Spirans. Part 12.[1] Stereochemical Control in the Oxidative Cyclisation of Bisnaphthols

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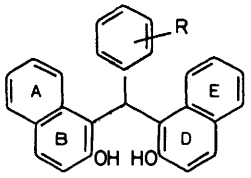
Almost all oxidising agents cyclise benzylidene-1,1'-bis-2-naphthol (1a) to the stereoisomers (2a) and (3a) of phenylnaphtho[2,1-*b*]furan-2(1*H*)-spiro-1'(2'*H*)-naphthalen-2'-one. A few are stereospecific. Hypobromite and persulphate give (2a), whereas iodine oxyacids and (diacetoxyiodo)benzene are specific for (3a). Radical-type oxidants such as hexacyanoferrate(III) and 2,4-di-t-butyl-6-phenylphenoxyl (4) give mixtures. Horseradish peroxidase behaves like hexacyanoferrate(III). The presence in the benzylidene residue of methoxy, nitro, fluoro, and other groups has little effect upon the isomer ratios, which are believed to be determined mainly by the bulk of the benzylidene group and the limits it imposes upon conformations during the oxidation processes. Oxidation by (diacetoxyiodo)benzene occurs through a cyclic intermediate (9) and gives the less-hindered (3a); oxidation of hypobromite occurs not directly but by exchange through an aryl hypobromite (Scheme) which halogenates its opposite naphthol nucleus and then substitutes the halogen, with inversion, thus leading to the more-hindered isomer (2a).

DISCHENDORFER [2] used alkaline hypobromite to oxidise the bisnaphthol (1a) to a compound shown later [3] to be the (racemic) spiran (2a) in which the phenyl substituent is on the side of the molecule away from the carbonyl group (the *R*S** configuration). The later work also



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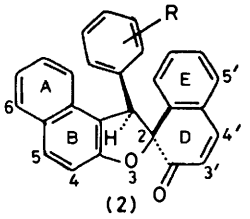
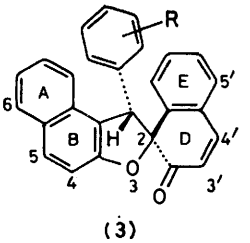


(2)

R	
a	H
b	2-OMe
c	3-OMe
d	4-OMe
e	2-F
f	3-F
g	4-F
h	3,4-$(OMe)_2$
i	3,4,5-$(OMe)_3$
j	4-Pr^i
k	3-NO_2

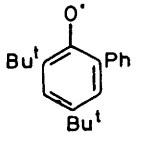


(3)

showed that some oxidants could produce the geometrical isomer (3a) with the phenyl substituent on the same side as the carbonyl group (the *R*R** configuration). Since such control over the stereochemistry is a novel feature in oxidative cyclisations we have extended these observations and discovered that a few oxidants are highly specific for one geometrical isomer or the other, though many have no specificity. The results allow only a limited insight into how the stereochemistry is determined, but show that reagents commonly used for phenolic coupling (and also peroxidase) have little specificity. It appears that specificity is associated with 'two-electron' oxidants operating through what are really substitution reactions rather than with 'one-electron' oxidants.

A selection of results is presented in Table 1; the reagents were used as they usually are for phenol oxidations so that the conditions vary widely and the yields are not optimised. It is clear that Dischendorfer's isomer (2a) is much the less common one although most oxidants give mixtures. It is also clear that a few oxidants are highly specific for one isomer or the other and that solvents and other circumstances can affect the specificity

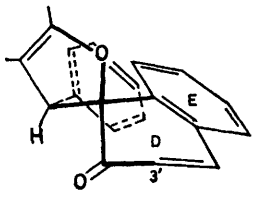
From Table 1 we selected four oxidants for more detailed study; (diacetoxyiodo)benzene because it is specific for isomer (3a), hypobromite because it is specific for isomer (2a), hexacyanoferrate(III) (ferricyanide) because it is the oxidant most commonly used in phenolic coupling studies, and the aryloxyl radical [4] (4) because many phenolic coupling reactions are believed to have radical intermediates. Since the orientation of the μ-phenyl group is the object of study, a series (1) of bisnaphthols substituted on this phenyl group with fluorine or one methoxy-group was examined in order to determine, if possible, whether the orientation is affected by electronic factors. The results (Tables 2 and 3) disclose no variation that can be directly ascribed to electronic effects in the μ-phenyl substituent, and we con-



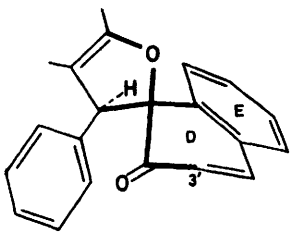
(4)

clude that the orientation is determined mainly by steric (bulk) effects. Spirans with other substituents could also be obtained specifically (Tables 5, 6), although these oxidations were not conducted under analytical conditions. Structural assignments *etc.* are described in the following paper.[5]

The spiran framework can exist in either of two conformations. The μ-phenyl group always collides with



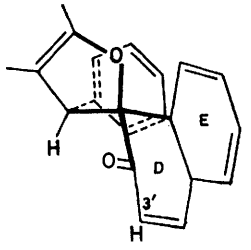
(5a)



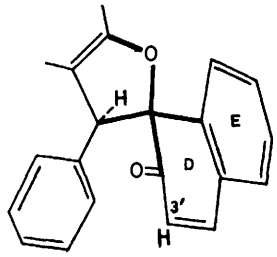
(5b)

either ring E or the carbonyl group and collisions are greatest in the conformations (5a) and (5b) with the oxygen atom vertical. Thus the spirans should ordinarily exist with the oxygen atom in plane [5] as in (6a) and (6b), although during formation, orbital overlap requirements are properly met only in the more hindered conformations (5a) and (5b).

