarylbutyl iodoarylpropyl sulphide (39), and the corresponding sulphone (40) have been prepared, and each treated with tetrakis(triphenylphosphine)-nickel(0). Two new *m,m*-bridged biaryls (29) (31%) and (34) (49%) were obtained; the sulphur compounds were deiodinated in preference to coupling. These reactions are compared with those used previously in myricanol synthesis and the factors affecting ring closure are discussed. Steric effects at the coupling sites appear more important in determining product yield than torsional strain in the products.

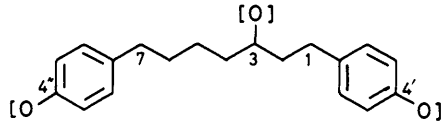
' Diarylheptanoids ' are a small group of natural phenolics based on the 1,7-diphenylheptane framework. Hydroxylation at C-4′, C-4″ is always observed, together with an oxygen function at C-3(1) *e.g.* centrolobol,[1] curcumin.[2] More elaborate diarylheptanoids include (i) a group of *meta,meta*-bridged biphenyls [3] (3) at similar oxidation levels, (ii) a few macrocyclic ethers (4),[3e,4] and (iii) various 9-phenylphenalenones.[5] Some biosynthetic questions have been discussed.[6-8]

m,m-Bridged biphenyls can plausibly be seen as products of C–C oxidative coupling (5) of a suitable diarylheptanoid. Methylene insertion into a biphenyl such as (6), from cinnamate coupling, is an alternative possibility; such fragments occur in lignin). Oxidative C–O coupling in (5) could lead to bridged ethers, *cf.* (4).

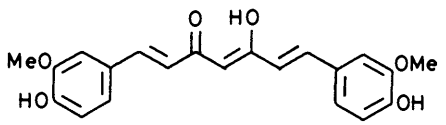
In synthetic work [9,10] we have shown that the phenol (7) provided the macrocycle (8) on oxidation with thallium bis(trifluoroacetate). No products arising from C–C coupling were observed on phenolic oxidation of (7), or the corresponding alcohol, with a wide variety of oxidants. However, nickel(0) treatment of the bisiodides (9) and (10) produced the desired metacyclophanes (11) and (12); [10] the mechanism of this reaction is uncertain, but reactant geometry in the transition state is presumably similar to that in phenolic coupling. The yields in these nickel(0) reactions were low (*ca.* 10%), and were little higher in photochemically induced radical insertion.[10] However, Semmelhack and Ryono [11] reported a reasonable yield, 53%, for the nickel(0)-induced formation of dimethylalnusone (13) from a linear bisiodide (14). This observation led us to reflect on the factors involved in large ring formation from linear heptanoids and stimulated the experiments which are the subject of this paper.

The cyclisation of bisiodides such as (9), (10), and (14) would be subject to the following constraints: (i) torsional strain in the ring system; (ii) steric interactions between hydrogens inside the large ring; (iii) steric effects around the coupling sites; and (iv) electronic effects on radical stability.

The structure of 16-bromomyricanol,[3a] as revealed by *X*-ray analysis, reveals clearly the first two of these factors. The biphenyl nucleus is distorted so that the biphenyl axis is bent in both dimensions from linearity, as shown in (15), and the resulting torsional strain drives a ready rearrangement to the unstrained *ortho,meta*-bridged isomer.[3a] This biphenyl deformation is required in myricanol in order to provide minimum separation for the hydrogens ' inside ' the ring, 8 H, 9 H, 11-H, and 12-H, and the two close aromatic protons (15). The degree of such interactions would appear, from a study of molecular models, to depend on the oxidation state of the linking C_7 chain. In biosynthesis, coupling may occur in a diarylheptanoid with this chain all of sp^3 carbons or at some oxidation state intermediate between (1) and (2) with one or



(1)



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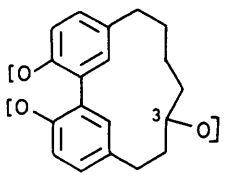

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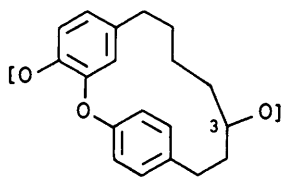

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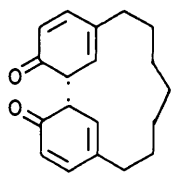

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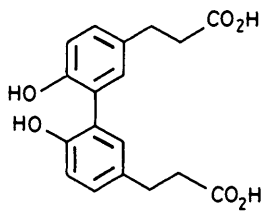

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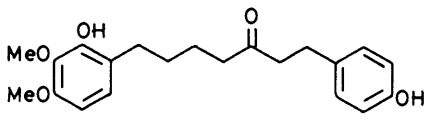

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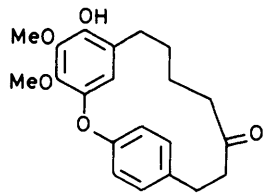

