Indole β-Nucleophilic Substitution. Part 7.[1] β-Halogenation of Indoles. Attempted Intramolecular β-Nucleophilic Substitution of α-Arylindoles

Lesley Dalton, Godfred L. Humphrey, Melanie M. Cooper, and John A. Joule *
Chemistry Department, Manchester University, Manchester M13 9PL

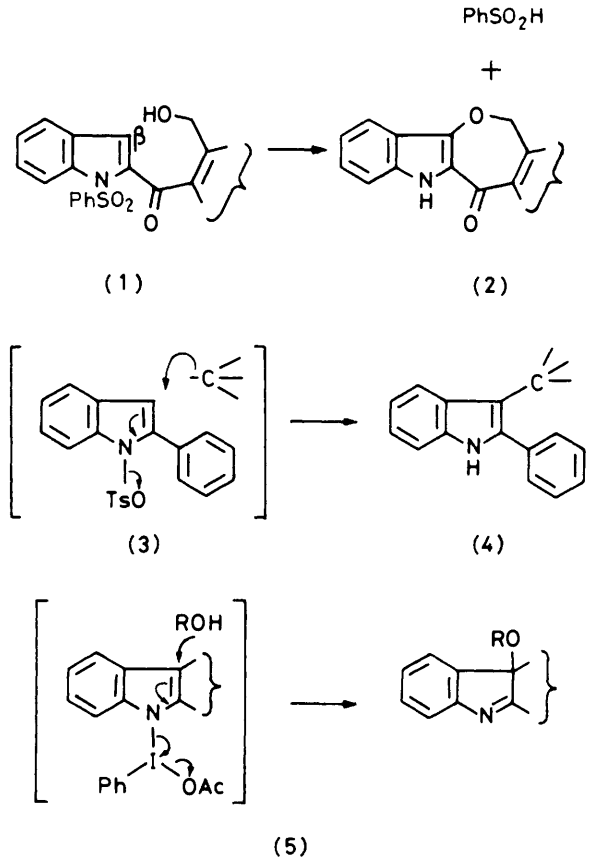
Intramolecular β-nucleophilic substitution of 2-aryl-1-phenylsulphonylindoles could not be achieved. *N*-Arylsulphonylation of 2-arylindoles with arylsulphonyl halides using phase-transfer conditions is accompanied by 3-halogenation in some cases; the proportion of 3-halogeno-arylsulphonyl-2-arylindole produced is greater with more electron rich 2-substituents supporting the view that the 3-halogenation is electrophilic in character.

We have described [2,3] the efficient process whereby systems of the form (1) can be transformed into oxepino-indoles (2) in a sequence which involves nucleophilic attack by alkoxide oxygen at the indole β-position with concomitant, or subsequent, loss of the nitrogen substituent as benzenesulphinate. The process is the ümpolung of the typical susceptibility of indoles to electrophilic attack at the β-position. The conjugation with an α-acyl group is a prerequisite for the operation of the process.

Prior to our investigations there were few examples of the direct introduction of a nucleophile at an unsubstituted indole β-position. Perhaps of closest analogy is the formation [4] of 3-cyano-2-ethoxycarbonyl-3-tosyloxy-3*H*-indole on reaction of 3-cyano-2-ethoxycarbonyl-1-hydroxyindole with tosyl chloride in triethylamine and the more recently described [5] conversions of 1-bromo-3-methyl (and 3-phenyl) 2-ethylsulphonylindoles into their 3-bromo-3*H*-indole isomers in refluxing carbon tetrachloride. For each of these examples a possible mechanism would involve intermolecular nucleophilic attack at the β-position with expulsion of the nitrogen substituent as a leaving group; an alternative would involve an intramolecular rearrangement of *N*-substituent to the β-position. In this connection it is relevant to recall the rearrangement of the tosylate of *N*-hydroxy-1-isoquinolone to the 4-tosyloxyisoquinolone which was shown to proceed in an intramolecular fashion *via* a tight ion pair.[6]

The rearrangement of tosylate [7] and 4-nitrobenzoate [4] esters of 1-hydroxy-2-phenylindole to 3-tosyloxy- and 3-(4-nitrobenzoyloxy)-2-phenylindoles are also examples which could involve β-nucleophilic attack with expulsion of the nitrogen leaving group. In those examples α-carbonyl or α-sulphonyl conjugation is replaced with α-aryl conjugation. More recently it was reported [8] that comparable rearrangements could be achieved with 4-nitrobenzenesulphonate, benzoate, and acetate esters. Further, reaction of the 2-phenyl-1-hydroxyindole with tosyl chloride in the presence of carbon nucleophiles such as cyanoacetate led [8] to the introduction of the carbon nucleophile at the indole β-position *via*, it was suggested, the *O*-tosylate undergoing displacement of tosylate by carbon nucleophilic β-attack as implied in the summarising equation (3) ⟶ (4); in these last examples an intramolecular N→C-β rearrangement cannot explain the products.