Thus steric effects are therefore large during the formation of the spirans, and models clearly show that the avoidance of a collision between the μ-phenyl group and ring E in structure (5a) is the decisive requirement. In the absence of any other factors, therefore, oxidative cyclisation of bisnaphthol (1a) should give spiran (3a) rather than Dischendorfer's isomer (2a). As noted



(6a)



(6b)

already, Dischendorfer's isomer is indeed seldom the favoured one (Table 1).

Isomers of the series (2) exhibit in their ^1H n.m.r. spectra [5] a doublet near δ 6.1 (vinylic H-3′) as in the

TABLE 1

General survey of oxidations of bisnaphthol (1a) to spirans (2a) and (3a) [a]

Oxidant	Medium	Total spiran yield (%)	Isomer ratios (%) [b] Spiran (2a)	Spiran (3a)	Notes
MnO_2	$CHCl_3$	71	53	47	
$KMnO_4$	acetone	48	0	99	Oxidant added to substrate
		52	20	80	Substrate added to oxidant
$Mn(acac)_3$	CS_2	91	33	67	Reflux 12 h
	MeCN	76	27	73	Long reflux
$Co(acac)_3$	CS_2	28	22	78	Long reflux
$FeCl_3$	AcOH				Mainly formation of dibenzoxanthen
	Aq. EtOH	60	30	70	
	Tetrahydrofuran	17	26	74	
$Pb(OAc)_4$	EtOAc	40	37	63	
	Pyridine	63	39	61	
	Benzene	56	51	49	
	$CHCl_3$–SiO_3	90	34	66	
Cu_2Cl_2–pyridine–oxygen	1,2-Dichlorobenzene	60	17	83	
$(Ph_3P)_3RhCl$–O_2	Benzene	23	26	74	
	Benzene	33	12	88	After reduction of catalyst by H_2
Pd–C–O_2	EtOAc	65	39	61	
OsO_4	Ether				Bisnaphthol recovered from brown solution
$K_2S_2O_8$	5% Aq. KOH	40	99	0	By isolation only
KOBr	5% Aq. KOH	59	95	5	
KOI	5% Aq. KOH	38	62	38	
HIO_4	Bu^tOH–H_2O (5 : 1 v/v)	62	25	75	
$NaIO_4$	AcOH	94	0	99	
PhIO	Benzene	50	0	99	
$PhIO_2$	Benzene	21	0	99	
$PhI(OAc)_2$	Benzene	82	0	99	
$PhCO_3H$	$CHCl_3$	63	13	87	
	AcOH–NaOAc	33	29	71	
$K_3Fe(CN)_6$	Aq. pyridine	51	45	55	
	2M-aq. NaOH–EtOH	76	72	28	Oxidation very slow at pH 6
$K_2(SO_3)_2NO$	5% KOH in aq. MeOH	28	35	65	
	5% Aq. KOH–benzene	72	41	59	
1-Chlorobenzotriazole	CH_2Cl_2	27	12	88	
Aroxyl radical (4)	Benzene	84	51	49	
	Ether–pentane	90	46	54	
Tetrachloro-1,2-benzoquinone	EtOAc	47	13	87	Very slow; reflux 7 h
	benzene	20	0	99	Very slow; reflux 7 h

[a] At 22—25 °C except where indicated. In general, reaction mixtures contained 1—2% (w/v) of the substrate and 1.5 mol equiv. of oxidant except for slow reactions or those utilising oxygen where an excess was employed. [b] Isomer ratios were usually determined by ^1H n.m.r. analysis.

spectrum of the parent spiran with no μ-phenyl group. In contrast, isomers of series (3) exhibit the resonance at *ca.* δ 5.4, the upfield shift being due to shielding by the μ-phenyl group, in accordance with structure (6b). The two series can also be distinguished merely by inspection, all isomers of series (2) being bright yellow (as is the parent spiran without the μ-phenyl group) while those of series (3) are only very faintly yellow or cream. Presumably in the excited state the carbonyl oxygen atom will bear an increased π-electron density that will be repelled by the electrons of the phenyl group when this is on the same side. The effect is known elsewhere.[6]

TABLE 2

Oxidation of bisnaphthols of series (1a—g) by (diacetoxyiodo)benzene

		In benzene			In pyridine			In acetic acid		
		Total spiran(s)	Isomer ratios (%)		Total spiran(s)	Isomer ratios (%)		Total spiran(s)	Isomer ratios (%)	
Bisnaphthol structure	R	Yield (%)	Series (2a—g)	Series (3a—g)	Yield (%)	Series (2a—g)	Series (2a—g)	Yield (%)	Series (2a—g)	Series (3a—g)
(1a)	H	85	0	99	80	1	99	79	15	85
(1b)	2-OMe	90	1	99	72	2	98	52	35	65
(1c)	3-OMe	68	2	98	83	2	98	87	13	87
(1d)	4-OMe	62	2	98	82	2	98	68	21	79
(1e)	2-F	98	2	98	84	2	98	75	25	75
(1f)	3-F	87	0	99	87	2	98	86	17	83
(1g)	4-F	88	0	99	81	1	99	80	0	99

the reactions are not reversible and the results are not attributable to changes from kinetic to thermodynamic control.

