Umpolung of *o*-Phenylenediamines by Conversion into Isobenzimidazole. An Expedient Approach to Heterocycles with Nucleophilic Substituents

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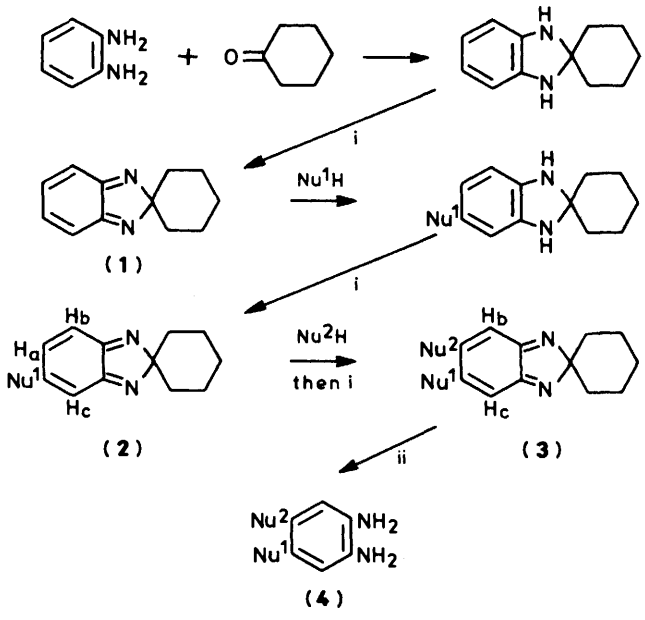
Isobenzimidazole-2-spirocyclohexane (**1**) can be made to react with nitrogen, oxygen, sulphur, and carbon nucleophiles to give mono- and di-substituted derivatives. On reductive ring-opening the correspondingly substituted *o*-phenylenediamine is obtained. The scope of this synthetic principle has been studied and the reaction used to prepare various heterocycles with substituents that are difficult to introduce by conventional methods. Selenadiazole or its 4-chloro and 4,5-dichloro derivatives were found to be unsuitable alternatives to (**1**).

We briefly reported[1] on the reactions and synthetic utility of isobenzimidazole-2-spirocyclohexane (2*H*-benzimidazole-2-spirocyclohexane) (**1**) for the preparation of nucleophilically substituted *o*-phenylenediamines. We now wish to give the experimental details which, through modification, led in some cases to higher yields than previously[1] stated. Also, some further examples of this synthetic principle which utilizes the readily available isobenzimidazole as a synthon are described.

o-Phenylenediamine, an important starting material for a range of *N*-heterocycles,[2] readily undergoes electrophilic substitution (nitration, halogenation) either directly or *via* protection as a benzothia-[3] or benzoselena-diazole.[4] In contrast, the introduction of a nucleophile necessitates a cumbersome reaction sequence[5] which is reflected in the dearth of the literature quoting *o*-phenylenediamine-derived heterocycles with nucleophilic groups in the benzene ring.

Conversion of the *o*-phenylenediamine into the isobenzimidazole (Scheme 1) results in an 'umpolung,'[6] since the heterocycle acting as a 'diamine equivalent' is amenable to the introduction of nucleophiles. This occurs by 1,4-addition followed by oxidation, and reductive cleavage generates a nucleophilically mono- or di-substituted diamine [*cf.* compound (**4**)]. The reactivity of *o*-phenylenediamine is thus reversed by a temporary transformation into a 2*H*-benzimidazole (**1**).

The ready addition of nucleophiles to isobenzimidazole is predictable on the grounds that the substrate (**1**) can be regarded as an *o*-benzoquinone di-imine that is stabilised by an sp^3 carbon bridge supplied by a cyclohexyl ring. Isolation of the parent *o*-benzoquinone di-imine was first attempted by Willstätter[7] and has remained a challenge, although systematic studies in the field of *o*-benzoquinone di-imine have continued.[8] Our attempts to produce isobenzimidazoles by an analogous condensation with smaller or larger rings or acyclic ketones led to 2,3-dihydro-1*H*-1,5-benzodiazepines.[9] Only by a circuitous route[10] involving benzofurazan *N*-oxide and nitroalkanes could isobenzimidazoles with other than spirocyclohexyl rings be produced; these proved, however, to be unstable. The reluctance of cyclic ketones other than cyclohexanone to produce a dihydrobenzimidazole is probably best explained by the concept of I-strain:[11] Formation of a dihydrospirobenzimidazole entails a change from sp^2 to sp^3 in the bond hybridisation of the cyclic ketone. In cyclohexanone this leads to a stable chair conformation free from bond opposition, thus favouring an $sp^2 \rightarrow sp^3$ transition. However, such a change in the bond hybridisation introduces additional bond opposition in cyclopentanone and in other medium sized ring ketones, hence disfavouring condensation with *o*-phenylenediamine. However, some stable dihydrobenzimidazoles associated with a five-membered spiro-ring obtained from aromatic *o*-diamines and isatin have been reported.[12] The situation is in fact analogous to the cyanohydrin formation[11] from cycloalkanones, the equilibrium constant[13] of which is highest for cyclohexanone of the common, and medium-sized ring ketones.



Scheme 1. *Reagents:* i, [O]; ii, Pd/H_2, AcOH

Reaction with Nitrogen Nucleophiles.—Examples of products (**2**) and (**3**) resulting from the interaction of primary and secondary amines with the isobenzimidazole (**1**) are listed in Table 1 as well as of the tetracyclic systems (**5**; R = Me, Y = NMe, *n* = 2 or 3). The phenazine (**6**) (or its tautomer) was obtained in high yield from *o*-phenylenediamine as the nucleophile; the monoaminoisobenzimidazoles [*e.g.* (**2**; $Nu^1 = C_5H_{10}N$)] are red or orange ($\lambda_{max.}$ 480 nm) while the diamino compounds [*e.g.*(**3**; $Nu^1 = Nu^2 = C_5H_{10}N$)] are yellow ($\lambda_{max.}$ 380 nm). In compounds (**3**) hindrance prevents either amino group from becoming coplanar with the isobenzimidazole ring, and thereby from co-conjugation. The 5-chloro-6-piperidinoisobenzimidazole (**3**; $Nu^1 = Cl$, $Nu^2 = C_5H_{10}N$) obtained as one of the products from 5-chloroisobenzimidazole and piperidine was orange ($\lambda_{max.}$ 416 nm) indicating that chlorine

Table 1. Mono- and di-amino substituted isobenzimidazoles

Compound (2) Nu¹	Yield (%)	M.p. (°C)	Found (%) (Required) C	H	N	Formula	δ(CDCl₃; 60 MHz)/p.p.m. $H_a + H_b$	H_c	Aliphatics
C_4H_8N	65	178	75.1 (75.3)	8.6 (8.3)	16.2 (16.5)	$C_{16}H_{21}N_3$	7.3 (br)	5.8 (br)	3.4 (4 H, m), 2.2—2.5 (14 H, m)
$C_5H_{10}H$	68	99	75.4 (75.8)	8.4 (8.6)	15.9 (15.6)	$C_{17}H_{23}N_3$	7.1 (br)	6.25 (br)	3.3 (4 H, m), 1.6—1.8 (16 H, m)
Morpholino	58	103	70.4 (70.8)	7.8 (7.8)	15.6 (15.5)	$C_{16}H_{21}N_3O$	7.2 (br)	6.3 (br)	3.9 (4 H, m), 3.3 (4 H, m), 1.8 (10 H)
$CH_2CH_2N(Me)CH_2CH_2N$	34	120	71.7 (71.8)	8.6 (8.5)	19.6 (19.7)	$C_{17}H_{24}N_4$	7.2 (br)	6.25 (br)	3.3 (4 H, m), 2.6 (4 H, m), 2.3 (3 H, s), 1.8 (10 H, m)
$C_6H_{12}N$	32	109	76.3) (76.3)	8.9 (8.9)	15.0 (14.8)	$C_{18}H_{25}N_3$	7.1 (br)	5.9 (br)	3.4 (4 H, m), 1.6 (18 H, m)
MeNH	30	219	72.2 (72.5)	8.2 (8.0)	19.2 (19.5)	$C_{13}H_{17}N_3$	7.2 (br)	5.8 (br)	3.1 (3 H, d), 1.8 (10 H, m)
$C_6H_{11}NH$	21	204	76.0 (76.3)	8.8 (8.9)	14.8 (14.8)	$C_{18}H_{25}N_3$	7.0 (d) 6.6 (d)	5.8 (s)	4.9 (d, NH), 3.3 (1 H, m), 1.7 (20 H, m)
PhNH	29	77	77.8 (78.0)	7.1 (6.9)	15.3 (15.2)	$C_{18}H_{19}N_3$	6.6—7.4 (7 H, m)	6.4 (s)	5.2 (1 H, br, NH), 1.5—2.0 (10 H, m)
Compound (3) Nu¹	Nu²						$H_b + H_c$		
$C_5H_{10}N$	$C_5H_{10}N$	35	174	74.9 (75.0)	9.3 (9.2)	15.9 (15.9)	$C_{22}H_{32}N_4$	6.5 (s)	3.1 (8 H, m), 1.7 (22 H, m)
Morpholino	Morpholino	39	222	67.1 (67.4)	7.9 (7.9)	15.6 (15.7)	$C_{20}H_{28}N_4O_2$	6.6 (s)	3.9 (8 H, m), 3.3 (8 H, m), 1.8 (10 H, m)
$CH_2CH_2N(Me)CH_2CH_2N$	$CH_2CH_2N(Me)CH_2CH_2N$	28	206	69.1 (69.1)	9.0 (8.9)	21.8 (22.0)	$C_{22}H_{34}N_6$	6.6 (s)	3.3 (8 H, m), 2.6 (8 H, m), 2.4 (6 H, s), 1.8 (10 H, m)
$C_5H_{10}N$	$CH_2CH_2N(Me)CH_2CH_2N$	38	181	71.8 (71.9)	9.1 (9.1)	18.8 (19.1)	$C_{22}H_{33}N_5$	6.5 (s)	3.2 (8 H, m), 2.7 (4 H, m), 2.4 (3 H, s) 1.7 (16 H)
PhNH	PhNH	36	218	78.4 (78.2)	6.2 (6.6)	15.3 (15.2)	$C_{24}H_{24}N_4$		7.5 (12 H, m), 6.33 (1 H, s), 1.9 (10 H, m)*
$MeN[CH_2]_2NMe$		28	192	71.2 (71.1)	8.2 (8.2)	20.7 (20.7)	$C_{16}H_{22}N_4$	5.9 (s)	3.4 (4 H, s), 3.0 (6 H, s), 1.8 (10 H, m)
$MeN[CH_2]_3NMe$		17	140	71.4 (71.8)	8.8 (8.5)	19.7 (19.2)	$C_{17}H_{24}N_4$	6.1 (s)	3.4 (4 H, t), 3.0 (6 H, s), 1.8 (12 H, m)

* N.m.r. in CF_3CO_2H.

poses less hindrance than an amino group. Addition to the 5-piperidino compound (**2**; $Nu^1 = C_5H_{10}N$) of methyl iodide gave a deep-red salt (**11**; $R^1, R^2 = [CH_2]_5$, R^3 = Me) in almost quantitative yield.