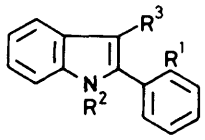
It has also been recently demonstrated [9,10] that the β-chlorination of 2-phenylindole and even of 2-methylindole and indole itself, which would previously have been considered to be halogenation of either the indole or the N-deprotonated indole anion by direct electrophilic attack at the β-position, in fact proceed *via* an *N*-chloroindole which rearranges; again, one pathway for the rearrangement would involve chloride nucleophilic attack at the indole β-position with departure of chloride from nitrogen, and another the intramolecular rearrangement of halogen.



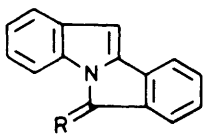
The β-alkoxylation of 2,3-dialkylindoles using iodosobenzene diacetate and the alcohol was pictured [11] as proceeding *via* a species (5), alcohol attack [arrows on (5)] then leading to the product with the displacement of the *N*-substituent.

These results led us to speculate that conjugation with an α-aryl substituent might allow the operation of intramolecular substitution processes analogous to those which we have described for 1-phenylsulphonyl-2-acylindoles [(1)→(2)]. We have now prepared the alcohol (6a) and the amide (6b) to test this possibility.

The lactam (7a) [12] was hydrolysed with aqueous methanolic sodium hydroxide. In the hope that the desired alcohol (6a) could be obtained in two steps by *N*-phenylsulphonylation and then reduction, the acid (6c) was treated with benzenesulphonyl chloride under phase-transfer conditions; it reverted smoothly to the lactam (7a). Reduction of the acid gave the alcohol (6d) which, in the hope that selective *N*-phenyl-

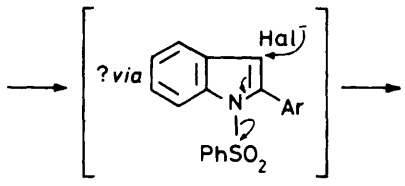


(6)	R^1	R^2	R^3
a;	$HOCH_2$	$PhSO_2$	H
b;	PhCONH	$PhSO_2$	H
c;	HO_2C	H	H
d;	$HOCH_2$	H	H
e;	$THPOCH_2$	H	H
f;	$THPOCH_2$	$PhSO_2$	H
g;	O_2N	H	H
h;	O_2N	$PhSO_2$	H
i;	H_2N	$PhSO_2$	H
j;	PhCONH	H	H
k;	Br	H	H
l;	Br	$PhSO_2$	H
m;	Br	$PhSO_2$	Cl
n;	$THPOCH_2$	$PhSO_2$	Cl
o;	H	H	H
p;	H	$PhSO_2$	Cl
q;	NH_2	H	H
r;	NH_2	$PhSO_2$	Cl
s;	H	$PhSO_2$	Br
t;	H	$4\text{-}MeC_6H_4SO_2$	Cl
u;	H	$MeSO_2$	H
v;	H	PhCO	H
w;	$HOCH_2$	$PhSO_2$	Cl



a; R = O
b; R = CH_2

(7)



(8)

sulphonylation could be achieved, was similarly treated: only the tetracycle (7b) was obtained. Both these reclosures probably involve N→O phenylsulphonyl transfer followed by intramolecular *N*-acylation and -alkylation respectively. Protection of the alcohol as its tetrahydropyranyl ether [→(6e)] and then phase-transfer catalysed phenylsulphonylation yielded (6f), mild acidic hydrolysis of which produced (6a).

2-(2-Nitrophenyl)indole (6g) [13] underwent smooth *N*-phenylsulphonylation under phase-transfer conditions [→(6h)] catalytic reduction then producing the amine (6i) and benzoylation the amide (6b).

Treatment of the alcohol (6a) under conditions which had proved successful in the 2-acyl series [2,3] led only to the hydrolysed alcohol (6d). Formation of the oxy-anion utilising sodium hydride in tetrahydrofuran (THF) was equally unprofitable in bringing about the desired process: the tetracycle (7b) was formed smoothly.

Attempts to cyclise the amide (6b) to the known indolo-[3,2-*b*]indole system [14] were no more successful. A prolonged period under reflux with sodium hydride in THF gave only the de-phenylsulphonylated amide (6j).