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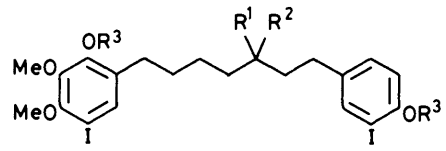
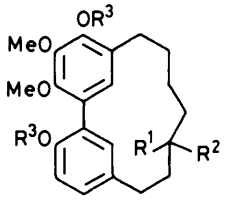
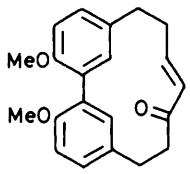


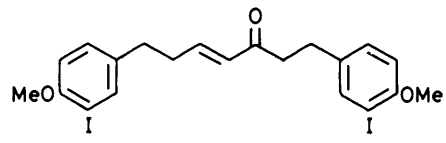
(9) R^1,R^2 = O=, R^3 = CH_2Ph
(10) R^1 = H, R^2 = OAc, R^3 = CH_2Ph





(11) R^1,R^2 = O=, R^3 = CH_2Ph
(12) R^1 = H, R^2 = OAc, R^3 = CH_2Ph

(13)



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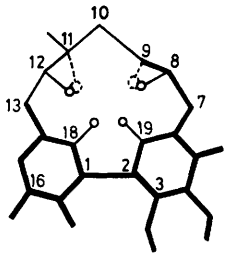

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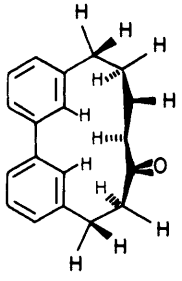
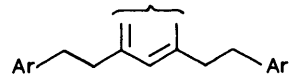


(17)

more carbons sp^2 in character. Models suggest that sp^2 carbons at C-3, C-4, and C-5 as in (16) would be a favourable case, leading to a less strained macrocycle (17). The relatively successful coupling of the enone (14), and the co-occurrence [3d] in Nature of alnusone [*cf.* (13)] and 1,7-bis(*p*-hydroxyphenyl)hept-4-en-3-one, lend weight to this suggestion. A particularly favourable case appeared to be the tetrahydrocurcumin structure (18); since the enol function of (18) would not be compatible with a nickel(0) reagent, we chose to examine aryl-aryl coupling in a model isoxazole (19) which is geometrically close to the keto-enol system of (18) and is readily hydrolysed to it. For comparison we also selected the acetate (20) (chain of sp^3 carbons), the sulphide (21), and the sulphone (22). Synthesis and intramolecular coupling of the compounds are now discussed.

1-(4-Methoxyphenyl)butan-3-one (23) was prepared by hydrogenation of the corresponding butenone,[12] and converted into the oxime (24). ^1H N.m.r. and ^{13}C n.m.r. spectroscopy indicate this product to be *ca.* 70% *E*-oxime, 30% *Z*-oxime. The dianion (25) was formed using 2 mol equiv. of n-butyl-lithium and was treated with the ester (26) to provide the desired isoxazole (19), albeit in only 26% yield [based on *E*-oxime; only this geometry leads to the required *syn*-dianion (25) [13,14]]. No improvement was obtained using



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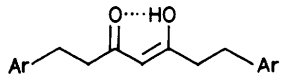

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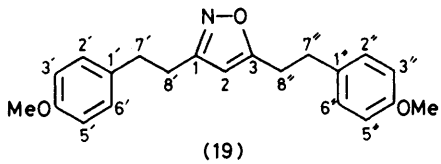

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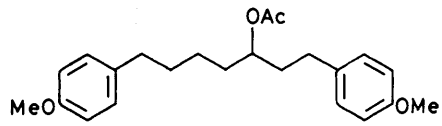

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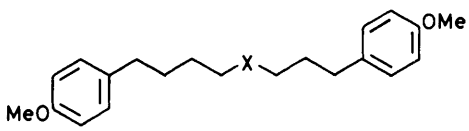
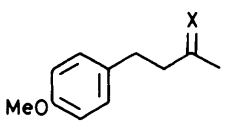
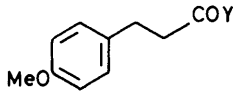


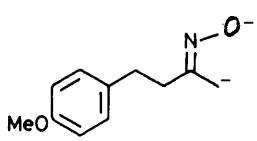
(21) X = S
(22) X = SO_2



(23) X = O
(24) X = NOH



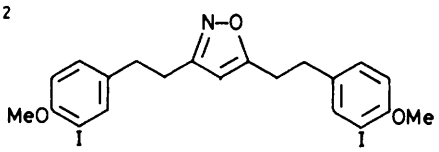
(26) Y = OMe
(27) Y = NMe_2



(25)

(26)

(19)



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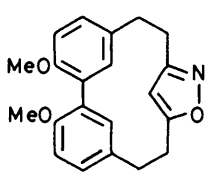


(29)