Reaction with Oxygen Nucleophiles.—These (RONa) reacted only slowly with compound (**1**), but readily with the 5-chloro derivative (**7**) to give on treatment with sodium methoxide in methanol the 5-mono- (**8**; R = Me) and, unexpectedly, the 4,6-di-substituted derivative (**9**; R = Me). On being heated with piperidine, compound (**9**; R = Me) gave a mixture of 4-methoxy-6-piperidino- (**9**; 4-R = Me, 6-RO = $C_5H_{10}N$) and 4,6-dipiperidinoisobenzimidazole (**9**; RO = $C_5H_{10}N$). The 6-MeO group thus appears to be more reactive than the 4-MeO substituent. The monoalkoxy derivative (**8**; R = Me) gave only the 5,6-dipiperidino compound (**3**; $Nu^1 = Nu^2 = C_5H_{10}N$) on reflux in piperidine, *i.e.* a product expected after initial replacement of the 5-methoxy group in compound (**8**; R = Me). Examples are listed in Table 2.

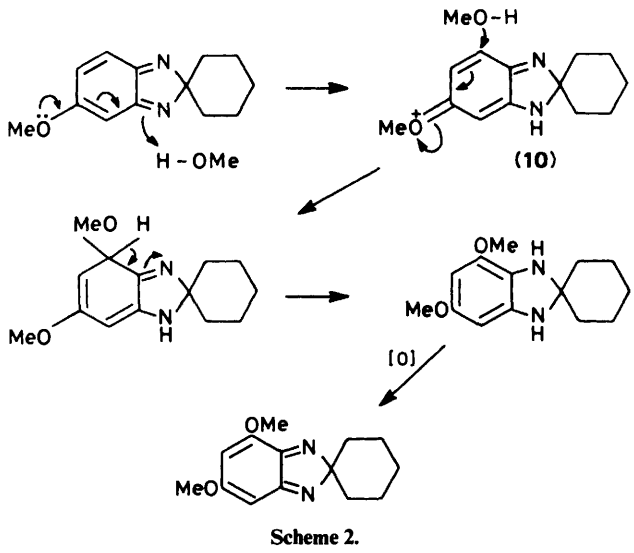
The unexpected directing effect of an alkoxy group to give the 4,6-dialkoxy derivative [(**8**)→(**9**)] is in our view best

Reagents: i, RONa

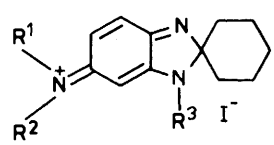
Table 2. Thio- and oxy-substituted isobenzimidazoles

Compound (3) Nu¹	Nu²	Yield (%)	M.p. (°C)	Found (%) (Required) C	H	N	Formula	δ/p.p.m. H_b, H_c, ArH	Aliphatics
Bu^nS	Bu^nS	48	51	65.6 (66.2)	8.4 (8.3)	7.7 (7.7)	$C_{20}H_{30}N_2S_2$	6.64 (1 H, s), 6.38 (1 H, s)	3.0 (4 H, m), 1.3—2.0 (18 H, m) 1.0 (6 H, t)
PhS	PhS	27	203	71.7 (71.6)	5.5 (5.5)	7.0 (7.0)	$C_{24}H_{22}N_2S_2$	6.5 (2 H, s), 7.5 (10 H)	1.4—2.0 (10 H, m)
o-$NH_2C_6H_4S$	o-$NH_2C_6H_4S$	12	202	66.5 (66.6)	5.9 (5.6)	12.7 (13.0)	$C_{24}H_{24}N_4S_2$	6.5 (2 H, s), 7.5—6.7 (8 H, m)	4.4 (4 H, b, NH_2), 1.4—2.0 (10 H, m)
PhS	$C_5H_{10}N$	71	167	73.3 (73.2)	7.2 (7.2)	11.1 (11.1)	$C_{23}H_{27}N_3S$	6.6 (1 H, s), 6.4 (1 H, s), 7.45 (5 H, m)	3.1 (4 H, m), 1.8 (20 H, m)
o-NHC_6H_4S		15	238	70.2 (70.3)	5.6 (5.6)	13.6 (13.7)	$C_{18}H_{17}N_3S$	6.8—7.6 (6 H, m)*	1.2—2.2 (10 H, m)
$NH[CH_2]_2S$		35	174	64.4 (64.8)	6.6 (6.6)	16.0 (16.7)	$C_{14}H_{17}N_3S$	7.0 (1 H, s), 5.9 (1 H, s)†	3.5 (2 H, m), 3.1 (2 H, m), 1.7 (10 H, b)
Compound (8) R								H_a, H_b, H_c, ArH	
Me		80	112	72.0 (72.3)	7.4 (7.4)	12.9 (13.0)	$C_{13}H_{16}N_2O$	7.2 (1 H, d), 6.8 (1 H, q), 6.3 (1 H, d)	3.8 (3 H, s) 1.4—2.3 (10 H, m)
Ph		65	163	77.3 (77.7)	6.6 (6.5)	10.5 (10.1)	$C_{18}H_{18}N_2O$	6.7—7.7 (7 H, m), 6.2 (1 H, d)	1.2—2.3 (10 H, m)
Compound (9) R								H_a, H_c	
Me		45	172	67.8 (68.3)	7.4 (7.3)	11.3 (11.4)	$C_{14}H_{18}N_2O_2$	6.0 (1 H, d, 5.8 (1 H, d)	3.9 (3 H, s), 3.8 (3 H, s), 1.4—2.1 (10 H, m)
Et		41	122	70.2 (70.0)	8.0 (8.1)	10.1 (10.2)	$C_{16}H_{22}N_2O_2$	5.9 (1 H, s), 5.8 (1 H, s)	4.0 (4 H, m), 1.8 (10 H, m), 1.4 (6 H, t)

* In CF_3CO_2H. † In $[^2H_6]$-DMSO.



Scheme 2.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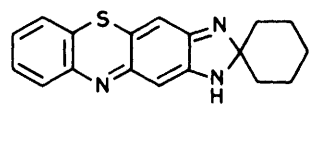
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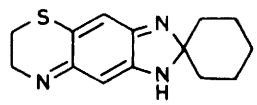
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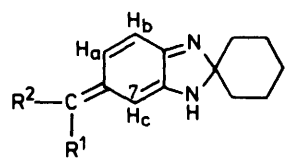
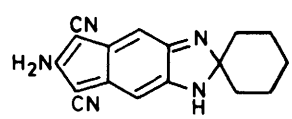

(14)

a; R^1 = CN, R^2 = CO_2Et
b; R^1 = CO_2Et, R^2 = CN


(15)

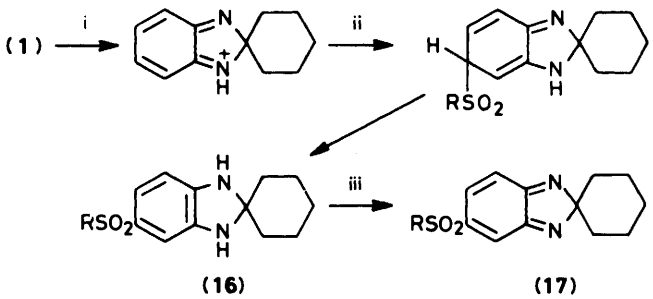
explained by the sequence shown in Scheme 2:* the orientation of the product is determined by the intermediate oxonium ion attracting the incoming nucleophile to the 4-position (**10**). The different substitution pattern observed with N or S nucleophiles (see below) can probably be ascribed to a smaller contribution of the analogous immonium or sulphonium structure due to a reduced conjugative interaction. However, the unexpected behaviour of O nucleophiles and their ready replacement by N nucleophiles widens the scope of the method for the preparation of disubstituted *o*-phenylenediamines.

* We are indebted to Professor W. D. Ollis, F.R.S. for a discussion of this mechanism.