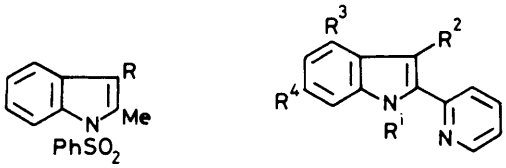
In the course of an attempt to prepare (6a) the 2-(2-bromophenyl)indole (6k) was *N*-phenylsulphonylated by the phase-transfer method [→(6l)]. A minor chlorine-containing by-product was isolated and shown, by the absence of the usual indole β-proton ^1H n.m.r. signal, to have structure (6m). A comparable chloro by-product (6n) was also produced during the transformation of (6e) into (6f). In the context of our work and of the precedents cited above it appeared possible that these 3-halogenoindoles might well be being produced *via* a sequence involving firstly *N*-phenylsulphonylation, secondly intermolecular chloride β-nucleophilic attack with displacement of benzenesulphinate [arrows on (8)] and, finally, re-*N*-phenylsulphonylation. An investigation (see below) however showed that this is *not* the route by which these β-halogenoindoles are formed.

2-Phenylindole (6o) subjected to the same conditions gave, in good yield, as the only characterisable product, 3-chloro-2-phenyl-1-phenylsulphonylindole (6p). This must be contrasted with comparable treatment of 2-(2-nitrophenyl)indole (6g) which gave no β-chlorination product, producing only (6h), and with 2-(2-bromophenyl)indole (6k) from which the 3-chloro-derivative was only a minor product. Conversely, 2-(2-aminophenyl)indole (6q) was converted smoothly into the β-chlorinated product (6r) under the same conditions. These results show that the more electron-rich 2-aryl substituents led to more 3-chlorination—the reverse of the result which would have been anticipated on the basis of the route implied by the arrows on (8).

When the phenylsulphonylation of 2-phenylindole was conducted in the presence of a large excess of sodium bromide, in the hope that bromide might intervene as a nucleophile and produce, at least some, of the 3-bromo-derivative (6s), *none* was produced. However the use of benzenesulphonyl bromide with the same substrate under the same conditions *did* produce the bromide (6s), in good yield. Phase-transfer *N*-benzoylation of 2-phenylindole with benzoyl chloride though inefficient, probably due to easy hydrolysis of the *N*-benzoyl product, produced no β-chloro-derivative. Finally, treatment of 2-benzoylindole with benzenesulphonyl chloride under phase-transfer conditions produced only an *N*-phenylsulphonylated product, no chlorine being introduced.

These results show clearly that the benzenesulphonyl halide is acting as an electrophilic halogenating agent in these processes although the results allow no comment as to whether the halogenation is at nitrogen first followed by rearrangement or directly at the β-position. There is a precedent [15] for toluenesulphonyl chloride acting in this manner: reaction of the sodium salt of ethyl acetoacetate gave ethyl 2-chloroacetoacetate.

2-Phenylindole was transformed under phase-transfer conditions with toluenesulphonyl chloride into (6t). Reaction with methanesulphonyl chloride in contrast produced only the *N*-mesyl derivative (6u) no trace of ring halogenation being detected. Although phase-transfer *N*-phenylsulphonylation of indole itself is a convenient and efficient method for preparing



(9)	R	(10)	R^1	R^2	R^3	R^4
a;	H	a;	H	H	H	H
b;	Cl	b;	H	H	H	$PhSO_2$
		c;	H	H	$PhSO_2$	H
		d;	H	$PhSO_2$	H	H
		e;	$PhSO_2$	Cl	H	H
		f;	$PhSO_2$	H	H	H
		g;	$PhSO_2$	$PhSO_2$	H	H

this compound, 2-methylindole produced a mixture with the β-chlorinated material (9b) representing 25% of the total, the remainder being the normal product (9a). It was shown that (9b) was not formed from (9a) under the conditions of the reaction.

A recent report [16] of the reaction of 2-(2-pyridyl)indole (10a) with benzenesulphonyl chloride under phase-transfer conditions stated that three products were formed (10b), (10c), and (10d) (m.p. 111—112, 125, and 136 °C respectively), none of them containing chlorine, with the former predominating. Because of the similarity to the work described above we have attempted to reproduce this work. In our hands, phase-transfer phenylsulphonylation of (10a) gave three crystalline compounds, m.p. 146—148, 148—149, and 208—210 °C respectively, to which we assign the structures (10e) (major), (10f), and (10g).

Experimental

General Method for Reaction of Indoles with Benzenesulphonyl Halides.—To a mechanically stirred solution of the indole (*a* mg) in tetrahydrofuran (*b* ml) containing tetra-n-butylammonium hydroxide solution (40%, *c* drops) was added aqueous sodium hydroxide (50%, *d* ml), followed after 5 min by dropwise addition, during 10 min, of a solution of benzenesulphonyl halide (*f* mg) in tetrahydrofuran (*b* ml). The mixture was stirred for a further 60 min. The tetrahydrofuran was removed by evaporation under reduced pressure and the residue partitioned between ethyl acetate and water; the organic layer was washed with water, dried (K_2CO_3), and evaporated under reduced pressure to give the product (*g* mg).