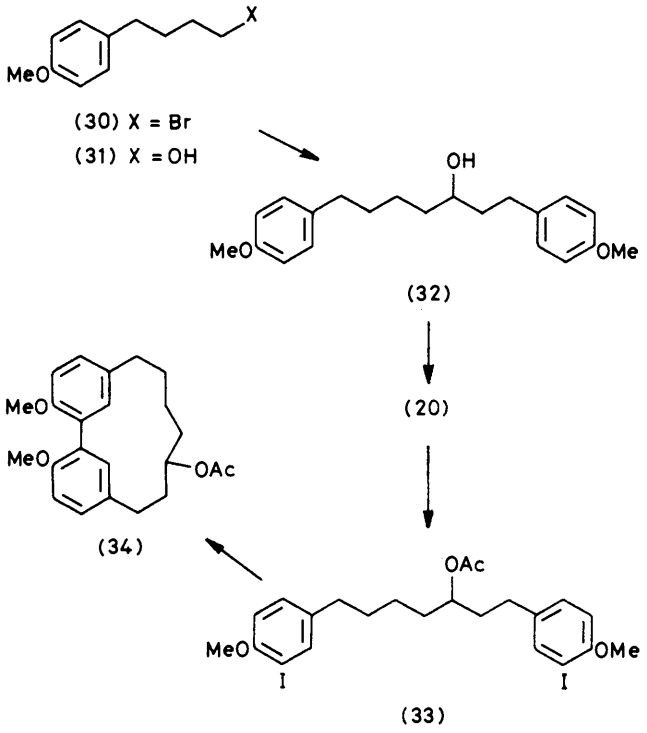
Scheme 1.

the amide (27) or the corresponding imidazolide, or on using LDA as base. The accumulated material from these trials was smoothly iodinated to the required bis(iodide) (28); treatment of this with tetrakis(triphenylphosphine)-

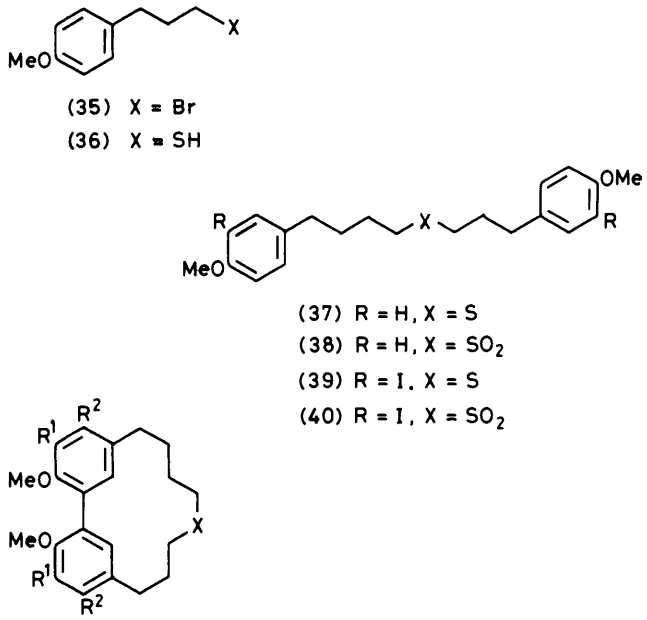
Table. ^{13}C N.m.r. data for the isoxazoles (19), (28), and (29)

Carbon [a]	(19)	(28)	(29)
1	172.2	171.8	198.2
2	100.1	101.1	94.9
3	163.2	162.9	163.8
	28.1	28.0	30.3
7′,7″,8′,8″	28.8	28.6	32.9
	32.8	32.3	38.3
	33.6	33.0	43.8
1′,1″	132.4	134.4	136.3
	132.9	135.1	136.3
2′,2″	129.3	129.3	129.4
	129.3	129.3	129.4
3′,3″	114.0	111.1	111.1
	114.0	111.1	111.1
4′,4″	158.3	156.8	156.5
	158.3	156.9	157.0
5′,5″	114.0	86.0	134.5
	114.0	86.1	134.5
6′,6″	129.3	139.3	139.2
	129.3	139.3	139.3

[a] For comparison purposes the numbering system given in cipher (19) is used for each compound.



Scheme 2.



Scheme 3.

nickel(0), prepared *in situ*, gave the macrocyclic biphenyl (29) as an oil (31%). Spectroscopic data for (29) support the structure assigned; the u.v. spectrum is significantly different from those of the precursors (19) and (28), and the expected ^1H n.m.r. is seen, with the isoxazole proton (τ 5.04) markedly shielded in comparison with its counterpart (τ 4.36) in (19). ^{13}C N.m.r. data for the isoxazoles, (19), (28), and (29) are shown in the Table, with group assignments. Some interesting features emerge: the non-equivalence of the two arylethyl groups in (19) is observable in the three pairs of atoms (8′, 8″; 7′, 7″; 1′, 1″) closest to the heterocycle; in (28) five pairs are resolved (8′, 8″; 7′, 7″; 5′, 5″; 4′, 4″; 1′, 1″); and in (29) the 'inside' aryl carbons (6′, 6″) are distinguished, and the separations of 8′ and 8″ and 7′ and 7″ increase.