Oxidations with (Diacetoxyiodo)benzene.—In benzene or pyridine the bisnaphthols (1) all give high yields of a product consisting almost entirely of spirans of series (3)—that is, the less-hindered isomers (Table 2). A mechanism dependent upon simple, neutral phenoxyl radicals would have given results like those from oxidations with hexacyanoferrate(III) or aryloxyl radical (4), *i.e.* mixtures not strongly favouring either isomer (Table 3); it is therefore ruled out. But a mechanism dependent upon cation radicals (especially phenoxenium oxygen [7]) might well produce the observed result if, for example, the μ-phenyl group stabilised the cation radical by interacting with an oxygen atom (the one destined to become

TABLE 3

Oxidations of bisnaphthols of series (1a—g) by hypobromite, hexacyanoferrate(III), and aryloxyl radical (4)

		KOBr in toluene–water			$K_3Fe(CN)_6$ in benzene–water			Aryloxyl (4) in benzene		
		Total spiran(s)	Isomer ratios (%)		Total spiran(s)	Isomer ratios (%)		Total spiran(s)	Isomer ratios (%)	
Bisnaphthol structure	R	yield (%)	Series (2a—g)	Series (3a—g)	yield (%)	Series (2a—g)	Series (3a—g)	yield (%)	Series (2a—g)	Series (3a—g)
(1a)	H	98	99	0	96	40	60	78	67	33
(1b)	2-OMe	97	99	0	99	33	67	93	48	52
(1c)	3-OMe	98	99	0	96	32	68	97	56	44
(1d)	4-OMe	96	99	0	99	37	63	90	88	12
(1e)	2-F	97	99	0	96	33	67	93	67	33
(1f)	3-F	96	99	0	99	42	58	88	62	38
(1g)	4-F	98	99	0	99	37	63	84	60	40

For selected bisnaphthols the total spiran product was usually isolated and subjected to n.m.r. analysis to determine the isomer proportions (Tables 2 and 3); if by-products appeared to be interfering then a chromatographic step was interposed and the spiran fractions re-combined for analysis. Reliance was placed mainly on the vinylic resonances (H-3′) which are well separated, but whenever possible other resonances and isomer isolations were used in support. Oxidations were usually

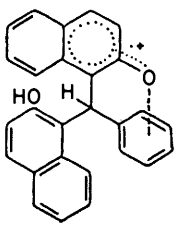
TABLE 4

Radical oxidations

				Isomer ratios (%)	
Bisnaphthol	R	Mode of addition [a]	Total spiran yield (%)	Series 2	Series 3
(1d)	4-OMe	Direct	90	88	12
(1d)	4-OMe	Inverse	85	78	22
(1j)	4-$CHMe_2$	Direct	73	68	32
(1j)	4-$CHMe_2$	Inverse	78	57	43

[a] Direct—bisnaphthol added to radical. Inverse—radical added to bisnaphthol.

the carbonyl oxygen atom) as in diagram (7). However, the results are so little affected by a wide range of substituents in the μ-phenyl group, including strongly elec-



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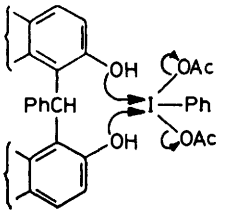
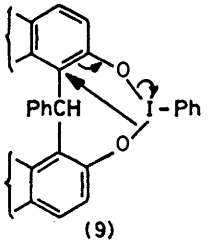


(8)

tron-attracting substituents, that this explanation is also rejected.

A study of the kinetics of oxidations of 1,2-glycols by this reagent led Pausacker to suggest a cyclic intermediate as in oxidations by periodate.[8] As written in



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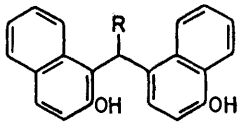
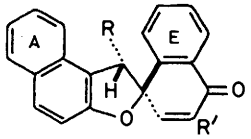


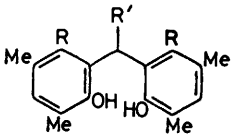
(10) a; R = Ph
b; R = H

diagram (8) for the present case, the cyclic intermediate is formed by two nucleophilic displacements of a kind that have been observed for azide ion [9] and for methanol [10] and shown to be reversible. Thus once a cyclic intermediate is formed it could collapse as in diagram (9) to give a spiran (provided that the stereochemistry is favourable) or dissociate (if it is not). Models confirm once again that the bulk of the μ-phenyl can be decisive; there is no bar to the formation of spirans of series (3), but for series (2) the μ-phenyl group abuts the position that should be occupied by the oxygen atom as it comes in to form the heterocyclic ring.