2-Indol-2-ylbenzoic Acid (6c).—The lactam (7a) (8.72 g) was dissolved in methanol (50 ml) and then treated with aqueous sodium hydroxide (3M; 25 ml) and the mixture heated on a steam-bath for 15 min. The solvent was removed under reduced pressure and the residue acidified and extracted with chloroform. The chloroform extract was dried and evaporated under reduced pressure to give a brown oil which was crystallised from ethanol (6.31 g, 67%), m.p. 157—159 °C (lit.,[12] m.p. 159 °C).

2-(2-Hydroxymethylphenyl)indole (6d).—The acid (6c) (180 mg) was reduced with lithium aluminium hydride (120 mg) in THF reflux under nitrogen for 2 h. After the mixture had cooled, it was diluted with water and extracted with ethyl acetate. Evaporation of the extract, gave a gum which crystallised; this was recrystallised from ethyl acetate to give the *alcohol* (6c) (160 mg), m.p. 84—86 °C, $\lambda_{max.}$ (EtOH) 235sh and 305 nm (log ε 4.22 and 4.15); $\nu_{max.}$ (Nujol) 3 420m cm^{-1}; τ ($CDCl_3$) – 1.12 (1 H, NH), 1.55—2.88 (9 H, m, ArH), 3.23 (1 H, s, indole-3-H), 5.33 (2 H, s, CH_2O), and 7.7 (1 H, OH); *m/z* 223 (M^+, 30%) and 204 (100) [Found: C, 77.8; H, 6.2; N, 5.9%. *M* (by mass spectrometry), 223.099. $C_{17}H_{13}NO$ requires C, 80.7; H, 5.8; N, 6.3%; *M*, 223.099].

6H-Isoindolo[2,1-a]indole (7b).—(*a*) The alcohol (6a) (10 mg) in solution in dry tetrahydrofuran (10 ml) was stirred with sodium hydride (5 mg; 50% dispersion in oil) at room temperature for 18 h. The solvent was evaporated under reduced pressure and the residue partitioned between water and ethyl acetate. The organic layer was dried and evaporated to yield the *isoindoloindole* (7b) (6 mg). (*b*) To a well stirred solution of the alcohol (6a, 150 mg) in benzene (15 ml), containing tetra-n-butylammonium hydroxide solution as catalyst, was added aqueous sodium hydroxide (10 ml; 50%). After stirring for 5 min at room temperature, benzenesulphonyl chloride (438 mg) in benzene (15 ml) was added during *ca.* 15 min. The benzene layer was separated, washed with water, dried, and evaporated to give a yellow oil, which was crystallised from methanol to give the tetracycle (7b) (80 mg) as white plates, m.p. 233—235 °C, $\lambda_{max.}$ (EtOH) 224, 249sh, 257, 312sh, 324, and 337 nm (log ε 4.18, 3.91, 3.94, 4.14, 4.20, and 4.00); τ ($CDCl_3$) 2.26 (2 H, t, *J* 7 Hz, ArH), 2.48—2.90 (7 H, m,ArH), 3.34 (1 H, s indole-3-H), and 4.9 (2 H, s,CH_2); *m/z* 205 (M^+, 100%), 204 (94), and 176 (8) [Found (by mass spectrometry, *M*, 205.089. $C_{15}H_{11}N$ requires *M*, 205.088].

2-(2-Tetrahydropyran-2-yloxymethylphenyl)indole (6e).—The alcohol (6d) (2.23 g) in solution in dichloromethane (5 ml) containing dihydropyran (1.4 ml) and pyridinium toluene-*p*-sulphonate (0.251 g) was stirred at room temperature, under nitrogen, for 5 h. The solution was washed with water, dried, and evaporated under reduced pressure to give the *ether* (6e) as a brown gum (2.98 g, 97%) which could not be crystallised, $\lambda_{max.}$ (EtOH) 219sh, 233sh, and 304 nm; $\nu_{max.}$ 3 360 cm^{-1}; τ ($CDCl_3$) −0.20 (1 H, bs, NH), 2.30 (2 H, t, *J* 7 Hz, ArH), 2.55—2.72 (3 H, m, ArH), 2.73—2.90 (3 H, m, ArH), 3.27 (1 H, s, indole-3-H), 5.14 (1 H, d, *J* 12 Hz, CH_AH_BO), 5.21 (1 H, m, OCHO), 5.44 (1 H, d, *J* 12 Hz, CH_AH_BO), 6.07 (1 H, m, CHO), 6.46 (1 H, m, CHO) and 8.05—8.50 [6 H, m, $(CH_2)_3$]; *m/z* 307 (M^+ 22%), 234 (4), 223 (87), 205 (100), and 204 (100) [Found (by mass spectrometry): *M*, 307.158. $C_{20}H_{21}NO_2$ requires *M*, 307.158].