The alcohol (32) was prepared from the Grignard reagent obtained from the bromide (30) (using active magnesium) and *p*-methoxydihydrocinnamaldehyde. The bromide (30) was obtained from anisoylpropionic acid [15] *via* sequential reduction to the alcohol (31) and reaction of the corresponding tosylate with lithium bromide. Acetylation and iodination of the alcohol (32) provided the bis(iodide) (33), which furnished the desired bridged biaryl (34) (49%). Finally, the bromide (30) reacted with arylpropanethiol (36) (prepared from the corresponding aldehyde, *via* the bromide (35) to yield the sulphide (37). Oxidation with *m*-chloroperbenzoic acid gave the sulphone (38), and direct iodination of (37) and (38) gave the corresponding bis(iodides) (39) and (40). On treatment with tetrakis(triphenylphosphine)nickel(0), under various conditions, neither (39) nor (40) gave any of the corresponding macrocycle (41) or (42); the major reaction was reduction to regenerate (37) and (38) respectively.

It is apparent from these intramolecular aryl couplings that the best yield (49%) of *m,m*-bridged biphenyl is obtained in the case of (34). Thus the poor yields in the coupling step in myricanol and myricanone syntheses, *i.e.* (9) or (10) ⟶ (11) or (12), *cannot* be ascribed to torsional strain inherent in the metacyclophane constitution. Structuring of the C_7 bridge in an attempt to reduce 'inside' H–H interactions does not assist cyclisation, since (29) was formed in 31% yield, and 53% of (13) from (14) was reported.[11] Also, increasing the length of the bridge to reduce torsional strain was not effective in raising yield; (43) was formed in only 10% yield,[10] while the sulphide (39), with reduced H–H interactions and a longer chain, fails to cyclise at all. Strain effects therefore, although real in product, must be less important in the transition state, and make a relatively small contribution to activation energy. What then caused the low yield of, *e.g.* (12), compared to

(34)? At high dilution, intermolecular coupling is not a complication. Although little is known about the mechanism of nickel(0)-induced coupling, electronic factors are probably not the cause since ether substituents do not, in general, inhibit the reaction, and indeed the related Ullmann reaction [16] is considered to be activated by ether functions. Since the nickel(0) coupling is sensitive to steric effects (failing if one site has two *ortho* substituents) it seems most likely that, with one aryl ring pentasubstituted, stereochemical difficulties arise in the formation of the necessary bis(iodide)–catalyst complex.

Experimental

For experimental generalisations, see ref. 9. Bridged biaryls are numbered as in (15).

4-(4-*Methoxyphenyl*)*butan*-2-*one Oxime*.—4-(4-Methoxyphenyl)butan-2-one (23 g, 0.12 mol) in ethanol (50 cm^3) was treated with hydroxylamine hydrochloride (20 g) in water (20 cm^3) followed by aqueous ammonia (*d* 0.88; 10 cm^3), and the mixture heated on steam for 15 min. An oil which separated on cooling was set aside. The aqueous layer was extracted with dichloromethane. The combined extracts and oil were washed (water and brine) and dried. Evaporation gave the *title compound* (23.9 g, 95%), m.p. 66—68 °C (Found: C, 68.35; H, 7.85%; M^+, 193.111. $C_{11}H_{15}NO_2$ requires C, 68.4; H, 7.75%; *M*, 193.110); τ 2.84 (2 H, d, *J* 9 Hz, 2′-H, 6′-H), 3.12 (2 H, d, *J* 9 Hz, 3′-H, 5′-H), 6.2 (3 H, s, OMe), 7.2—7.6 (4 H, m), and 8.12 (3 H, s, Me).

N,N-*Dimethyl*-3-(4-*methoxyphenyl*)*propionamide*.—3-(4′-Methoxyphenyl)propionamide (2 g, 0.011 mol) was stirred in xylene (50 cm^3) with sodium hydride (1.5 g) for 24 h. Methyl iodide (18.6 cm^3) was added, and the mixture was refluxed for 24 h. The product was filtered and distilled to yield the *title compound* (1.57 g, 68%), b.p. 164—166 °C/0.05 mmHg (Found: C, 69.3; H, 8.4. $C_{12}H_{17}NO_2$ requires C, 69.55; H, 8.2%), τ 2.96 (2 H, d, *J* 9 Hz), 3.28 (2 H, d, *J* 9 Hz), 6.32 (3 H, s, OMe), 7.16 (6 H, s, NMe_2), and 7.1—7.6 (4 H, m).