Spirans are still formed where a cyclic intermediate

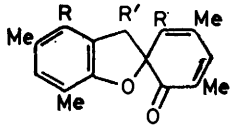


(11) a; R = Ph, R' = H
b; R = R' = H
c; R = Ph, R' = Br



(12) a; R = H, R' = Ph
b; R = Me; R' = H

is improbable but the yields are poor. Thus, the bisnaphthol (10a) is oxidised to spiran (11a) despite the distance between the hydroxy-groups. The only isomer detected had structure (11a) with the μ-phenyl group away from ring E, which tends to confirm that the selective



(13) a; R = H; R' = Ph
b; R = Me; R' = H

orientation is not a result of some interaction between the μ-phenyl group and the incipient carbonyl group but merely a bulk effect.

TABLE 5

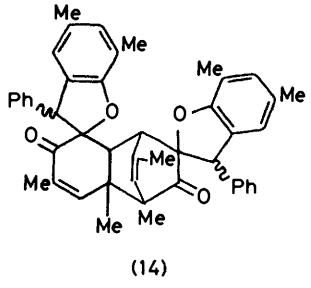
Analytical characterisation of bisnaphthols of series (1b—k)

Structure	R	Solvent [b]	M.p. (°C)	Found (%) C	Found (%) H	M [c]	I.r. (cm^{-1}) [a] OH	I.r. (cm^{-1}) [a] C:O
(1b)	2-OMe	EA–LP	189—190	82.8	5.7	406 [d]	3 300	
acetate		EA–LP	192—193	77.8	5.4	490 [e]		1 742
(1c)	3-OMe	EtOH	199—200	82.8	5.7	406 [d]	3 300	
acetate		EA–LP	187	78.2	5.3	490 [e]		1 742
(1d)	4-OMe	EtOH	186—187	82.6	5.6	406 [d,f]	3 300	
(1e)	2-F	Aq. EtOH	192	82.1	4.8	394 [g]	3 300	
acetate		EA–LP	159	78.1	5.1	478 [h]		1 742
(1f)	3-F	Aq. EtOH	114	81.9	4.8	394 [g]	3 300	
acetate		EA–LP	219—220	78.1	4.9	478 [h]		1 741
(1g)	4-F	Aq. EtOH	109—110	82.2	4.7	394 [g]	3 300	
acetate		EA–LP	218	77.6	4.7	478 [h]		1 742
(1h)	3,4-(OMe)$_2$	EA	206—208	79.95	5.65	436 [i]	3 300	
acetate		EA	195—197	76.1	5.6	520 [j]		1 740
(1i)	3,4,5-(OMe)$_3$	EA	205—207	77.3	5.55	466 [k]	3 360	
acetate		EA	199—200	74.3	5.4	550 [l]		1 740
(1j)	4-Pr^i	EA	175—177	86.1	6.4	418 [m]	3 300	
acetate		EA	197—198	81.1	5.9	502 [n]		1 742
(1k) [q]	3-NO$_2$	B	189—191	78.0	4.8	421 [o]	3 300	
acetate [q]		EA	250—252	73.4	4.6	505 [p]		1 740

EA = EtOAc, LP = light petroleum, B = benzene.

[a] From mulls in paraffin. [b] All compounds crystallised as needles. [c] From mass spectra. [d] $C_{28}H_{22}O_3$ requires C, 82.7; H, 5.45%; *M*, 406. [e] $C_{32}H_{26}O_5$ requires C, 77.9; H, 5.4%; *M*, 490. [f] Lit. m.p. 190 °C (M. S. Kharasch and J. Porsche, *J. Org. Chem.*, 1936, **1**, 265). [g] $C_{27}H_{19}FO_2$ requires C, 82.1; H, 4.8%; *M*, 394. [h] $C_{31}H_{23}FO_4$ requires C, 78.25; H, 4.8%; *M*, 478. [i] $C_{29}H_{24}O_4$ requires C, 80.0; H, 5.5%; *M*, 436. [j] $C_{33}H_{28}O_6$ requires C, 76.1; H, 5.4%; *M*, 520. [k] $C_{30}H_{26}O_5$ requires C, 77.2; H, 5.6%; *M*, 466. [l] $C_{34}H_{30}O_7$ requires C, 74.2; H, 5.5%; *M*, 550. [m] $C_{30}H_{26}O_2$ requires C, 86.1; H, 6.3%; *M*, 418. [n] $C_{34}H_{30}O_4$ requires C, 81.25; H, 6.0%; *M*, 502. [o] Calc. for $C_{27}H_{19}NO_4$: C, 76.95; H, 4.5%; *M*, 421. [p] Calc. for $C_{31}H_{23}NO_6$: C, 73.65; H, 4.6%; *M*, 505. [q] M. Zenoni, *Gazzetta*, 1893, **23***II*, 218.

In passing, we note that (diacetoxyiodo)benzene may be a reagent of choice for oxidative cyclisations at oxygen. For example, the bisphenol (10b) lacks a μ-phenyl group and no oxidising agent except this one gave the spiran (11b); even so, the yield was poor presumably because of side reactions.[11] Oxidation of the bisphenol (12a), which does possess a μ-phenyl group, was again very successful although the product was not the spiran (13a) itself but a dimer (14) formed in a fast (2 + 4) cycloaddition; the analytical and spectroscopic properties of the product conform with this structure which is otherwise based upon close analogy.[12] One more methyl substituent is enough to prevent the dimerisation; accordingly, the bisphenol (12b) did yield the expected spiran (13b). Similarly, the diol (15) supplied the spiran (16). The chloro-diol (17) gave the chlorospiran (18), and again the only stereoisomer encountered had the μ-phenyl group *away* from ring E.