2-(2-Hydroxymethylphenyl)-1-phenylsulphonylindole (6a) *and 3-Chloro-2-(2-hydroxymethylphenyl)-1-phenylsulphonylindole* (6w).—The tetrahydropyranyl ether (6e) was treated with benzenesulphonyl chloride as described earlier; *a* = 360, *b* = 10, *c* = 3, *d* = 7, *f* = 180, *g* = 512, to give a mixture of 1-phenylsulphonyl-2-(2-tetrahydropyran-2-yloxymethylphenyl)-indole (6f) and 3-chloro-1-phenylsulphonyl 2-(2-tetrahydropyran-2-yloxymethylphenyl)indole (6n) as a gum which could not be separated, *m/z* 483, 481 (M^+, 0.5, 1.5%), 447 (M^+, 1%) 399, 397 (5, 13), 363 (6), 347 (13), 222 (29), 206 (46), and 85 (100) [Found (by mass spectrometry): *M*, 447.151. $C_{26}H_{25}NO_4S$ requires *M*, 447.150 and *M*, 481.112. $C_{26}H_{24}ClNO_4S$ requires *M*, 481.111], and was used for the next step. A solution of the tetrahydropyranyl ethers (6f) and (6n) (512 mg) in ethanol (11 ml) was stirred with pyridinium toluene-*p*-sulphonate (34 mg) at 55 °C for 24 h. The solvents were evaporated under reduced pressure and the residue was dissolved in chloroform and the solution washed with water, dried, and then evaporated to give a brown oil; this was purified by chromatography on silica when 5% ethyl acetate in toluene eluted the pure *alcohol* (6a) (130 mg) as a pale brown gum, $\lambda_{max.}$ (EtOH) 267 nm; $\nu_{max.}$ 3 400s cm^{-1}; τ ($CDCl_3$) 1.57 (1 H, d, *J* 8 Hz, ArH), 2.19 (2 H, d, *J* 8 Hz, ArH), 2.40—2.57 (5 H, m, ArH), 2.58—2.68 (4 H, m, ArH), 2.97 (1 H, d, *J* 8 Hz, ArH), 3.42 (1 H, s, indole-3-H), 5.32 (1 H, d, *J* 12 Hz,

CH_AH_BO), 5.50 (1 H, d, *J* 12 Hz, CH_AH_BO), and 7.62 (1 H, bs, OH); *m/z* 363 (M^+, 36%), 222 (100), and 204 (75) [Found (by mass spectrometry): *M*, 363.092. $C_{21}H_{17}NSO_3$ requires *M*, 363.092]; and the pure *chloro-alcohol* (6w) (40 mg) also as a pale brown gum $\lambda_{max.}$ (EtOH) 262 nm; $\nu_{max.}$ 3 380 cm^{-1}; τ ($CDCl_3$) 1.53 (1 H, d, *J* 8 Hz, ArH), 2.24 (2 H, d, *J* 8 Hz, ArH), 2.32—2.70 (9 H, m, ArH), 5.49 (2 H, s, CH_2O), and 7.79 (1 H, bs, OH); *m/z* 397, 399 (M^+, 26, 10%), 256, 258 (25, 8), and 220 (100) [Found (by mass spectrometry): *M*, 397.053. $C_{21}H_{16}ClNO_3S$ requires *M*, 397.053].

2-(2-*Nitrophenyl*)-1-*phenylsulphonylindole* (6h).—2-(2-Nitrophenyl)indole [13] was treated with benzenesulphonyl chloride as described above; *a* = 1 061, *b* = 20, *c* = 5, *d* = 10, *f* = 2 000, *g* = 1 134, the *phenylsulphonylindole* (6h) had m.p. 159—161 °C (from methanol), $\lambda_{max.}$ (EtOH) 212, 254, and 318sh nm (log ε 4.46, 4.30, and 3.32); $\nu_{max.}$ (Nujol) 1 525s, 1 450s, 1 370s, and 1 180s cm^{-1}; τ ($CDCl_3$) 1.75 (1 H, d, *J* 9 Hz, ArH), 1.82 (1 H, d, *J* 6 Hz, ArH), 2.30—2.80 (11 H, m, ArH), and 3.40 (1 H, s, indole-3-H); *m/z* 378 (M^+, 67%), 237 (72), 209 (17), 190 (20), and 179 (67) (Found: C, 63.3; H, 3.6; N, 7.4; S, 8.6. $C_{20}H_{14}N_2O_4S$ requires C, 63.5; H, 3.7; N, 7.4; S, 8.5%).