3,5-*Bis*(4-*methoxyphenylethyl*)*isoxazole*.—n-Butyl-lithium (in n-hexane, 3.1 cm^3, 0.005 mol) was added during 10 min to a stirred solution of 4-(4-methoxyphenyl)butan-2-one oxime (0.5 g, 0.003 mol) in tetrahydrofuran (100 cm^3) at 0 °C. Stirring was continued for 1 h when *N*,*N*-dimethyl-3-(4-methoxyphenyl)propionamide (0.51 g, 0.003 mol) in tetrahydrofuran (10 cm^3) was added dropwise during 10 min. The reaction was allowed to proceed at 0 °C for 2 h, when the mixture was poured into water (54 cm^3) containing tetrahydrofuran (19 cm^3) and sulphuric acid (11 cm^3). After this solution had been stirred for 30 min the tetrahydrofuran was evaporated, and the aqueous residue was extracted with dichloromethane. The extracts were washed with aqueous sodium hydrogencarbonate, water, and brine, and then evaporated. Trituration of the residual oil gave the *title compound* (103 mg, 12%), m.p. 109—110 °C (from ethanol) (Found: C, 74.7; H, 6.8; N, 4.25%; M^+, 337.168. $C_{21}H_{23}NO_3$ requires C, 74.8; H, 6.8; N, 4.15%; *M*, 337.167); $\lambda_{max.}$ 226 (4.64), 277 (4.55), and 285 nm (4.54); τ 2.94 (4 H, d, *J* 9 Hz, 2′, 2″, 6′, 6″-ArH), 3.20 (4 H, d, *J* 9 Hz, 3′, 3″, 5′, 5″-ArH), 4.36 (1 H, s, CH=C), 6.20 (6 H, s, 2 × OMe), and 7.0 (8 H, br).

A similar reaction, on a 0.012 molar scale, but using methyl 3-(4-methoxyphenyl)propionate instead of the corresponding dimethylamide, gave the same product (26%).

3,5-*Bis*(3-*iodo*-4-*methoxyphenylethyl*)*isoxazole*.—3,5-Bis(4-methoxyphenylethyl)isoxazole (312 mg, 0.9 mmol) and silver trifluoroacetate (300 mg, 1.34 mmol) were stirred together in dichloromethane (50 cm^3) at ambient temperature. Iodine (350 mg, 2.74 mg-atom) was added in portions during 1.5 h. The reaction was allowed to proceed for 90 h, when the mixture was filtered. The filtrate was washed (aqueous sodium hydrogenbisulphite, water, and brine), dried, and evaporated, to provide the *title compound* (442 mg, 83%), m.p. 124—126 °C (from ethanol) (Found: C, 43.0; H, 3.75; N, 2.35%; M^+, 588.963. $C_{21}H_{21}I_2NO_3$ requires C, 42.95; H, 3.6; N, 2.40%; *M*, 588.961); $\lambda_{max.}$ 229 (4.63), 277 (4.55), and 285 nm (4.54); τ 2.36 (2 H, s, 2′-H, 2″-H), 2.89 (2 H, d, *J* 9 Hz, 6′-H, 6″-H), 3.24 (2 H, d, *J* 9 Hz, 5′-H, 5″-H), 4.28 (1 H, s, CH=C), 6.12 (6 H, s, 2 × OMe), and 7.08br (8 H, 4 × CH_2).

Preparation of the [7.0]-*Metacyclophane* (29).—Bis(triphenylphosphine)nickel(II) dichloride (177 mg, 0.45 mmol), zinc powder (31 mg, 0.45 mg-atom), triphenylphosphine (273 mg, 0.9 mmol) were stirred under nitrogen in dry deoxygenated dimethylformamide (20 cm^3) at ambient temperature for 1 h. 3,5-Bis(3-iodo-4-methoxyphenylethyl)-isoxazole (272 mg, 0.45 mmol) in dry dimethylformamide (5 cm^3) was added to the dark red solution. The mixture was stirred at 65 °C for 48 h, cooled, and diluted with 2% aqueous hydrochloric acid. The product was extracted with chloroform. The extracts were washed (water and brine), dried, and evaporated. The residue was purified by p.l.c. to afford the *metacyclophane* (29) (47 mg, 31%) as a colourless gum (one spot only on t.l.c. in ether–n-hexane, 4 : 1 and 1 : 1) (Found: M^+, 335.151. $C_{21}H_{21}NO_3$ requires *M*, 335.152); $\lambda_{max.}$ 235 (4.62), 294 (4.53), and 303 nm (4.51); τ 2.44 (2 H, s, 18-H, 19-H), 2.96 (2 H, d, *J* 9 Hz, 4-H, 16-H), 3.34 (2 H, d, *J* 9 Hz, 5-H, 15-H), 5.04 (1 H, s, 10-H), 6,16 (6 H, s, 2 × OMe), and 7.1—7.8 (8 H, m).