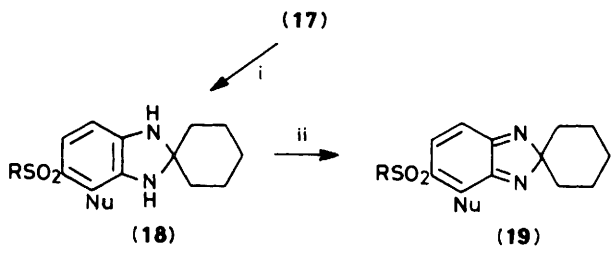
Reaction with Sulphur Nucleophiles.—The reaction with thiols was usually slightly exothermic and resulted in 5,6-disubstituted products (**3**; Nu^1 = Nu^2 = RS) after oxidation of the intermediate dihydro compound owing to the greater nucleophilic activity of S than that of N nucleophiles. A small quantity of the corresponding disulphide (RSSR) was invariably formed owing to a redox reaction between thiol and isobenzimidazole. The 5-piperidino derivative (**2**; Nu^1 = $C_5H_{10}N$) gave the disubstituted compound (**3**; Nu^1 = $C_5H_{10}N$, Nu^2 = PhS) when made to react with benzenethiol. The bidentate nucleo-

Table 3. Products obtained from 5-phenylsulphonylisobenzimidazole (**17**) and amines in benzene

Product (**19**) Nu	Yield (%)	M.p. (°C)	Found (%) (Required) C	H	N	Formula	δ(CDCl$_3$)/p.p.m.
a; $C_5H_{10}N$	83	100	67.6 (67.45)	6.7 (6.65)	10.2 (10.3)	$C_{23}H_{27}N_3O_2S$	7.6—7.9 (5 H, m), 7.2—7.3 (1 H, d, *J* 9 Hz), 6.6—6.7 (1 H, d, *J* 9 Hz), 3.65 (4 H, br), 1.6—1.9 (16 H, br)
b; Morpholino	89	128	64.2 (64.2)	6.3 (6.1)	10.3 (10.2)	$C_{22}H_{25}N_3O_3S$	7.5—8 (5 H, m), 7.3—7.45 (1 H, d, *J* 9 Hz), 6.8—6.9 (1 H, d, *J* 9 Hz), 3.6 (8 H, br), 1.5—2.0 (10 H)
c; $CH_2CH_2N(Me)CH_2CH_2N$	93	108	66.8 (66.8)	6.4 (6.4)	10.5 (10.6)	$C_{23}H_{28}N_4O_2S$	7.5—8 (5 H, m), 7.3—7.4 (1 H, d, *J* 9 Hz), 6.7—6.8 (1 H, d, *J* 9 Hz), 3.6 (4 H, t), 2.4 (4 H, t), 2.2 (3 H, s), 1.5—2.0 (10 H, m)
d; C_4H_8N	87	110	64.9 (65.1)	6.6 (6.65)	12.9 (13.2)	$C_{22}H_{25}N_3O_2S$	7.5—8.0 (5 H, m), 7.0—7.15 (1 H, d, *J* 9 Hz), 6.2—6.3 (1 H, d, *J* 9 Hz), 3.9 (4 H, s), 1.2—2.0 (14 H, m)
e; Et_2N	85	96	66.4 (66.5)	6.8 (6.8)	10.5 (10.6)	$C_{22}H_{27}N_3O_2S$	7.5—8.1 (5 H, m), 7.7—7.8 (1 H, d, *J* 9 Hz), 7.0—7.1 (1 H, d, *J* 9 Hz), 4.8 (4 H, q), 1.5—2.0 (10 H, m), 1.25 (6 H, t)
f; NH_2	55	140	63.3 (63.3)	5.6 (5.6)	12.25 (12.3)	$C_{18}H_{19}N_3O_2S$	7.5—8.0 (5 H, m), 7.15—7.25 (1 H, d, *J* 9 Hz), 6.7 (2 H, br, D_2O removable), 6.5—6.4 (1 H, d, *J* 9 Hz), 1.5—2.0 (10 H)
g; Me_2CHNH	41	60	65.8 (65.8)	6.5 (6.6)	11.1 (11.0)	$C_{21}H_{25}N_3O_2S$	7.5—8.0 (6 H, m), 7.3—7.4 (1 H, d, *J* 9 Hz), 6.4—6.5 (1 H, d, *J* 9 Hz), 5.0—4.4 (1 H, m) 1.5—2.0 (10 H, m)



Scheme 3. *Reagents:* i, HOAc; ii, RSO_2H; iii, MnO_2



Scheme 4. *Reagents:* i, NuH; ii, [O]

philes 2-aminobenzenethiol and 2-aminoethanethiol gave only small yields of the benzothiazines (**12**) (6%) and (**13**) (34%), to which we ascribe the quinonoid structure because of their deep-red colour. The conditions for these reactions (*e.g.* concentration) were, however, not optimised.

Reaction with Carbon Nucleophiles.—The surprising behaviour of tetracyanoethylene (TCNE), which gave the same dicyano compound (**14**; $R^1 = R^2 = CN$, $R^3 = Me$) as malononitrile when made to react with 2,2-dimethylisobenzimidazole, was reported[10] by us. Similarly, the spirocyclohexyl compound (**1**) produced the same dicyano compound (**14**; $R^1 = R^2 = CN$, $R^3,R^3 = [CH_2]_5$) from malononitrile and TCNE. With an excess of malononitrile, a green by-product (**15**), which arises from the interaction of the above dicyano compound with another molecule of malononitrile, was also isolated. Cyanoacetic ester interacted with compound (**1**) to give a purple solid which on the basis of its ^1H n.m.r. spectrum in trifluoroacetic acid (TFA) was, as expected, a mixture of geometrical isomers (**14**). In [^2H]-TFA, both the NH and H_c protons are exchanged, thus demonstrating the enaminic nature of 7-H. On the basis of the two double doublets due to H_a and H_b (*J* 9 Hz) at δ 7.05 and 8.85 and at 7.00 and 7.8, the proportions of the isomers were estimated to be 40:60.

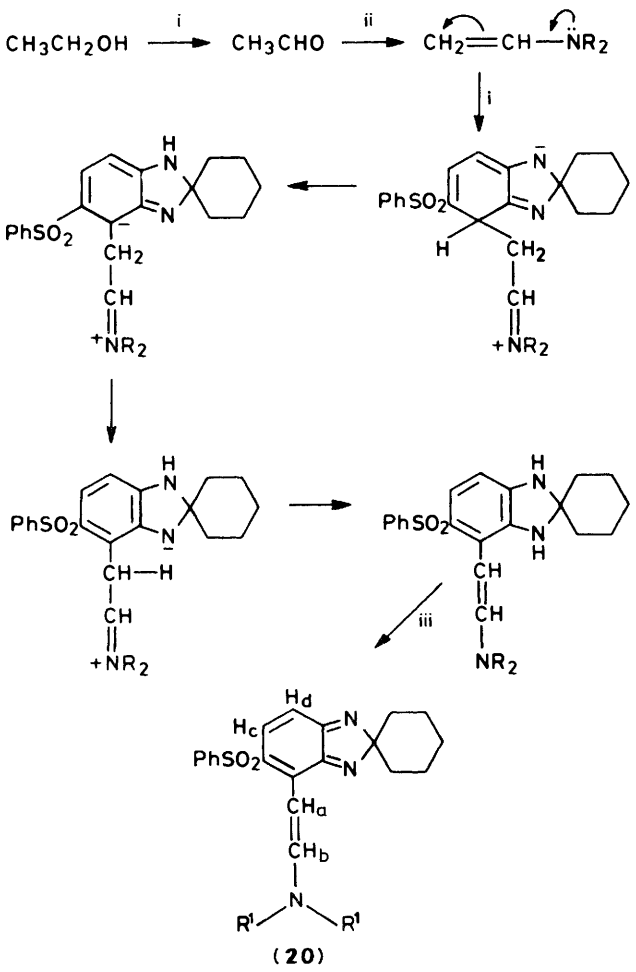
Reactions with Inorganic Salts.—A series of inorganic salts ($NaNO_2$ $NaHSO_3$, KSCN) could not be made to react with compound (**1**) even on heating with dimethyl sulphoxide (DMSO). However, 5-chloroisobenzimidazole (**2**; $Nu^1 = Cl$) reacted with NaN_3 and KCN to give 5-azido- and 5-cyano-isobenzimidazole (**2**; $Nu^1 = N_3$, CN) in good yield.

Reactions of 5-Sulphonylisobenzimidazoles (**17**).—Russian workers have reported the synthesis and reactions of some anthracenoimidazolediones[14] and 5-sulphonyldihydroimidazole-2-spirocyclohexanes[15] (**16**; R = Me or Ph) from isobenzimidazole (**1**) and the corresponding sodium sulphinates. Since the latter reaction occurs in acetic acid, it appears that compound (**1**) reacts in its protonated form, with the sulphinic acid behaving as an S nucleophile, yielding a stable dihydro compound (**16**) after a prototropic shift as shown in Scheme 3. Oxidation (MnO_2) leads to the corresponding isobenzimidazole (**17**). We have confirmed this reaction and also prepared some dihydro-5-arylsulphonylbenzimidazoles (**16**; R = *p*-MeC_6H_4, *p*-ClC_6H_4, 2,5-$Cl_2C_6H_3$). Anionic substitution of an 5-arylsulphone [*e.g.* (**17**; R = Ph)] leads to a 4,5-disubstituted product (**19**) (Scheme 4). The strongly electron-withdrawing sulphone group thus directs the incoming nucleophile into a different position from an amino group [*cf.* (**2**)→(**3**)]. This widening of the scope of using isobenzimidazole as a protected *o*-phenylenediamine prompted further investigation.