2-(2-*Aminophenyl*)-1-*phenylsulphonylindole* (6i).—The nitro-compound (6h) (500 mg) in suspension in ethanol (30 ml) with 5% palladium on carbon (500 mg) was shaken under 3 atm of hydrogen at 60 °C for 12 h. The resultant solution was filtered through Celite then evaporated under reduced pressure to give the *amino-indole* (6i) as off-white crystals (420 mg), m.p. 151—156 °C (from ethanol), $\lambda_{max.}$ (EtOH) 208, 242, and 286sh nm (log ε 4.49, 4.27, and 3.84); $\nu_{max.}$ (Nujol) 3 450m and 3 370m cm^{-1}; τ ($CDCl_3$) 1.57 (1 H, d, *J* 8 Hz, ArH), 2.41—2.48 (4 H, m, ArH), 2.54 (1 H, t, *J* 8 Hz, ArH), 2.58—2.70 (4 H, m, ArH), 3.01 (1 H, d, *J* 8 Hz, ArH), 3.17 (1 H, d, *J* 8 Hz, ArH), 3.18 (1 H, t, *J* 6 Hz, ArH), 3.38 (1 H, s, indole-3-H), and 6.0—7.0 (2 H, bs); *m/z* 348 (M^+, 18%) and 207 (100) (Found: C, 68.7; H, 4.5; N, 7.9; S, 8.9. $C_{20}H_{16}N_2O_2S$ requires C, 69.0; H, 4.6; N, 8.1; S, 9.2%).

2-(2-*Benzamidophenyl*)-1-*phenylsulphonylindole* (6b).—The amine (6i) (203 mg) in solution in pyridine (5 ml) was treated with benzoyl chloride (100 mg) at room temperature for 4 h. The solution was poured into water (50 ml) and extracted with ethyl acetate; the extracts were washed with 2M-hydrochloric acid, dried, and evaporated under reduced pressure to give the *benzamide* (6b) as off-white crystals (240 mg), m.p. 151—153 °C (from ethanol), $\lambda_{max.}$ (EtOH) 212sh, 256, and 280sh nm (log ε 4.52, 4.35, and 4.19); $\nu_{max.}$ (Nujol) 3 390s and 1 660s cm^{-1}; τ ($CDCl_3$) 1.50—1.57 (2 H, m, ArH), 1.60 (1 H, bs, NH), 2.24—2.88 (16 H, m, ArH), and 3.34 (1 H, s, indole-3-H); *m/z* 452 (M^+, 8%), 311 (26), 294 (2), 205 (5), and 105 (100) (Found: C, 71.6; H, 4.1; N, 6.1; S, 7.1%. $C_{27}H_{20}N_2O_3S$ requires C, 71.7; H, 4.4; N, 6.2; S, 7.1%).

2-(2-*Benzamidophenyl*)*indole* (6j).—The amide (6b) (15 mg) in solution in dry tetrahydrofuran (10 ml) was heated at reflux with stirring under nitrogen with sodium hydride (5 mg; 50% dispersion in oil) for 24 h. The solvent was removed under reduced pressure and the residue partitioned between water and ethyl acetate. The organic layer was dried and evaporated under reduced pressure to give a brown oil, which was purified by chromatography over silica, when toluene eluted the pure *benzamidophenylindole* (6j) (4 mg), as a gum, $\lambda_{max.}$ (EtOH) 219, 279, and 302 nm; $\nu_{max.}$ (Nujol) 3 360s and 1 660s cm^{-1}; τ ($CDCl_3$) 1.12 (1 H, bs, NH), 1.35 (1 H, bs, NH), 1.36 (1 H, d, *J* 6 Hz, ArH), 2.17 (2 H, d, *J* 6 Hz, ArH), 2.25 (1 H, d, *J* 6 Hz, ArH), 2.40—2.56 (6 H, m, ArH), 2.60—2.76 (4 H, m, ArH), and 3.22 (1 H, s, indole-3-H); *m/z* 312 (M^+, 45%), 295 (12), 235 (5), 206 (7), and 105 (100) [Found (by mass spectrometry); *M*, 312.127. $C_{21}H_{16}N_2O$ requires *M*, 312.126].