1,7-*Bis*(4-*methoxyphenyl*)*heptan*-3-*ol*.—Anhydrous magnesium chloride (0.91 g, 9.6 mmol), anhydrous potassium iodide (0.72 g, 4.3 mmol), and potassium metal (0.67 g, 17.2 mg-atom) were stirred in refluxing tetrahydrofuran (30 cm^3) for 2 h, under nitrogen. The resulting black suspension was cooled and 4-(4-methoxyphenyl)butyl bromide (1.28 g, 4.2 mmol) was added. The mixture was stirred for 1 h. 3-(4-Methoxyphenyl)propanal (0.69 g, 4.2 mmol) was added during 20 min, and the mixture was stirred overnight. It was quenched with aqueous ammonium chloride and organic products were extracted into ether. The dried extracts were evaporated and the residue separated by p.l.c. (ether–n-hexane, 4 : 1), to yield the *title compound* (386 mg, 29%) as an oil (Found: C, 77.1; H, 8.3%; M^+, 328.205. $C_{21}H_{28}O_3$ requires C, 76.85; H, 8.55%; *M*, 328.204), $\nu_{max.}$ (film) 3 300br (OH), 2 900, 1 610, and 1 520 cm^{-1}; τ 3.00 (4 H, d, *J* 9 Hz, 2′-H, 2″-H, 6′-H, 6″-H), 3.28 (4 H, d, *J* 9 Hz, 3′-H, 3″-H, 5′-H, 5″-H), 6.25 (6 H, s, 2 × OMe), 6.2—6.6br (1 H, m, 3-H), 7.2—7.6br (4 H, 1-H_2, 7-H_2), and 8.1—8.8br (9 H, 2-H_2, 4-H_2, 5-H_2, 6-H_2, OH). Acetylation with pyridine–acetic anhydride (1 : 1, excess), gave the corresponding *acetate* (20) (80%) as an oil (Found: C, 74.8; H, 8.0%; M^+, 370.212. $C_{23}H_{30}O_4$ requires C, 74.60; H, 8.10%; *M*, 370.214), $\nu_{max.}$ 1 740 cm^{-1}; τ 3.0 (4 H, d, *J* 9 Hz, 2′-H, 2″-H, 6′-H, 6″-H), 3.28 (4 H, d, *J* 9 Hz, 3′-H, 3″-H, 5′-H, 5″-H), 5.6—6.1br (1 H, m, 3-H), 7.1—7.6 (4 H, m, 1-H_2, 7-H_2) 8.04 (3 H, s, COMe), and 8.1—8.4br (8 H, 2-H_2, 4-H_2, 5-H_2, 6-H_2).

1,7-*Bis*(3-*iodo*-4-*methoxyphenyl*)*heptan*-3-*yl Acetate*.—To a mixture of the acetate (20) (140 mg, 0.38 mmol) in dichloromethane (20 cm^3) and silver trifluoroacetate (83 mg, 0.38

mmol) was added, dropwise and with stirring, iodine (191 mg, 1.52 mg-atom) in dichloromethane (25 cm^3), during 3 h. The mixture was stirred at room temperature for a further 72 h, when it was filtered. The filtrate was washed (10% aqueous sodium metabisulphite, water, and brine), dried, and evaporated to yield the *title compound* (184 mg, 78%) as an oil, one spot on t.l.c. (Found: M^+, 619.991. $C_{23}H_{28}I_2O_4$ requires M, 619.992), $\lambda_{max.}$ 284 (4.54) and 292 (4.53) nm; $\nu_{max.}$ 1 740 cm^{-1}; τ 2.76 (2 H, s, 2′-H, 2″-H), 3.24 (2 H, d, J 9 Hz, 6′-H, 6″-H), 3.62 (2 H, d, J 9 Hz, 5′-H, 5″-H), 6.1—6.3 (1 H, m, 3-H), 6.36 (6 H, s, 2 × OMe), 7.3—7.8br (4 H, m, 1-H_2, 7-H_2), 8.08 (3 H, s, COMe), and 8.1—8.4br (8 H, 2-H_2, 4-H_2, 5-H_2, 6-H_2).

Preparation of the [7.0]-*Metacyclophane* (34).—Bis(triphenylphosphine)nickel(II) dichloride (114 mg, 0.29 mmol) zinc powder (20 mg, 0.29 mg-atom), triphenylphosphine (176 mg, 0.58 mmol), and dimethylformamide (15 cm^3; dry and deoxygenated) were stirred together under nitrogen at 55 °C for 1 h. A dark-red solution was formed, to which was added the preceding iodide (33) (180 mg, 0.29 mmol) in dimethylformamide (2 cm^3). The reaction mixture was stirred for 24 h at 55—60 °C and for a further 24 h at 60—65 °C and then the cooled solution was poured into 2% hydrochloric acid (30 cm^3). The product was extracted with chloroform. The extracts were washed (water and brine), dried, and evaporated. The residue was separated by p.l.c. (ether–n-hexane, 1 : 1). The major band afforded the *metacyclophane* (34) (52 mg, 49%), as a clear oil (one spot on t.l.c.) (Found: C, 75.3; H, 7.4%; M^+, 368.198. $C_{23}H_{28}O_4$ requires C, 75.0; H, 7.6%; M, 368.171), $\lambda_{max.}$ 259 (3.35), 277 (3.46), and 284 nm (4.54); $\nu_{max.}$ 1 740 cm^{-1}; τ 2.96 (2 H, s, 18-H, 19-H), 3.20 (2 H, d, J 9 Hz, 5-H, 15-H), 3.48 (2 H, d, J 9 Hz, 4-H, 16-H), 6.0—6.2 (1 H, m, 11-H), 6.36 (6 H, s, 2 × OMe), 7.4—7.6br (4 H, m, 7-H_2, 13-H_2), 8.04 (3 H, s, COMe), and 8.1—8.4br (8 H, 8-H_2, 9-H_2, 10-H_2, 12-H_2).