Table 4. Products obtained from 5-phenylsulphonylisobenzimidazole (**17**) and secondary amines in ethanol in the dark

Products (% yield)		M.p.	Found (%) (Required)				δ(CDCl$_3$)
(**19**)*	(**20**)	(°C)	C	H	N	Formula	*cf.* text
(**19a**) (23)	$R^1,R^1 = [CH_2]_5$ (16)	180	68.9 (68.9)	6.7 (6.7)	9.7 (9.65)	$C_{25}H_{29}N_3O_2S$	
(**19b**) (24)	$R^1,R^1 = [CH_2]_2O[CH_2]_2$ (18)	175	65.8 (65.9)	6.3 (6.2)	9.6 (9.6)	$C_{24}H_{27}N_3O_3S$	8.7—8.8 (1 H, d, *J* 12.6 Hz), 7.65—7.75 (1 H, d, *J* 9 Hz), 7.5—8.0 (5 H, m), 6.7—6.8 (1 H, d, *J* 9 Hz), 6.35—6.45 (1 H, d, *J* 16.6 Hz), 3.3—3.7 (8 H, br), 1.2—2.0 (10 H, m)
(**19c**) (25)	$R^1,R^1 = [CH_2]_2NMe[CH_2]_2$ (17)	142	66.5 (66.6)	6.7 (6.7)	12.0 (12.4)	$C_{25}H_{30}N_4O_2S$	8.7—8.9 (1 H, d, *J* 12.6 Hz), 7.7—7.8 (1 H, d, *J* 9 Hz), 7.5—8.0 (5 H, m), 6.7—6.8 (1 H, d, *J* 9 Hz), 6.3—6.45 (1 H, d, *J* 12.6 Hz), 3.4 (4 H, t), 2.4 (4 H, t), 2.3 (3 H, s), 1.2—2.0 (10 H, m)
(**19d**) (20)	$R^1,R^1 = [CH_2]_4$ (16.5)	183	68.4 (68.4)	6.6 (6.45)	10.1 (10.0)	$C_{24}H_{27}N_3O_2S$	8.9—9.0 (1 H, d, *J* 12.6 Hz), 7.2—8.0 (6 H, m), 6.5—6.4 (1 H, d, *J* 9 Hz), 6.0—6.1 (1 H, d, *J* 12.6 Hz), 3.3 (4 H, br), 1.2—2.0 (14 H, m)
(**19e**) (18)	R^1 = Et (30)	162	68.0 (68.0)	6.9 (6.9)	9.9 (9.9)	$C_{24}H_{29}N_3O_2S$	9.0—9.1 (1 H, d, *J* 12.6 Hz), 7.4—8.0 (5 H, m), 7.7—7.8 (1 H, d, *J* 9 Hz), 6.6—6.7 (1 H, d, *J* 9 Hz), 6.2—6.3 (1 H, d, *J* 12.6 Hz), 3.2—3.4 (4 H, q), 1.2 (6 H, t), 1.5—2.0 (10 H, m)

* See Table 3 for substituents on (**19a—e**).



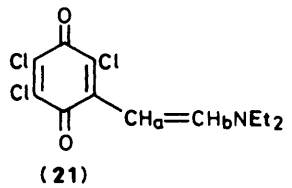
Scheme 5. *Reagents:* i, 5-PhSO$_2$-isobenzimidazole; ii, R_2NH; iii, MnO_2

Reaction of the 5-Phenylsulphone (**17**; R = Ph) *with Nitrogen Nucleophiles.*—Reaction with secondary amines in benzene gave deep-red 4-amino-5-phenylsulphonylisobenzimidazole (**19**; R = Ph, Nu = tertiary amino group), examples of which are listed in Table 3. The reactions were carried out in the presence of manganese dioxide to by-pass the intermediate dihydro stage (**18**). When ethanol was used as the solvent a second dark-blue product was also isolated. Its yield was notably decreased if the reaction was carried out in the dark. For instance, with piperidine in ethanol the expected 4-piperidino compound (**19**; R = Ph, Nu = $C_5H_{10}N$) was obtained in 23 and the blue product in 16% yield, while in daylight the yields were 30 and 24% respectively. The elemental analyses and spectral data show the blue compound to be the dialkylaminovinylisobenzimidazoles (**20**). For instance, for the piperidino compound (**20**; $R^1,R^1 = [CH_2]_5$), 4,5-disubstitution was indicated by two doublets at δ 7.8 and 6.65 (H_c, H_d *J* 9 Hz) while the olefinic protons of the enamine (H_a and H_b) also showed two doublets at δ 8.9 and 6.4 (*J* 12.6 Hz). The aromatic protons appear as multiplets at δ 8.0—7.4, with the remaining aliphatic signals as broad singlets at δ 3.35 (4 H, *i.e.* α-CH_2's of piperidine) and as a multiplet at δ 2.0—1.5 due to the remaining piperidine and cyclohexyl protons. Details for these products are given in Table 4. The mechanism we propose (*cf.* Scheme 5) for the formation of the blue compounds involves the intermediacy of a probably unstable dialkylvinylamine[16] derived from the secondary amine and acetaldehyde. The latter reagent arises from dehydrogenation of ethanol by the isobenzimidazole and, to a small extent, from the added MnO_2. The enamine formed *in situ* reacts as a nucleophile with the 5-phenylsulphonyl compound. Some confirmatory evidence for this was obtained when acetaldehyde replaced ethanol and the blue piperidinoenamine (**20**; $R^1,R^1 = [CH_2]_5$) was the only product. In an analogous reaction, Henbest *et al.*[17] prepared a series of dialkylaminovinylquinones [*e.g.* (**21**)] from halogenated quinones, acetaldehyde, and secondary amines to give blue compounds which show two doublets due to the olefinic protons [*cf.* (**21**) H_a and 6-H] at δ 8.4 and 5.6. These signals*

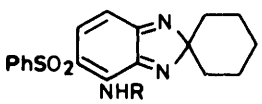
Table 5. Products obtained from 5-phenylsulphonylisobenzimidazole (**17**; R = Ph) and diamines in ethanol

Diamine $NH_2[CH_2]_nNR_2$	Product*	Yield (%)	M.p. (°C)	Found (%) (Required) C	H	H	Formula	δ($CDCl_3$)/p.p.m.
n = 2, R = H	(**25**) n = 2	15.7	152	64.0 (64.4)	5.7 (5.6)	12.2 (11.9)	$C_{38}H_{40}N_6O_4S_2$	8.4 (br, 2NH, D_2O removable), 7.5—8.0 (10 H, m), 7.2—7.3 (2 H, d, J 9 Hz), 6.45—6.6 (2 H, d, J 9 Hz), 4.4 (4 H, m), 1.5—1.8 (20 H)
n = 4, R = H	(**25**) n = 2	25.5	162	65.1 (65.2)	6.3 (6.0)	11.4 (11.4)	$C_{40}H_{44}N_6S_2O_4$	8.2 (br, 2NH, D_2O removable), 7.5—8.0 (10 H, m), 7.3—7.4 (2 H, d, J 9 Hz), 6.4—6.5 (2 H, d, J 9 Hz), 4.1—4.2 (4 H, m), 1.5—2.0 (24 H)
n = 6, R = H	(**25**) n = 6	11.0	157	66.0 (65.9)	6.4 (6.3)	11.0 (11.0)	$C_{42}H_{48}N_6O_4S_2$	8.2 (br, 2NH, D_2O removable), 7.5—8.0 (10 H, m), 7.25—7.35 (2 H, d, J 9 Hz), 7.4—7.5 (2 H, d, J 9 Hz), 4.0—3.2 (4 H, m), 1.5—2.0 (28 H, m)
n = 2, R = Me	[**19**; Nu = $Me_2N(CH_2)_2NH$, R = Ph]	50	133	64.2 (64.0)	7.0 (6.85)	13.35 (13.6)	$C_{22}H_{28}N_4O_2S$	8.4 (br, NH, D_2O removable), 7.5—8.0 (5 H, m), 7.4—7.5 (1 H, d, J 9 Hz), 6.4—6.5 (1 H, d, J 9 Hz), 4.0—4.2 (2 H, m), 2.5—2.6 (2 H, t), 7.35 (6 H, s), 1.5—2.0 (10 H, m)

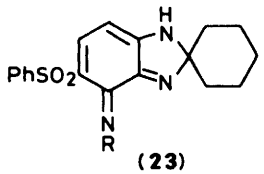
* This was accompanied in each case by the 4-amino compound (**19**; R = Ph, Nu = NH_2) (*ca.* 6%).



(**21**)



(**22**)



(**23**)

compare favourably with those of our blue compound [*cf.* (**20**; R^1,R^1 = $[CH_2]_5$] in as much as they show strongly shielded (H_a) and deshielded (H_b) doublets in the enamine moiety ($\bar{C}H_aCH_b=\overset{+}{N}R_2$).

The reaction of compound (**17**; R = Ph) with primary amines (*e.g.* isopropylamine, ammonia) gave lower yields than with secondary amines, and the products presumably exist in the imino form [(**22**)→(**23**)] since they could not be acylated. Aniline gave unexpectedly, 5,6-dianilinoisobenzimidazole (**3**; Nu^1 = Nu^2 = PhNH) *via* initial replacement of the 5-phenylsulphone group (**17**; R = Ph) to give the 5-anilino compound (**2**; Nu^1 = PhNH), which then directs the second aniline molecule as expected (*cf.* above). Three primary aliphatic diamines (**24**; n = 2, 4, and 6) reacted with the sulphone (**17**; R = Ph) in ethanol or benzene to give the corresponding substituted bisdiamines (**25**; n = 2, 4, and 6). The unsymmetrical *N,N*-dimethylethylenediamine gave the expected 4-(*N,N*-dimethylaminoethylene)-5-phenylsulphonyl derivative (**19**; R = Ph, Nu = $Me_2NCH_2CH_2NH$). The results of these reactions are given in Table 5. Invariably a small quantity (4—6%) of 4-amino-5-phenylsulphonylisobenzimidazole (**19**; R = Ph, Nu = NH_2) was formed in all these reactions. The possibility that ammonia is present as an impurity in the diamines was excluded by analysis, and since it was found that the diamines (**25**) degraded to the 4-amino compound (**19**; R = Ph, Nu = NH_2) very slowly on standing in ethanolic solution, we ascribe the formation of this product to a redox reaction (*cf.* Scheme 6). The dehydrogenation step (**25**)→(**26**) was noticeably accelerated by the addition of the isobenzimidazole (**1**) or (**17**) to a solution of the diamine. The hydrolysis (**26**)→(**27**) usually occurs during chromatography, but was also quickly engendered by addition of base, acid, or water to an ethanolic solution of the product. The application of the dehydrogenation properties of isobenzimidazoles is at present being studied.