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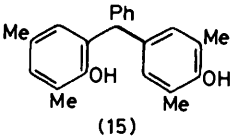

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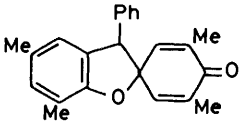

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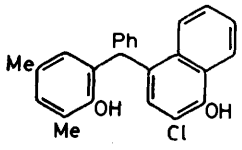

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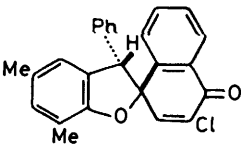


(18)

TABLE 6

Analytical and spectroscopic characterisation of spirans of the series (2b—k) and (3b—k)

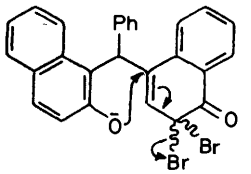
Structure	R	Config.	Solvent †	Habit	M.p. (°C)	Found (%) C	Found (%) H	M [a]	I.r.[b] ν(CO)/cm⁻¹	¹H N.m.r. (δ) [c] CHAr₂	3′-H [d]	OMe
(2b)	2-OMe	1*R**, 2*S**	B–E	Yellow needles	194—196	83.3	5.0 [e]	404	1 681	5.86	6.17	3.45
(3b)	2-OMe	1*R**, 2*R**	B	Pale yellow needles	229	83.1	5.1 [e]	404	1 678	5.91	5.44	3.58
(2c)	3-OMe	1*R**, 2*S**	B	Yellow needles	192—194	83.0	5.0 [e]	404	1 685	5.32	6.18	3.46br
(3c)	3-OMe	1*R**, 2*R**	B–E	Pale yellow needles	230—232	83.1	5.2 [e]	404	1 677	5.15	5.53	3.58br
(2d)	4-OMe	1*R**, 2*S**	B	Yellow needles	195—197	83.4	5.05 [e]	404	1 682	5.33	6.02	3.58
(3d)	4-OMe	1*R**, 2*R**	B	Pale yellow needles	227—229	82.7	5.2 [e]	404	1 678	5.13	5.50	3.65
(2e)	2-F	1*R**, 2*S**	B	Yellow needles	226—228	82.6	4.3 [f]	394	1 684	5.74	6.17	
(3e)	2-F	1*R**, 2*R**	B–H	Cream rhombs	215—217	82.7	4.6 [f]	394	1 675	5.63	5.50	
(2f)	3-F	1*R**, 2*S**	B–E	Yellow needles	225	82.7	4.5 [f]	394	1 678	5.37	6.27	
(3f)	3-F	1*R**, 2*R**	B–H	Cream needles	221—223	82.6	4.6 [f]	394	1 678	5.16	5.38	
(2g)	4-F	1*R**, 2*S**	E–H	Yellow needles	145	82.6	4.4 [f]	394	1 681	5.39	6.27	
(3g)	4-F	1*R**, 2*R**	E–H	Cream needles	214	82.6	4.5 [f]	394	1 676	5.18	5.55	
(2h)	3,4-$(OMe)_2$	1*R**, 2*S**	A	Yellow rhombs	185	80.1	5.1 [g]	434	1 680	5.32	6.25	3.69 3.37br
(3h)	3,4-$(OMe)_2$	1*R**, 2*R**	EA	Pale yellow rhombs	218—220	80.1	5.2 [g]	434	1 670	5.23	5.62	3.88 3.68br
(2i)	3,4,5-$(OMe)_3$	1*R**, 2*S**	B	Yellow needles	197—198	77.8	5.4 [h]	464	1 680	5.30	6.24	3.64 3.38br
(3i)	3,4,5-$(OMe)_3$	1*R**, 2*R**	B	Cream needles	196—198	77.6	5.4 [h]	464	1 670	5.14	5.62	3.82 3.65br
(2j)	4-Pr^i	1*R**, 2*S**	B	Yellow needles	200—201	86.8	6.0 [i]	416	1 680	5.36	6.26	
(3j)	4-Pr^i	1*R**, 2*R**	A	Pale yellow needles	207—209	86.7	6.0 [i]	416	1 678	5.21	5.54	
(2k)	3-NO_2	1*R**, 2*S**	B	Yellow rods	225—227	77.4	4.2 [j,k]	419	1 690	5.49	6.33	
(3k)	3-NO_2	1*R**, 2*R**	B	Pale yellow needles	241—243	77.0	3.8 [k,l]	419	1 678	5.29	5.57	

[a] From mass spectra. [b] In paraffin mulls. There were no OH bands. [c] In $CDCl_3$ at 100 MHz. [d] Doublets, *J* 10 Hz. [e] $C_{28}H_{20}O_3$ requires C, 83.15; H, 5.0%. [f] $C_{27}H_{19}FO_2$ requires C, 82.6; H, 4.4%. [g] $C_{29}H_{22}O_4$ requires C, 80.2; H, 5.1%. [h] $C_{30}H_{24}O_5$ requires C, 77.6; H, 5.2%. [i] $C_{30}H_{24}O_2$ requires C, 86.5; H, 5.8%. [j] Found: N, 3.3%. [k] $C_{27}H_{17}NO_4$ requires C, 77.3; H, 4.1; N, 3.3%. [l] Found: N, 3.4%.