2-(2-*Bromophenyl*)*indole* (6k).—2-Bromoacetophenone (5 g) and phenylhydrazine (2.7 g) were heated at reflux in ethanol (30 ml) with acetic acid (1 ml) for 10 min. The solvent was evaporated and the residue partitioned between water and ethyl acetate. The dried organic phase gave an orange oil (7.6 g) on evaporation, which was then heated with stirring with polyphosphoric acid (34 g) at 100—120 °C for 10 min. Aqueous sodium hydroxide (50 ml; 5 M) was added to the cooled reaction mixture and stirring continued for 4 h. The yellow precipitate was filtered off, washed with water, dried, and recrystallised from hexane to give the *indole* (6k) (3.5 g) as white plates, m.p. 75—77 °C, $\lambda_{max.}$ (EtOH) 237sh and 306 nm (log ε 4.16 and 4.22); $\nu_{max.}$ (Nujol) 3 380m cm^{-1}; τ ($CDCl_3$) 1.72 (1 H, bs, NH), 2.36–3.0 (8 H, m, ArH), and 3.24 (1 H, s, indole-3-H); *m/z* 273, 271 (M^+, 100%), 191 (27), and 165 (78) (Found: C, 61.9; H, 3.6; Br, 29.6; N, 5.2. $C_{14}H_{10}BrN$ requires C, 61.8; H, 3.7; Br, 29.4; N, 5.1%).

2-(2-*Bromophenyl*)-1-*phenylsulphonylindole* (6l) *and* 2-(2-*Bromophenyl*)-3-*chloro*-1-*phenylsulphonylindole* (6m).—Using the general method, the bromoindole (6k) (2.26 g) in benzene (100 ml) with benzenesulphonyl chloride (1.59 g) for 1 h gave a mixture separated by chromatography over silica with toluene–ether (5 : 1) as eluant to give the *indole* (6l) (2.84 g) as a yellow gum, pure by t.l.c. analysis, $\lambda_{max.}$ 250sh, 262sh, 272sh, and 280sh nm; τ ($CDCl_3$) 1.7 (1 H, d, *J* 8 Hz, ArH), 2.34—2.73 (12 H, m, ArH), and 3.4 (1 H, s, indole-3-H); *m/z* 413, 411 (M^+, 25%), 371 (20), 332 (2), 270 (33), and 191 (100) [Found (by mass spectrometry): *M*, 410.992. $C_{20}H_{14}BrNO_2S$ requires *M*, 410.991], and as the second compound eluted the *chloroindole* (6m) (250 mg) as a yellow gum, $\lambda_{max.}$ (EtOH) 236sh, 267sh, and 290sh nm; τ ($CDCl_3$) 1.14 (1 H, d, *J* 8 Hz, ArH) and 2.32—2.67 (12 H, m, ArH); *m/z* 449, 447, 445 (M^+, 45, 62, 19%), 306 (100), 225 (46), and 190 (56) [Found (by mass spectrometry): *M*, 449.954. $C_{20}H_{13}BrClNO_2S$ requires *M*, 449.953].

3-*Chloro*-2-*phenyl*-1-*phenylsulphonylindole* (6p).—Using the general method, 2-phenylindole (6o) (1.92 g) in benzene (40 ml), with benzenesulphonyl chloride (10.5 g) for 15 h gave crude material which was passed down a silica column in toluene; the eluate was evaporated and the residue crystallised from methanol to give the *chloroindole* (6p) (2.3 g), m.p. 115—116 °C, $\lambda_{max.}$ (EtOH) 219, 250sh, and 295sh nm (log ε 4.45, 4.13, and 3.88); τ ($CDCl_3$) 1.62 (1 H, d, *J* 8 Hz, ArH), 2.48—2.75 (13 H, m, ArH); *m/z* 369, 367 (M^+, 39%), 226 (100), and 199 (37) (Found: C, 65.3; H, 3.8; Cl, 9.2; N, 3.8; S, 8.5. $C_{20}H_{14}ClNO_2S$ requires C, 65.3; H, 3.8; Cl, 9.6; N, 3.8; S, 8.7%).

2-(2-*Aminophenyl*)*indole* (6q).—2-(2-Nitrophenyl)indole (900 mg) in suspension in ethanol (70 ml) was shaken under 3 atm of hydrogen with 5% palladium on carbon (700 mg) at room temperature for 12 h. The resultant solution was filtered through Celite and then evaporated under reduced pressure to give the *amine* (6q) as off-white crystals (650 mg, 83%), m.p. 155—158 °C (from ethanol); $\lambda_{max.}$ (EtOH) 224, 246sh, 286sh, 295, and 318 nm (log ε 4.49, 4.17, 3.97, 4.02, and 4.05); $\lambda_{max.}$ (EtOH–H^+) 216sh, 234sh, and 302 nm (log ε 4.37, 4.25, and 4.17); $\nu_{max.}$ (Nujol) 3 400m, 3 380m, 3 300m, and 3 200s cm^{-1}; τ [$(CD_3)_2SO$] 2.42 (1 H, d, *J* 9 Hz, ArH), 2.50—2.62 (2 H, m, ArH), 2.80—3.00 (3 H, m, ArH), 3.10—3.28 (2 H, m, ArH), 3.34 (1 H, s, indole-3-H), 5.50 (2 H, bs, NH_2), and 6.40 (1 H, bs, NH); *m/z* 208 (M^+, 100%), 180 (8), and