Reaction of the 5-*Phenylsulphone* (**17**; R = Ph) *with Sulphur Nucleophiles.*—Benzenethiol in the presence of MnO_2 gave the 5-phenylsulphonyl-4,6-diphenylthioisobenzimidazole (**28**; R^1 = R^2 = PhS) while 2-methylpropane-2-thiol furnished a mixture of the mono- (**28**; R^1 = H, R^2 = Me_3CS) and di-thiol compound (**28**; R^1 = R^2 = Me_3CS) in 20 and 40% yield respectively. The formation of a monothiol in the latter case is possibly due to the steric hindrance caused by the bulky t-butyl group.

Conversion of Substituted Isobenzimidazoles into Other Heterocycles.—Various substituted isobenzimidazoles [(**2**) and (**3**)] were ring-opened by catalytic reduction or by treatment with sodium dithionite to give the corresponding *o*-phenylenediamines (**4**) which were converted into various heterocycles [(**29**)—(**32**); *cf.* Table 6] by an established procedure.

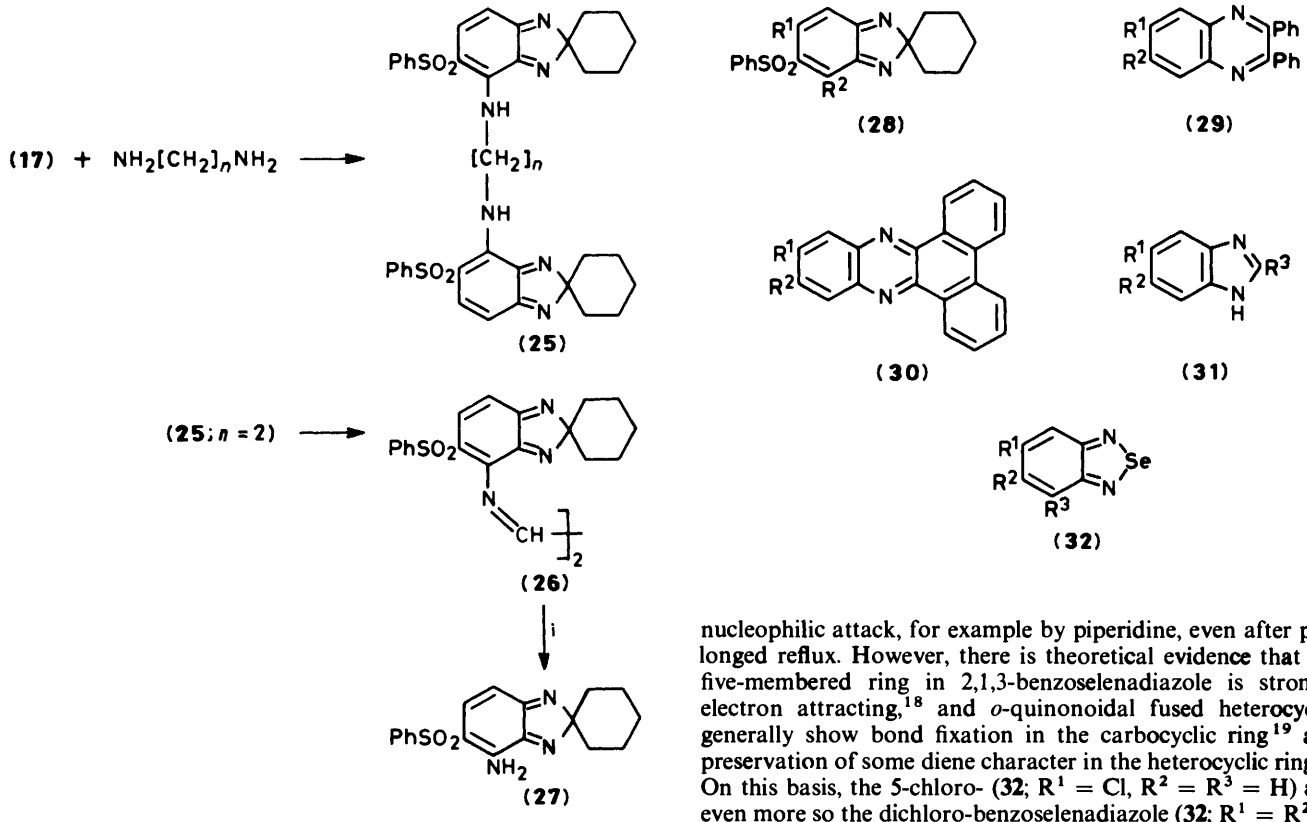
The 'umpolung' of *o*-phenylenediamines by conversion into the isobenzimidazole, enabling the introduction of nucleophiles to take place, is thus complementary to the protection of these diamines as 2,1,3-benzoselenadiazoles[4] or benzothiadiazole[3] for introducing electrophiles. The benzoselenadiazole (**32**; R^1 = R^2 = R^3 = H) was found not to be amenable to

* We are indebted to Dr. I. D. Entwistle of Shell, Sittingbourne Research Centre for this n.m.r. spectrum.

Table 6. Heterocycles prepared from the isobenzimidazoles (2) and (3)

Compound	R^1	R^2	R^3	Yield* (%)	M.p. (°C)	Found (%) (Required) C	H	N	Formula
(29)	$C_5H_{10}N$	H		76	171	81.6 (82.1)	6.4 (6.3)	11.4 (11.5)	$C_{26}H_{23}N_3$
(30)	$C_5H_{10}N$	H		52	186	82.3 (82.6)	5.8 (5.8)	11.5 (11.6)	$C_{25}H_{21}N_3$
(30)	C_4H_8N	H		42	235	82.2 (85.5)	5.8 (5.5)	11.9 (12.0)	$C_{24}H_{19}N_3$
(30)	Morpholino	H		60	228	78.7 (78.9)	5.2 (5.2)	11.5 (11.5)	$C_{24}H_{19}N_3O$
(30)	$C_6H_{12}N$	H		48	203	82.3 (82.7)	6.2 (6.1)	11.1 (11.1)	$C_{26}H_{23}N_3$
(30)	$C_5H_{10}N$	$C_5H_{10}N$		63	245	80.4 (80.7)	6.7 (6.8)	12.5) (12.5	$C_{30}H_{30}N_4$
(30)	Bu^nS	Bu^nS		72	157	73.4 (73.7)	6.2 (6.1)	6.1 (6.1)	$C_{28}H_{28}N_2S_2$
(30)	PhS	PhS		81	288	77.2 (77.4)	4.1 (4.1)	5.6 (5.6)	$C_{32}H_{20}N_2S_2$
(31)	$C_5H_{10}N$	H	Me	63	172	72.3 (72.5)	7.8 (8.0)	19.2 (19.5)	$C_{13}H_{17}N_3$
(31)	$C_5H_{10}N$	H	Et	76	158	73.2 (73.3)	8.4 (8.4)	18.0 (18.3)	$C_{14}H_{19}N_3$
(31)	$C_5H_{10}N$	H	CF_3	55	193	57.8 (58.0)	5.4 (5.2)	15.5 (15.6)	$C_{13}H_{14}N_3F_3$
(31)	$C_5H_{10}N$	$C_5H_{10}N$	Me	83	281	72.2 (72.4)	8.6 (8.8)	18.8 (18.8)	$C_{18}H_{26}N_4$
(32)	$C_5H_{10}N$	H		55	105	49.9 (49.6)	5.0 (4.9)	15.8 (15.8)	$C_{11}H_{13}N_3Se$
(32)	$C_5H_{10}N$	$C_5H_{10}N$		76	171	55.2 (55.2)	6.4 (6.1)	16.0 (16.1)	$C_{16}H_{22}N_4Se$

* Based on substituted isobenzimidazole.



Scheme 6. i, Hydrolysis

nucleophilic attack, for example by piperidine, even after prolonged reflux. However, there is theoretical evidence that the five-membered ring in 2,1,3-benzoselenadiazole is strongly electron attracting,[18] and *o*-quinonoidal fused heterocycles generally show bond fixation in the carbocyclic ring[19] and preservation of some diene character in the heterocyclic ring.[20] On this basis, the 5-chloro- (**32**; R^1 = Cl, R^2 = R^3 = H) and even more so the dichloro-benzoselenadiazole (**32**; R^1 = R^2 = Cl, R^3 = H) are expected to be prone to nucleophilic attack,

and the subsequent ring-opening of the product could represent a feasible alternative to the isobenzimidazole method for the preparation of nucleophilically substituted *o*-phenylenediamines. Indeed the 5-chloro compound (**32**; R^1 = Cl, R^2 = R^3 = H) was found to react with various secondary amines (piperidine, pyrrolidine, and morpholine) under reflux to give the corresponding 5-dialkylamino-2,1,3-benzoselenadiazoles in >20% yield. Oxygen nucleophiles (RONa; R = Me, Et, or Ph) and sodium thiophenoxide could not be made to react even on prolonged reflux in DMSO. Among the C nucleophiles [$MeCH_2NO_2$, $MeNO_2$, $CH_2(CN)CO_2Et$, and $CH_2(CN)_2$] only the last gave the expected product [**32**; R^1 = $CH(CN)_2$, R^2 = R^3 = H], which did not exist in the tautomeric imino form (no exchange with D_2O) unlike the corresponding product from isobenzimidazole {*cf.* (**14**; R^1 = R^2 = CN, R^3,R^3 = $[CH_2]_5$)}. Reaction of the 5,6-dichloro compound (**32**; R^1 = R^2 = Cl, R^3 = H) with morpholine gave the mono derivative (**32**; R^1 = morpholino, R^2 = Cl) while with piperidine and pyrrolidine a mixture of the corresponding 5-t-amino-6-chloro- (**32**; R^1 = Cl, R^2 = $C_5H_{10}N$ or C_4H_8N, R^3 = H) and 4-t-amino-6-chloro-benzoselenadiazole (**32**; R^1 = Cl, R^2 = H, R^3 = $C_5H_{10}N$ or C_4H_8N) was obtained; the last-named compound was obviously formed by an aryne mechanism. Sodium methoxide and ethoxide, on reflux in dimethylformamide, gave the corresponding disubstituted product (**32**; R^1 = R^2 = OMe or OEt, R^3 = H) with the former also yielding some of the monosubstituted derivative (**32**; R^1 = OMe, R^2 = R^3 = H). In view of the generally low yields of the substitution reactions and the difficulty of effecting the ring-opening of the substituted benzoselenadiazoles this approach is not considered a viable alternative to the isobenzimidazole method.