† A = Acetone, B = benzene, E = diethyl ether, EA = ethyl acetate, H = hexane.

Oxidation by Hypobromite.—The chief result to be explained by the present study is the remarkable oxidation by hypobromite of the bisphenols (1) to the spirans of series (3)—that is, the more hindered products (Table 3). Yet the oxidant is the smallest of those studied and so least able to exert a bulk steric effect. It is also the least likely to form any sort of cyclic ester or complex with special requirements. Moreover, intermediary cations or cation radicals also seem to be excluded since once again a wide range of substituents on the μ-phenyl group has little or no effect upon the outcome. And simple radicals should have given mixtures. Because the oxidations were normally conducted with the substrate in toluene floating upon the aqueous oxidant, however, an interface phenomenon might have been important with the oxygen atoms mainly in the water and the hydrocarbon residues bunched together in the organic layer, an arrangement that would strongly favour the spirans of series (2). But similar oxidations conducted wholly in water showed the high specificity, although the yields were lower, so the interface is not significant.

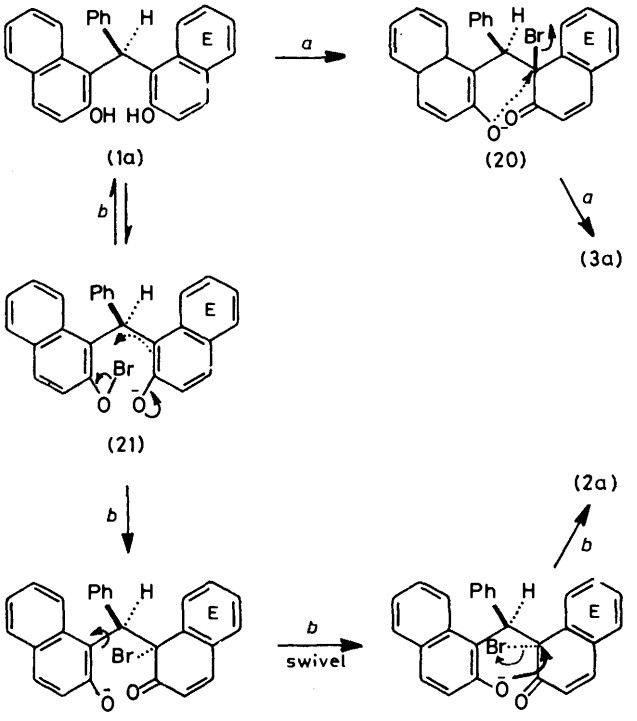
There is evidence that hypobromite acts by substitution rather than simple oxidation by electron-withdrawal. Thus the bisnaphthol (10a) affords the bromospiran (11c). Since the reagent does not brominate unsaturated ketones the bromine must have been introduced before cyclisation with the dibromo-ketone (19) as the most likely intermediate. The resulting spiran (11c) is now the less, not the more, hindered stereoisomer because (19) can obviously give either depending upon which bromine atom is lost.



(19)

In contrast, the bisnapthols of series (1) can take up only one bromine at either α-position and must then cyclise by internal nucleophilic substitution (Scheme). Shearing and Smiles [13] have indeed reported that bromo- and chloro-ketones similar to (20) can be isolated from related hypohalite reactions and have suggested that they are intermediates in spiran formation. Other analogies exist.[14] Before this mechanism can be accepted, however, it must be shown to be capable of explaining the unexpected specificity for the more-hindered products. Cyclisation by nucleophilic substitution (Scheme) cannot be of S_N1 type since stereospecificity would be lost. However, the carbonyl group in (20) can be expected to ensure S_N2 characteristics even in a benzylic halide, and therefore the problem is to decide how the configuration of the bromide (20) was determined. If the bisnaphthol takes up any propellor conformation [15] then one naphthol nucleus is screened from bromination on *both* sides, while the other is open on one side only. This situation would certainly provide stereochemical control, but models show that the spirans of series (3) would result instead of the observed ones (route *a*).

Hence bromination of the bisnaphthol by an external reagent does not lead to the correct result. But bromination can be internal; halogen exchanges can lead first to a naphthyl hypobromite (21) (Scheme; route *b*). Either naphthol nucleus can be involved and conformation

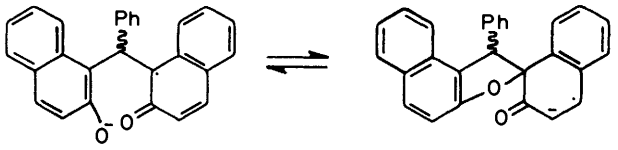


SCHEME

plays no part until internal bromination occurs as indicated in (21) when the μ-phenyl group interferes unless it is kept near the nascent carbonyl group and away from ring E. This establishes that the configuration of the bromo-ketone will be the *less* hindered one. But for the S_N2 substitution leading to cyclisation the oxide residue must be swivelled to the opposite side (route *b*), and this movement brings the μ-phenyl group into collision with ring E and spirans of series (2) result. Briefly, then, we consider that the same steric factor, *i.e.* repulsion between the μ-phenyl group and ring E, determines the configuration in *both* series of spirans (2) and (3), the differences arising from the fact that the hypobromite reaction includes an S_N2 inversion step. The results in Table 1 contain only two other oxidising agents leading specifically to a spiran of series (2); one is persulphate, which can be supposed to react exactly as does bromine giving intermediates with sulphate residues instead of bromine. The other is hypoiodite, and its imperfect stereospecificity can be attributed either to the greater tendency for iodides to react by S_N1 processes or to a minor pathway of the kind suggested for (diacetoxyiodo)-benzene.