3-(4-*Methoxyphenyl*)*propane*-1-*thiol*.—3-(4-Methoxyphenyl)propan-1-ol (from *p*-methoxycinnamic acid) was treated with toluene-*p*-sulphonyl chloride (2 mol equiv.) at 0 °C, in pyridine, for 4 h, to yield the corresponding *tosylate* (81%), m.p. 41—43 °C (Found: C, 63.6; H, 6.1%; M^+, 320.110. $C_{17}H_{20}SO_4$ requires C, 63.75; H, 6.25%; M, 320.108). Treatment of the tosylate with lithium bromide in acetone at ambient temperature for 24 h gave 3-(4-*methoxyphenyl*)*propyl bromide* (87%) as an oil (Found: M^+, 228.017. $C_{10}H_{13}BrO$ requires M, 228.015). The bromide (5 g, 0.021 mol) and thiourea (2.2 g, 0.028 mol) were refluxed together in ethanol (30 cm^3) for 4 h. 10% Aqueous sodium hydroxide (40 cm^3) was added, and the solution heated at 80 °C for 2 h. The cooled mixture was extracted with ether. The extracts were washed (water and brine), dried, and evaporated. The oily residue was purified by dry column chromatography (silica) (chloroform elution), to provide the *title thiol* (36) (2.8 g, 71%) as an oil (Found: C, 65.8; H, 7.55%; M^+, 182.075. $C_{10}H_{14}OS$ requires C, 65.95; H, 7.7%; M, 182.076), τ 3.19 (2 H, d, J 9 Hz, 2′-H, 6′-H), 3.43 (2 H, d, J 9 Hz, 3′-H, 5′-H), 6.38 (3 H, s, OMe), 7.6br (4 H, 1-H_2, 3-H_2), and 8.2br (2 H, 2-H_2).

4-(4-*Methoxyphenyl*)*butyl Bromide*.—4-(4-Methoxyphenyl)-butan-1-ol [prepared from 3-(4-methoxybenzoyl)propionic acid] was converted, by the above method, into the corresponding *tosylate* (94%), an oil (Found: M^+, 334.125. $C_{18}H_{22}SO_4$ requires M, 334.123). Reaction with lithium bromide–acetone gave the *title bromide* (91%) as an oil, purified by dry column chromatography (Found: C, 54.65; H, 6.05. $C_{11}H_{15}BrO$ requires C, 54.3; H, 6.15%).

3-(4-*Methoxyphenyl*)*propyl* 4-(4-*Methoxyphenyl*)*butyl Sulphide*.—Sodium metal (1 g) was dissolved in ethanol (50 cm^3). 3-(4-Methoxyphenyl)propanethiol (6.5 g, 0.035 mol) was added, followed by 4-(4-methoxyphenyl)butyl bromide (7.1 g, 0.029 mol). The mixture was refluxed for 1.5 h, and the bulk of the ethanol then distilled off. The residue was diluted with ether and washed with water. Evaporation of the solvent and column chromatography of the residue gave the *title sulphide* (8.64 g, 71%) as a pale yellowish oil (Found: M^+, 344.181. $C_{21}H_{28}O_2S$ requires M^+, 344.180), $\lambda_{max.}$ 277 (4.55), and 284 nm (4.54); τ 3.32 (4 H, d, J 9 Hz, 2′-H, 2″-H, 6′-H, 6″-H), 3.58 (4 H, d, J 9 Hz, 3′-H, 3″-H, 5′-H, 5″-H), 6.44 (6 H, s, 2 × OMe), 7.6br (8 H, 2 × $ArCH_2$, 2 × CH_2S), and 8.4br (6 H, 3 × CH_2).

3-(4-*Methoxyphenyl*)*propyl* 4-(4-*Methoxyphenyl*)*butyl Sulphone*.—The above sulphide (4.9 g, 0.013 mol) in dichloromethane (100 cm^3) was stirred at 10 °C while *m*-chloroperbenzoic acid (7.6 g, 0.27 mol) in dichloromethane (75 cm^3) was added dropwise during 15 min. The reaction was allowed to proceed for 6 h. Precipitated acid was filtered off, and the filtrate was washed with aqueous sodium metabisulphite, aqueous sodium hydrogencarbonate, and water, and then dried. Evaporation of the solvent gave a solid residue which was recrystallised from ethyl acetate–light petroleum to yield the *title sulphone* (3.03 g, 58%), m.p. 127.5—129.5 °C (Found: C, 66.7; H, 7.7%; M^+, 376.171. $C_{21}H_{28}O_4S$ requires C, 67.0; H, 7.45%; M, 376.170); $\lambda_{max.}$ 277 (4.55) and 284 nm (4.54); $\nu_{max.}$ (KBr) 2 940, 1 600, 1 500, 1 450, 1 240, 1 170, 1 120, 1 030, and 800 cm^{-1}; τ 3.00 (4 H, d, J 9 Hz, 2′-H, 2″-H, 6′-H, 6″-H), 3.24 (4 H, d, J 9 Hz, 3′-H, 3″-H, 5′-H, 5″-H), 6.24 (6 H, s, 2 × OMe), 7.7br (8 H, 2 × $ArCH_2$, 2 × CH_2SO_2), and 8.2br (6 H, 3 × CH_2).