We are presently studying the use of isobenzimidazoles for the preparation of the rather inaccessible tetrasubstituted benzenes which are potential intermediates for linear and angular tricyclic heterocycles of biochemical interest.

Experimental

I.r. spectra were recorded for mulls between sodium chloride plates with a Perkin-Elmer 297 or 357 spectrometer, n.m.r. spectra with a Varian EM360 (60 MHz) Perkin-Elmer R 32 or a Varian EM390 (90 MHz) (^{1}H) spectrometer. Microanalyses (C, H, N) were carried out by Butterworth Laboratories Ltd. For column chromatography, alumina Type H (Merck) was employed. Light petroleum refers to the fraction of b.p. 60—80 °C, and ether to diethyl ether.

If not otherwise stated all n.m.r. spectra are given for 90 MHz.

Preparation of Benzimidazole-2(3H)-spirocyclohexanes.—(*a*) As an improvement of the literature method[21] and our own modification[24] the following procedure was the most convenient: a hot solution of *o*-phenylenediamine (54 g, 0.5 mol) was prepared by boiling an aqueous solution of the diamine (technical grade) with activated charcoal for a few minutes followed by filtration. Cyclohexanone (51.5 ml, 0.52 mol) was added with vigorous shaking causing the formation of a heavy white precipitate within minutes. The mixture was then heated for a further 10 min, cooled, and the precipitate filtered off. It was washed with hot water and, if necessary, recrystallised from ethanol.

(*b*) *5-Chlorobenzimidazole-2(3H)-spirocyclohexane.* Any of the above methods can be used, but the following preparation proved simplest: 4-chloro-*o*-phenylenediamine (7 g, 0.049 mol) and a large excess of cyclohexanone (51.5 ml, 0.5 mol) were heated on a water-bath for 10 min. Excess of solvent and water were driven off on a rotary evaporator and the residual oil chromatographed on alumina with light petroleum–ethyl acetate (5:1) as eluant. The first band gave the impure title compound which was recrystallised from light petroleum to furnish *5-chlorobenzimidazole-2(3H)-spirocyclohexane* (8.9 g, 80%), m.p. 85 °C, as white crystals (Found: C, 64.4; H, 6.8; N, 12.65. $C_{12}H_{15}ClN_2$ requires C, 64.7; H, 6.8; N, 12.6%).

Oxidation of Dihydrobenzimidazoles.—(*a*) A suspension of the dihydro compound (10—15 g) and activated MnO_2 (20—30 g; obtained by heating manganese oxalate to 250 °C for 6 h) in a solvent (benzene or methylene dichloride 150—200 ml) was vigorously stirred at room temperature for 1 h. Evaporation of the solvent after removal of the manganese dioxide gave the isobenzimidazole which was recrystallised from light petroleum or chromatographed on an alumina column by elution with light petroleum.

(*b*) Oxidation also occurred when a mixture of the dihydro compound (0.1 mol), toluene (100 ml), aqueous sodium hypochlorite (250 ml, 15%), and tetrabutylammonium bromide was shaken at room temperature for 1 h. The toluene layer was separated and driven off to leave the product usually in lower yield than in (*a*). The isobenzimidazole (**1**) (90%) had m.p. 64 °C (lit.,[22] m.p. 65—65.5 °C); *5-chloroisobenzimidazole-2-spirocyclohexane* (**7**) (90%) had m.p. 58 °C (Found: C, 65.1; H, 6.0; N, 13.0. $C_{12}H_{13}ClN_2$ requires C, 65.3; H, 5.9; N, 12.7%).

(*c*) A solution of potassium permanganate (4.2 g) in water (50 ml) was added to a solution of the dihydrobenzimidazole (5 g) in dichloromethane (50 ml); a catalytic amount of n-tetrabutylammonium bromide was then added and the two-phase reaction mixture stirred for 1 h at room temperature. The mixture was filtered through Kieselguhr and the organic layer, after separation and evaporation, gave the isobenzimidazole as a brown solid (70%).

(*d*) Oxidation also occurred on vigorous stirring of a suspension of alumina (type H, Merck) (20 g) in a toluene solution of the dihydro compound (2 g), giving the product in 80% yield.

Reaction of Nucleophiles with Isobenzimidazoles.— (*a*) *Nitrogen nucleophiles.* As a general method for monosubstituted products, the isobenzimidazole (0.1 mol), the amine (0.15 mol), MnO_2 (5 g), and ethanol (20—30 ml) were stirred at room temperature for 6 h. The solvent was removed on a rotary evaporator after filtration and the resultant oil chromatographed on alumina and eluted with light petroleum–ethyl acetate (5:1). The first band gave the isobenzimidazole followed by an orange band which on elution gave the 5-monoaminoisobenzimidazole as orange to red needles, recrystallisable from light petroleum (*cf.* Table 1); in the absence of MnO_2 the yields were smaller.

For diaminoisobenzimidazoles, an excess of amine (3 ×) was used under the conditions described above. The first band in the chromatogram gave starting material, the second gave the red to orange monoamine (**2**; Nu^1 = R_2N), and the third band the yellow diamino compound (**3**; Nu^1 = Nu^2 = R_2N).

For the diamino compounds with different amino substituents, the monoamine (**2**; Nu^1 = R^2N) was treated as above with the required second amine. All the reactions could be accelerated by using DMSO or sulpholane instead of ethanol and keeping the reaction mixture on a boiling water-bath for 2 h. The mixture was poured into water, then extracted with chloroform or ethyl acetate and the organic layer dried ($MgSO_4$) and evaporated. The residual oil was subjected to chromatography as described.

The reaction conditions for bidentate nucleophiles were as for monosubstitution. The effect of using high dilution was not investigated. For the preparation of the phenazine (**6**), *o*-phenylenediamine (1.1 g, 0.01 mol), the isobenzimidazole (1.9 g, 0.01 mol), and sulpholane (5 ml) were heated on a water-bath

for 10 h. The solution was cooled, poured into water and the yellow solid filtered off. 1,3-*Dihydro*-2H-*imidazo*[4,5-b]*phenazine*-2-*spirocyclohexane* (**6**) (2.64 g, 91%) had m.p. >360 °C (Found: C, 74.2; H, 6.4; N, 19.2. $C_{18}H_{18}N_4$ requires C, 74.5; H, 76.2; N, 19.3); M^+, 290; δ[$(CD_3)_2SO$] 8.3 (2 H, br, removed by D_2O), 7.7 (4 H, m), 6.45 (2 H, s), and 1.7 (10 H, m).

5-Chloroisobenzimidazole (**7**) (1.5 g) was treated with piperidine (1.5 ml) in ethanol (5 ml) at room temperature for 10 h. MnO_2 (5 g) was added and the mixture stirred for 2 h. The filtrate from the mixture was chromatographed (Al_2O_3) and eluted with light petroleum–ethyl acetate (10:1), to give as the first band 5-*chloro*-6-*piperidinoisobenzimidazole*-2-*spirocyclohexane* (**3**; $Nu^1 = C_5H_{10}N$, Nu^2 = Cl) (0.5 g), m.p. 175 °C (Found: C, 67.0; H, 7.5; N, 14.0. $C_{17}H_{22}ClN_3$ requires C, 67.2; H, 7.3; N, 13.8%), and as a second band 5,6-*dipiperidinoisobenzimidazole*-2-*spirocyclohexane* (**3**; $Nu^1 = Nu^2 = C_5H_{10}N$) (*cf.* Table 1) (0.4 g), m.p. 174 °C.

To the chloroisobenzimidazole (**7**) (5 g, 0.022 mol) dissolved in DMSO (25 ml) was added sodium azide (2 g, 0.03 mol) and the mixture kept stirring for 30 min at room temperature and then poured into water (500 ml). The solution was extracted with ether (3 × 100 ml) and the ethereal extract, after being dried ($MgSO_4$), evaporated to give an oily residue. Purification on alumina with light petroleum–ethyl acetate (8:2) gave 5-*azidoisobenzimidazole*-2-*spirocyclohexane* (**2**; $Nu^1 = N_3$) (4.0 g 60.6%), m.p. 54—55 °C (Found: C, 63.0; H, 5.9; N, 30.4. $C_{12}H_{13}N_5$ requires C, 63.4; H, 5.7; N, 30.8%); δ($CDCl_3$) 2.1 (10 H, br), 6.8 and 7.3 (2 H, 2 d, *J* 8 Hz), and 6.9 (1 H),

The cyano compound (**2**; Nu^1 = CN) was prepared from the chloroisobenzimidazole and KCN by an analogous method. It had m.p. 87 °C (lit.,[15] m.p. 89 °C).

(*b*) *Oxygen nucleophiles.* 5-Chloroisobenzimidazole (0.8 g), sodium methoxide (2 g), and methanol (15 ml) on being stirred overnight gave the 5-monomethoxy compound (**8**; R = Me) and, on reflux overnight, the 4,6-dimethoxy derivative (**9**; R = Me); δ($CDCl_3$) 6.03 (1 H, d), 5.85 (1 H, d), 3.89 (3 H, Me, s), 3.81 (3 H, Me, s), and 1.4—2.1 (10 H, m). Sodium phenoxide gave only the 5-monomethoxy derivative (**8**; R = Ph) (*cf.* Table 2).