Oxidations by Hexacyanoferrate(III).—The less-hindered isomers of series (3) preponderate roughly in the rati

2 : 1 (Table 3). Again substituents in the μ-phenyl group have little influence and the selectivity is presumed to have mainly steric origins. Some related cyclisations are considered [16] to involve the formation of a radical-anion which cyclises reversibly as shown for the present substrate:



The final step is removal of the second electron from the cyclised system. Because it contains a reversible stage this mechanism should ensure that the steric effect would limit spirans to series (3) under thermodynamic control. Since the energy barrier to phenoxyl radical dimerisation is very low [17] any biradical once formed should cyclise immediately whatever the orientation and in such a mechanism the stereoisomers should be formed in about equal amounts. The reagent is reported to form some kind of complex with phenolic chalcones; [18] but it oxidises the diol (10a) to the spiran (11a) so two *ortho*-hydroxy-groups are unnecessary and complex formation is unlikely. Nevertheless, a bulky oxidising agent would, if associated with the hydroxy-groups for an appreciable time, take up much of the space required by the μ-phenyl group on the incipient carbonyl side. That is, a bulky oxidising agent would favour spirans of series (2), if it had to operate by removing electrons from near the hydroxy-groups and not from more remote parts of the π-system. We favour this possibility for two reasons; first, in the oxidation of the bisnaphthol (10a) electrons can be removed from the *para*-hydroxy-group without any need for the reagent to approach the μ-phenyl group; accordingly, the product is the single spiran (11a) with the less hindered configuration. Second, the more bulky the oxidant the greater the proportion of hindered isomer it should produce, and our results are in accordance with this (see below).

Oxidations by Aryloxyl Radical (4).—Since phenolic coupling reactions are usually formulated with radical intermediates it is surprising that so little use has been made of aryloxyl radicals in general work. One cyclisation of a bisphenol to a spiran has been reported by other authors, who did not refer to the stereochemical aspect.[4] The more hindered spirans of series (2) preponderate roughly in the ratio 2 : 1 (Table 3). This preference is very readily explained by the bulk of the reagent, which is now extremely large. Placing the reagent near the naphthol oxygen atoms in order to abstract electrons inevitably causes a major collision with the μ-phenyl group if that is in the vicinity, and the change of orientation from the hexacyanoferrate oxidations is therefore understandable. Table 3 contains one unexpected feature that we cannot explain. The tendency to favour the more hindered isomer is noticeably greater when the η-phenyl group carries a 4-methoxy-substituent, no matter whether the oxidant is added to the bisnaphthol or *vice versa*. The cause can hardly be considered to be electronic in the absence of variations induced by other substituents, nor can it reasonably be considered to be steric since a 1-methylethyl group in position 4 has no such effect (Table 4).

Oxidation with Peroxidase.—Only the parent bisnaphthol (1a) was studied. A fine, aqueous dispersion was oxidised with hydrogen peroxide and a (commercial) horseradish peroxidase. The product (*ca.* 60%) was a mixture of the two spirans containing mainly the more hindered one (*ca.* 66%). Thus the enzyme resembles hexacyanoferrate(III) in its action in this respect as in others.[19]

EXPERIMENTAL

Derivatives of Benzylidene-1,1-bis-2-naphthol (1a).—These compounds were all prepared in the same way and characterised as their acetates obtained by the use of acetic anhydride and pyridine. Analytical results are listed in Table 5. The preparation of bisnaphthol (1d) is typical. Concentrated hydrochloric acid (1 ml) was added to 2-naphthol (5.8 g) and 4-methoxybenzaldehyde (2.7 g) in acetic acid (30 ml) at 0 °C and the mixture kept for 50 h. The pink-white solid that separated was washed with plenty of water, dried in air, and crystallised from ethyl acetate–light petroleum giving *p*-methoxybenzylidene-1,1′-bis-2-naphthol (1d) as needles (3 g).

Oxidations.—Conditions are given for the reactions used to compile Tables 2 and 3. General analytical details of the spirans of series (2) and (3) are listed in Table 6. Other oxidations are recorded in the following paper.[5]

(i) *(Diacetoxyiodo)benzene in benzene.* The oxidant [20] (500 mg) was added to a stirred solution of the appropriate diol (Table 4) (500 mg) in benzene (40 ml; dried by azeotropic distillation) at 22 °C. After 15 min the solvent was removed *in vacuo* without application of heat and the residual gum was chromatographed on neutral alumina (3% H_2O; 50 g) from benzene–light petroleum (b.p. 60—80 °C) (4 : 1 v/v). Fractions containing spirans were combined and the ratio of isomers determined by n.m.r. analysis in trichlorodeuteriomethane utilising the vinylic, methine, or methoxy-bands as appropriate. The averages for three runs are entered into Table 2. For preparative purposes chromatography of the oxidation product was unnecessary and the gum was recrystallised from a suitable solvent for analysis (Table 5).