3-(3-*Iodo*-4-*methoxyphenyl*)*propyl* 4-(3-*Iodo*-4-*methoxyphenyl*)*butyl Sulphone*.—The above sulphone (520 mg, 1.38 mmol) in dichloromethane (20 cm^3) with silver trifluoroacetate (350 mg, 1.57 mmol) was treated, dropwise during 1 h, with iodine (450 mg, 3.54 mg-atom) in dichloromethane (50 cm^3). The mixture was stirred at ambient temperature for 70 h and then filtered. The filtrate was washed with aqueous sodium metabisulphite, water, and brine, and evaporated. The residual oil was triturated with ether to yield a solid which on recrystallisation from ethanol–ethyl acetate gave the *title compound* (840 mg, 57%), m.p. 122.5—124.5 °C (Found: C, 40.5; H, 4.3%; M^+, 627.966. $C_{21}H_{26}I_2O_4S$ requires C, 40.15; H, 4.15%; M, 627.964), $\lambda_{max.}$ 277 (4.55) and 283 nm (4.54); $\nu_{max.}$ (KBr) 2 925, 1 590, 1 320, 1 270, 1 250, 1 120, 1 050, 1 020, and 890 cm^{-1}; τ 2.36 (2 H, s, 2′-H, 2″-H), 2.84 (2 H, d, J 9 Hz, 5′-H, 5″-H), 3.66 (2 H, d, J 9 Hz, 6′-H, 6″-H), 6.08 (6 H, s, 2 × OMe), 7.2br (8 H, 2 × $ArCH_2$, 2 × CH_2SO_2), and 8.3br (6 H, 3 × CH_2).

References

1 A. Aragao Craveiro, A. De Costa Prado, O. R. Gottlieb, and P. C. Welerson de Alburquerque, *Phytochemistry*, 1970, **9**, 1869.

2 J. Milobedzka, St. v. Kostanecki, and V. Lampe, *Ber.*, 1910, **13**, 2163; V. Lampe and J. Milobedzka, *ibid.*, 1913, **46**, 2235; V. Lampe, *ibid.*, 1918, **51**, 1347.

3 (*a*) M. J. Begley, R. V. M. Campbell, L. Crombie, B. Tuck, and D. A. Whiting, *J. Chem. Soc. C*, 1971, 3634, and refs. cited therein; (*b*) N. Nomura and T. Tokoroyama, *J. Chem. Soc., Chem. Commun.*, 1974, 65; (*c*) H. Sasatani and G. Izumiya, 'Research Bulletin of the College Experimental Forests, College of Agriculture,' Hokkaido University, 1974, **31**, 23; (*d*) M. Nomura, T. Tokoroyama, and T. Kubota, *J. Chem. Soc., Chem. Commun.*, 1975, 316; (*e*) T. Anthonsen, G. B. Loretzen,

and K. E. Malterud, *Acta Chem. Scand., Sect. B*, 1975, **29**, 529.
4 K. E. Malterud, T. Anthonsen, and J. Hjortas, *Tetrahedron Lett.*, 1976, 3069; M. Naji, M. Kubo, M. Fujita, T. Inoue, and M. Matsuo, *J. Chem. Soc., Chem. Commun.*, 1976, 388.
5 J. M. Edwards and U. Weiss, *Phytochemistry*, 1974, **13**, 1597; R. G. Cooke and R. L. Thomas, *Aust. J. Chem.*, 1975, **28**, 1053.
6 R. Thomas, *Biochemistry*, 1961, **78**, 807.
7 A. D. Harman and J. M. Edwards, *Tetrahedron Lett.*, 1977, 4471.
8 P. J. Roughley and D. A. Whiting, *J. Chem. Soc. C*, 1973, 2379.
9 P. Henley-Smith, D. A. Whiting, and A. F. Wood, *J. Chem. Soc., Perkin Trans. 1*, 1980, 614.
10 D. A. Whiting and A. F. Wood, *J. Chem. Soc., Perkin Trans. 1*, 1980, 623.
11 M. F. Semmelhack and L. S. Ryono, *J. Am. Chem. Soc.*, 1975, **97**, 3872.
12 *Org. Synth.*, 1930, **10**, 115.
13 C. F. Beam, M. C. D. Dyer, R. A. Schwarz, and C. R. Hanser, *J. Org. Chem.*, 1970, **35**, 1806; G. N. Barber and R. A. Olofson, *ibid.*, 1978, **43**, 3015.
14 W. G. Kofron and M. K. Yeh, *J. Org. Chem.*, 1976, **41**, 439.
15 F. Krollpfeiffer and W. Schäfer, *Ber.*, 1923, **56**, 620.
16 R. G. R. Bacon and H. A. O. Hill, *Q. Rev., Chem. Soc.*, 1965, 101; P. E. Fanta, *Synthesis*, 1974, 9; *Chem. Rev.*, 1964, **64**, 613.

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