When 4,6-dimethoxyisobenzimidazole (**9**; R = Me) (1.2 g) was refluxed in ethanol (15 ml) in the presence of piperidine (5 ml) and worked up in the usual way, 4,6-*dipiperidinoisobenzimidazole*-2-*spirocyclohexane* (0.4 g, 28%), m.p. 106 °C, was obtained (Found: C, 74.6; H, 9.1; N, 15.8. $C_{22}H_{32}N_4$ requires C, 74.9; H, 9.1; N, 15.9%); δ($CDCl_3$) 5.8 (2 H, s), 3.0—3.60 (8 H, m, 4α-CH_2), and 1.40—2.60 (22 H, m, 11 × CH_2). Further elution gave 4-*methoxy*-6-*piperidinoisobenzimidazole*-2-*spirocyclohexane* (41%), m.p. 100—102 °C (Found: C, 72.1; H, 8.5; N, 14.1. $C_{18}H_{25}N_3O$ requires C, 72.2; H, 8.4; N, 14.0%); δ($CDCl_3$) 6.2 (1 H, d), 5.9 (1 H, d), 4.0 (3 H, s, Me), 3.3 (4 H, 2 × CH_2), and 1.4—2.2 (16 H, m).

(*c*) *Sulphur nucleophiles.* The method was analogous to that used for *N*-nucleophiles. Addition of the thiol caused the reaction mixture to warm up. The first product from the chromatography (Al_2O_3) with light petroleum–ethoxyethane (10:1) as eluant was the corresponding disulphide (R_2S) and later fractions gave the thioethers (*cf.* Table 2).

In the case of 2-aminoethanethiol and of 2-aminobenzenethiol, the respective hydrochloride suspended in ethanol was slowly added to a mixture of the isobenzimidazole, sodium carbonate, and ethanol with vigorous stirring, and the resulting reaction mixture agitated for 20 h.

(*d*) *Carbon nucleophiles.* The isobenzimidazole (**1**) (0.62 g) and malononitrile (0.22 g) were dissolved in ethanol (25 ml) and the solution kept at ambient temperature for 8 h. Removal of the solvent and chromatography (Al_2O_3) of the crude product with light petroleum–ethyl acetate (3:1) gave first isobenzimidazole (0.1 g) and then the purple 5-*dicyanomethylene*-3,5-*dihydroisobenzimidazole*-2-*spirocyclohexane* (**14**; R^1 = R^2 = CN) (30%), m.p. 210 °C, $\nu_{max.}$ 2 230 and 2 210 (C≡N), 3 250 (NH), 1 660 (C=N), and 1 585 cm^{-1} (C=C); δ($CDCl_3$) 8.22 (br s, removed by D_2O), 7.28 (dd, H_a, $J_{a,c}$ 2 Hz, $J_{a,b}$ 8 Hz), 6.99 (H_b, $J_{a,b}$ 8 Hz), 6.07 (d, H_c) and 1.8 and 1.55 (10 H, m) (Found: C, 72.5; H, 5.6; N, 21.9. $C_{15}H_{14}N_4$ requires C, 72.0; H, 5.6; N, 22.4%). Further elution gave a green product (4%) which was also obtained from equimolar amounts of the above cyano compound and malononitrile (40% yield) and identified as the 6-*amino*-5,7-*dicyanoindeno*[5,6-d]*imidazole*-2(1H)-*spirocyclohexane* (**15**) (m.p. >260 °C). It showed bands at 3 480, 3 330 (NH_2), 3 170 (NH), 2 200 (CN), and 1 660 cm^{-1} (C=N) (Found: 65.1; H, 7.35; N, 16.5. $C_{17}H_{15}N_5 \cdot 3C_2H_5OH$ requires C, 64.9; H, 7.3; N, 16.5).

When tetracyanoethane and isobenzimidazole (equimolar quantities) were kept in ethanol at room temperature for 8 h, chromatography as above gave the purple cyano compound (**14**; $R^1 = R^2$ = CN) (26%), m.p. and mixed m.p. 210 °C.

Ethyl cyanoacetate (0.6 g) was added to a solution of isobenzimidazole (1.0 g) in ethanol (50 ml) and kept for 12 h. The product was filtered off and recrystallised from ethanol to give a mixture of the green cyanoesters (**14a**; R^1 = CN, R^2 = CO_2Et) and (**14b**; R^1 = CO_2Et, R^2 = CN) as described in the discussion (Found: C, 68.4; H, 6.0; N, 13.7. $C_{17}H_{19}N_3O_2$ requires C, 68.7; H, 6.4; N, 14.1%); δ(CF_3CO_2H) 8.85 [$J_{a,b}$ 9 Hz, d, H_a in (**14a**)], 7.8 [$J_{a,b}$ 9 Hz, H_a in (**14b**)], 7.05 [$J_{b,a}$ 9 Hz, d, H_b in (**14a**)], 7.00 [$J_{b,a}$ 9 Hz, d, H_b in (**14b**)], 4.1 (2 H, q), 1.45 (10 H, m), and 1.00 (3 H, t).

Preparation of the Heterocyclic Compounds (**29**)—(**32**).—*Ring opening of the substituted isobenzimidazole.* As an example, 5-piperidinoisobenzimidazole-2-spirocyclohexane (**2**; Nu = $C_5H_{10}N$) (9 g) was dissolved in acetic acid (150 ml) and the mixture was hydrogenated overnight at atmospheric pressure in the presence of Pd/C. After filtration and evaporation of the solvent, the residue was taken up without further purification in an appropriate solvent and condensed with the required reagent. The various products were purified over alumina in the usual way, yielding the heterocycles listed in Table 6.

Ring-opening could also be achieved by adding a large excess of sodium dithionite ($Na_2S_2O_4$) to an ethanolic solution of the isobenzimidazole with stirring, followed by heating for a short time on a water-bath (30 min). After removal of the solvent under reduced pressure the product was treated as above.

Preparation of 5-Arylsulphonylbenzimidazole-2(3H)-*spirocyclohexanes* (**16**).—In a typical example, to a solution of isobenzimidazole (28 g, 0.15 mol) dissolved in ethanol (200 ml) a solution of sodium benzenesulphinate (31 g, 0.19 mol) in water (60 ml) was added. On subsequent addition of acetic acid (12 ml) the mixture became warm and within a few minutes a pale yellow precipitate had formed. It was filtered off, washed with water and ethanol and recrystallised from benzene to give compound (**16**; R = Ph) (93%), m.p. 165 °C (lit.,[16] m.p. 168.5 °C). The following arylsulphonyl derivatives were prepared similarly: the p-*tolylsulphone* (**16**; R = 4-MeC_6H_4) (76%) had m.p. 151 °C (Found: C, 66.65; H, 6.5; N, 8.2. $C_{19}H_{22}N_2O_2S$ requires C, 66.6; H, 6.5; N, 8.2%); $\nu_{max.}$ 3 390 and 3 360 cm^{-1} (NH); The p-*chlorophenylsulphone* (**16**; R = p-ClC_6H_4) (81%) had m.p. 169 °C (Found: C, 59.6; H, 5.0; N, 7.7. $C_{18}H_{19}ClN_2O_2S$ requires C, 59.6; H, 5.3; N, 7.7%); $\nu_{max.}$ 3 400 cm^{-1} (NH). The 2,5-*dichlorophenylsulphone* (**16**; R = 2,5-$Cl_2C_6H_3$) (60%) had m.p. 156 °C (Found: C, 54.55; H, 4.8; N, 7.1. $C_{18}H_{18}Cl_2N_2O_2S$ requires C, 54.4; H, 4.6; N, 7.05%); $\nu_{max.}$ 3 450 cm^{-1} (NH).

5-*Arylsulphonylisobenzimidazole*-2-*spirocyclohexanones* (**17**).—Oxidation of the above dihydro compounds was carried out in benzene or methylene dichloride as for the dihydro-

benzimidazoles (*cf.* above) with MnO_2 at room temperature. 5-Phenylsulphonylisobenzimidazole (**17**) (86%) had m.p. 133 °C (lit.,[16] m.p. 134 °C). The other above-mentioned dihydro-5-arylsulphones were oxidised and made to react with nucleophiles in a one-pot reaction.

Reaction of Nucleophiles with the 5-Arylsulphones (**17**).—(*a*) *Nitrogen nucleophiles.* The arylsulphonylisobenzimidazole was dissolved in benzene with an equimolar amount of the required amine. In the case of ammonia this was passed as a gas for 1 h through the reaction mixture. To this solution a sufficient quantity of MnO_2 to oxidise the intermediate dihydro compound was added. The mixture was stirred for 6 h at ambient temperature after which time the MnO_2 was filtered off. The filtrate was removed on a rotary evaporator yielding usually the crude, crystalline product which was purified by recrystallisation (light petroleum) and chromatographed (Al_2O_3; ethyl acetate–light petroleum).

A solution of aniline and the 5-phenylsulphone (**17**) was kept for 2 days at room temperature, and the 5,6-dianilinoisobenzoimidazole-2-spirocyclohexane (40%), m.p. 216—218 °C was obtained (*cf.* Table 1).

When ethanol was used as the solvent and the reaction was carried out as above but in the dark, the crude product was obtained as an oil. Chromatography (Al_2O_3) with light petroleum–ethyl acetate (2:1) gave with the secondary amines first a red 4-dialkylamino-5-phenylsulphonylisobenzimidazole, followed by a blue band which yielded the corresponding dialkylaminovinylisobenzimidazole (**20**). Examples are listed in Table 4.

When a mixture of equimolar quantitites of acetaldehyde, piperidine, and 5-phenylsulphonylisobenzimidazole was allowed to stand in benzene for 5 h and then worked up as above, the piperidinoenamine (**20**; $R^1,R^1 = -[CH_2]_5-$) was obtained (28%) as the only substitution product.