Oxidation times of up to 20 h produced no change in isomer ratio; there was a slight fall in total yield of spirans. The spirans (2a) and (3a) were treated with oxidant as if they were bisnaphthols and were recovered unchanged.

(ii) *(Diacetoxyiodo)benzene in pyridine.* The procedure in (i) was adopted with pyridine (dried over molecular sieve and redistilled) in place of benzene and the products were isolated after 4 h. The mixture was poured into water (200 ml) and the precipitate collected, washed with dilute hydrochloric acid and then water, and dried in air. Further work-up and analysis followed the method in (i). The results are listed in Table 2.

(iii) *(Diacetoxyiodo)benzene in acetic acid.* The oxidant (500 mg) in acetic acid (20 ml) was added in drops to a stirred solution of the bisnaphthol (500 mg) in acetic acid (40 ml) at 22 °C. After 1 h the crude product was isolated

by pouring the mixture into water (200 ml) and washing the precipitate with much water. Purification and analysis followed the methods in (i) and (ii), and the results are entered into Table 2.

The spirans (2a) and (3a) were similarly treated as if they were diols but without significant change. Each spiran (500 mg) was left in acetic acid (50 ml) at 22 °C containing iodobenzene (0.5 ml) and a small amount (*ca.* 5 mg) of (diacetoxyiodo)benzene. The spirans were recovered after 2 h without significant loss.

(iv) *Hypobromite.* Bromine (1.0 g) was added to 10% aqueous potassium hydroxide (15 ml) cooled to 0 °C, and added slowly to a stirred solution of the bisnaphthol (500 mg) in toluene (50 ml) at 0 °C. After 30 min, the toluene layer was shaken with 10% aqueous potassium hydroxide and then water, and dried (Na_2SO_4). Removal of the toluene *in vacuo* left almost pure spiran not requiring chomatography (Table 3).

(v) *Hexacyanoferrate*(III). The bisnaphthol (200 mg) in benzene (50 ml) was stirred with potassium hexacyanoferrate(III) (3.0 g) in water (30 ml) containing potassium hydroxide (4.0 g). After 18 h the benzene layer was washed with brine (2 × 30 ml), dried (Na_2SO_4), and concentrated. The product was chromatographed on neutral alumina (3% H_2O; 20 g) from benzene. All fractions containing spirans were combined and the ratios of isomers determined spectroscopically (Table 3).

Solutions of spirans (2a) or (3a) in benzene were kept in contact with potassium hexacyanoferrate(II) in 2M-sodium hydroxide for 18 h. The recovered spirans showed no change.

(vi) 4,6-*Di-t-butyl-2-phenylphenoxyl* [4] (4). The apparatus consisted of a multiple-necked flask A, used to accommodate the phenoxyl radical, fitted with an outlet at the bottom that led into another multiple necked flask B used to receive spent solutions. Both flasks were flushed with nitrogen throughout the oxidations.

Potassium hexacyanoferrate(III) (8.0 g) in deaerated water (60 ml) was placed in flask A and flushing with nitrogen commenced. After 15 min 4,6-di-t-butyl-3-phenylphenol (500 mg) in benzene (30 ml) was added to flask A and the two phases mixed vigorously for 1.0—1.5 h by means of a magnetic stirrer. The aqueous layer was rejected into flask B. The organic layer was washed with deaerated water (3 × 50 ml) and the washings also disposed of into flask B.

A solution of the bisnaphthol (500 mg) in benzene (40 ml) was then slowly added to the stirred radical solution until the green colour became yellow. The benzene solution was then removed (it became green again in contact with air), dried (Na_2SO_4), and concentrated. Chromatography on alumina (3% H_2O; 25 g) from benzene–light petroleum (b.p. 60—80 °C) (4 : 1 v/v) gave firstly 4,6-di-t-butyl-2-phenylphenol and then spirans as listed in Tables 3 and 4.

For the bisnaphthols (1d) and (1i) additional oxidations were undertaken in which radical oxidant was added from flask A to the bisnaphthol solution in flask B until this took up a permanent green tinge. The results are in Table 4.

(vii) *Peroxidase.* The bisnaphthol (1a) (199 mg) was dissolved in a mixture of acetone and trichloromethane and Tween 80 (0.5 ml) was added. Removal of volatile materials left a yellow oil that was dissolved in tetrahydrofuran (3 ml) and injected suddenly into water (400 ml) to give a very fine suspension. Hydrogen peroxide (28%; 1.4 ml) and horseradish peroxidase (20 mg) were added and the mixture stirred for 20 h at 21 °C. Extraction with trichloromethane (4 × 50 ml) isolated a yellow solid (203 mg), recrystallisation of which from ethyl acetate gave spiran (3a), m.p. 265 °C. ^1H N.m.r. analysis showed that the yellow solid also contained the spiran (2a) in the proportion (2a) : (3a) : 33 : 67.

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