Alternatively, the dihydrosulphones (*cf.* above) were oxidised in solution (benzene) by addition of an excess of MnO_2 with stirring for 1 h before addition of the amine. By this procedure the various 2,3-dihydro-5-arylsulphonylbenzimidazoles (**16**) described above were made to react by passing a stream of gaseous ammonia through the solution to give the following 4-amino-5-arylsulphones: compound (**19**; R = MeC_6H_4, Nu = NH_2) (42%), m.p. 140 °C (Found: C, 64.2; H, 5.9; N, 12.0. $C_{19}H_{21}N_3O_2S$ requires C, 64.2; H, 6.0; N, 11.8%); compound (**19**; R = 4-ClC_6H_4, Nu = NH_2) (35%), m.p. 127—128 °C (Found: C, 57.6; H, 4.8; N, 11.2. $C_{18}H_{18}ClN_3O_2S$ requires C, 57.5; H, 4.8; N, 11.2%); and compound (**19**; R = 2,5-$Cl_2C_6H_3$, Nu = NH_2) (55%) (Found: C, 52.6; H, 4.25; N, 10.3. $C_{18}H_{17}Cl_2N_3O_2S$ requires C, 52.7; H, 4.2; N, 10.2%).

(*b*) *Sulphur nucleophiles.* The reaction conditions were similar to those described for amines with ethanol as solvent, but not in the dark. With 5-phenylsulphonylisobenzimidazole and thiophenol as the reactants, chromatography on Al_2O_3 with light petroleum–ethyl acetate (10:1) yielded diphenyl disulphide (20%) as the first band followed by *5-phenylsulphonyl-4,6-bisphenylthioisobenzimidazole-2-spirocyclohexane* (25%), m.p. 170 °C (from chloroform), $\nu_{max.}$ 1 320 and 1 150 cm^{-1} (SO_2); $\delta(CDCl_3)$ 6.9—8.0 (16 H, m), 2.3—1.9 (10 H, m) (Found: C, 66.4; H, 4.8; N, 5.2. $C_{30}H_{26}N_2O_2S_3$ requires C, 66.4; H, 4.8; N, 5.3%).

The crude oily product obtained from 1,1-dimethylethanethiol was chromatographed on alumina and eluted with light petroleum–ethyl acetate (5:1). The first band gave red *5-phenylsulphonyl-4,6-bis-t-butylthioisobenzimidazole-2-spirocyclohexane* (40%), m.p. 163—164 °C (from dichloromethane–light petroleum) (Found: C, 62.0; H, 6.4; N, 6.1. $C_{26}H_{34}N_2O_2S_3$ require C, 62.1; H, 6.8; N, 5.7%); $\nu_{max.}$ 1 300 and 1 150 cm^{-1} (SO_2); $\delta(CDCl_3)$ 7.5—8.1 (6 H, m), 1.5 (9 H, s), 1.25 (9 H, s), and 1.7—2.0 (10 H, m). The second band gave orange 5-phenylsulphonyl-4-t-butylthioisobenzimidazole (**19**; R = Ph, Nu = $CSMe_3$) (20%) m.p. 140—141 °C (from dichloromethane–light petroleum); $\nu_{max.}$ 1 300 and 1 140 cm^{-1} (SO_2); $\delta(CDCl_3)$ 7.5—8.1 (6 H, m), 7.25—7.35 (1 H, d), 1.25 (9 H, s), and 1.7—1.9 (10 H, m) (Found: C, 63.7; H, 6.4; N, 6.95. $C_{22}H_{26}N_2O_2S_2$ requires C, 63.75; H, 6.3; N, 6.8%).

Reactions of Nucleophiles with Chloro-substituted 2,1,3-*Benzoselenadiazoles.*—5-Chloro- (**32**; R^1 = Cl, R^2 = R^3 = H) and 5,6-dichloro-selenadiazole (**32**; R^1 = R^2 = Cl, R^3 = H) were prepared by a literature method[4] in practically quantitative yield. In a typical experiment a solution of 5-chloro-2,1,3-benzoselenadiazole (1.26 g, 0.006 mol) in an excess of piperidine was refluxed for 24 h. The mixture was then taken to dryness on a rotary evaporator and the residue chromatographed on silica with a mixture of light petroleum–ethyl acetate (5:1) to give as the second band orange crystals of *5-piperidino-2,1,3-benzoselenadiazole* (0.42 g, 27.3%), m.p. 169 °C (Found: C, 49.2; H, 4.9; N, 15.7. $C_{11}H_{13}N_3Se$ requires C, 49.6; H, 4.9; N, 15.8%); $\delta(CDCl_3)$ 7.6 (1 H, d, *J* 9 Hz), 7.3 (1 H, dd, *J* 9, 2 Hz), 6.88 (1 H, d), 3.3 (4 H, br), and 1.68 (6 H, br). Under similar conditions the following were also obtained: *5-pyrrolidino-2,1,3-benzoselenadiazole* (27.4%), m.p. 163 °C (Found: C, 47.6; H, 4.5; N, 16.8. $C_{10}H_{11}N_3Se$ requires C, 47.6; H, 4.4; N, 16.7%); $\delta(CDCl_3)$ 7.6 (1 H, d, *J* 9 Hz), 7.16 (1 H, dd, *J* 10, 2 Hz), 6.5 (1 H, d), 3.4 (4 H, t), 2.05 (4 H, t); and *5-morpholino-2,1,3-benzoselenadiazole* (22%), m.p. 151 °C (Found: C, 44.7; H, 4.0; N, 15.8. $C_{10}H_{11}N_3OSe$ requires C, 44.8; H, 4.1; N, 15.7%); $\delta(CDCl_3)$ 7.65 (1 H, d, *J* 10 Hz), 7.3 (1 H, dd, *J* 10, 2 Hz), 6.9 (1 H, d), 3.9 (4 H, m), and 3.28 (4 H, m).

5,6-Dichloro-2,1,3-benzoselenadiazole was treated with piperidine and morpholine at 50 °C for 48 h and with pyrrolidine at room temperature for 48 h to give the following products after chromatography of the residue (Al_2O_3; light petroleum–ethyl acetate, 9:1): orange *6-chloro-4-piperidino-2,1,3-benzoselenadiazole* (3.5%), m.p. 186 °C (Found: C, 43.8; H, 3.9; N, 13.8. $C_{11}H_{12}ClN_3Se$ requires C, 43.9; H, 4.0; N, 14.0%); $\delta(CDCl_3)$ 7.39 (1 H, d, *J* 2 Hz), 6.65 (1 H, d, *J* 2 Hz), 3.6 (4 H, m), and 1.74 (6 H, m); yellow *5-chloro-6-piperidino-2,1,3-benzoselenadiazole* (1.7%), m.p. 132 °C (Found: C, 4.37; H, 4.0; N, 13.9%); $\delta(CDCl_3)$ 7.97 (1 H, s), 7.35 (1 H, s), 3.2 (4 H, m), and 1.71 (6 H, m); yellow *5-chloro-6-morpholino-2,1,3-benzoselenadiazole* (18.5%), m.p. 165 °C (Found: C, 39.5; H, 3.4; N, 13.8. $C_{10}H_{10}ClN_3OSe$ requires C, 39.7; H, 3.3; N, 13.9%); $\delta(CDCl_3)$ 7.95 (1 H, s), 7.5 (1 H, s), 4.2 (4 H, m), and 3.75 (4 H, m); red *6-chloro-4-pyrrolidino-2,1,3-benzoselenadiazole* (37.8%), m.p. 179 °C (Found: C, 41.9; H, 3.4; N, 14.6. $C_{10}H_{10}ClN_3Se$ requires C, 41.9; H, 3.5; N, 14.7%); $\delta(CDCl_3)$ 7.04 (1 H, d, *J* 1 Hz), 6.0 (1 H, d, *J* 1 Hz), 3.61 (4 H, m), and 2.0 (4 H, m); yellow *5-chloro-6-pyrrolidino-2,1,3-benzoselenadiazole* (19%), m.p. 120 °C (Found: C, 41.9; H, 3.3; N, 14.8%); δ 7.76 (1 H, s), 6.92 (1 H, s), 3.5 (4 H, m), and 2.1 (4 H, m).

Refluxing a mixture of the 5,6-dichlorobenzoselenadiazole (1 g, 0.004 mol), sodium methoxide (0.008 mol), methanol (30 ml) and dimethylformamide (40 ml) for 24 h followed by the usual work-up (SiO_2, light petroleum–ethyl acetate) gave *5-chloro-6-methoxy-2,1,3-benzoselenadiazole* (27.6%), m.p. 197 °C (Found: C, 34.2; H, 2.0; N, 11.4. $C_7H_5ClN_2OSe$ requires C, 34.2; H, 2.0; N, 11.4%); $\delta(CDCl_3)$ 7.84 (1 H, s), 7.1 (1 H, s), 4.0 (3 H, s); and *5,6-dimethoxy-2,1,3-benzoselenadiazole* (32.2%), m.p. 142 °C (Found: C, 39.5; H, 3.5; N, 11.6. $C_8H_8N_2O_2Se$ requires C, 39.5; H, 3.3; N, 11.5%); $\delta(CDCl_3)$ 6.9 (2 H, s), 3.9 (6 H, s). Similar conditions using sodium ethoxide in ethanol gave *5,6-diethoxy-2,1,3-benzoselenadiazole* (70%), m.p. 141 °C (Found: C, 44.55; H, 4.7; N, 10.5. $C_{10}H_{12}N_2O_2Se$ requires C, 44.3; H, 4.5; N, 10.3%); $\delta(CDCl_3)$ 6.9 (2 H, s), 4.15 (4 H, q), and 1.6 (6 H, t).

Ring-opening of 2,1,3-*Benzoselenadiazole.*—Attempts to ring-open various 2,1,3-benzoselenadiazoles to give the corresponding *o*-diamine by addition of an excess of sodium dithionite to a boiling ethanolic solution of a diazole gave only starting material. Treatment with $SnCl_2$–HCl of some amino-substituted selenadiazoles [(**32**; $R^1 = R^3 = H$, $R^2 = C_5H_{10}N$ or C_4H_8N)] gave only small amounts (5—8%) of the corresponding *o*-phenylenediamines.

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