104 (7) (Found: C, 80.7; H, 5.7; N, 13.0. $C_{14}H_{12}N_2$ requires C, 80.8; H, 5.8; N, 13.5%).

2-(2-*Aminophenyl*)-3-*chloro*-1-*phenylsulphonylindole* (6r).—The amine (6q) was treated with benzenesulphonyl chloride as described before; $a = 101$, $b = 10$, $c = 3$, $d = 7$, $f = 170$, $g = 158$, to give the phenylsulphonyl derivative (6r), m.p. 170—172 °C (from ethanol), $\lambda_{max.}$ (EtOH) 219, 234sh, 256sh, and 290sh nm (log ε 4.48, 4.34, 4.19, and 3.89); $\nu_{max.}$ (Nujol) 3 500s, 3 400s, and 1 615s cm^{-1}; τ ($CDCl_3$) 1.62 (1 H, d, *J* 8 Hz, ArH), 2.04 (1 H, d, *J* 8 Hz, ArH) 2.40—2.80 (8 H, m, ArH), 3.08 (1 H, d, *J* 8 Hz, ArH), 3.15—3.27 (2 H, m, ArH), and 6.25 (2 H, bs, NH_2); *m/z* 382, 384 (M^+, 11, 4%), 241, 243 (7, 3), and 206 (100) (Found: C, 63.3; H, 4.0; N, 7.0; S, 8.4%. $C_{20}H_{15}ClN_2O_2S$ requires C, 62.8; H, 3.9; N, 7.3; S, 8.4%).

3-*Bromo*-2-*phenyl*-1-*phenylsulphonylindole* (6s).—To 2-phenylindole (100 mg) dissolved in tetrahydrofuran (10 ml) containing aqueous tetra-n-butylammonium hydroxide (40%; 2 drops) was added aqueous sodium hydroxide (50%; 5 ml). After 5 min, and with mechanical stirring of the solution, benzenesulphonyl bromide (0.42 g) in tetrahydrofuran (10 ml) was added dropwise during 4 h. The solvent was evaporated under reduced pressure and the residue partitioned between water and ethyl acetate. The organic layer was washed with water, dried, and evaporated under reduced pressure to give the *bromoindole* (6s) as off-white crystals (278 mg), m.p. 108—109 °C (from ethanol), $\lambda_{max.}$ (EtOH) 218sh, 264sh, 268, 275, and 280sh nm (log ε 4.46, 4.25, 4.28, 4.29, and 4.25); $\nu_{max.}$ 1 450s, 1 375s, and 1 185s cm^{-1}; τ ($CDCl_3$) 1.53 (1 H, d, *J* 8 Hz, ArH), 2.35—2.55 (11 H, m, ArH), and 2.62 (2 H, t, *J* 8 Hz, ArH); *m/z* 413, 411 (M^+, 21, 20%), 272, 270, (31, 31), and 191 (43) (Found: C, 59.0; H, 3.6; Br, 19.5; N, 3.2. $C_{20}H_{14}BrNO_2S$ requires C, 58.3; H, 3.4; Br, 19.4; N, 3.4%).

3-*Chloro*-1-(4-*methylphenylsulphonyl*)-2-*phenylindole* (6t).—To a vigorously stirred solution of 2-phenylindole (500 mg) in tetrahydrofuran (10 ml) containing tetra-n-butylammonium hydroxide (40%; 3 drops), was added aqueous sodium hydroxide (50%; 7 ml). After 5 min, toluene-*p*-sulphonyl chloride (1.2 g) in tetrahydrofuran (10 ml) was added during 10 min and the mixture stirred for a further 1 h. The solvents were removed and the residue partitioned between ethyl acetate and water; the organic phase was washed with water, dried, and evaporated under reduced pressure to give the N-*tosylindole* (6t) as pale yellow crystals (970 mg), m.p. 121—124 °C (from ethanol), $\lambda_{max.}$ (EtOH) 224, 241sh, 278sh, and 288 nm (log ε 4.45, 4.37, 4.24, and 4.27); $\nu_{max.}$ (Nujol) 1 600s, 1 450s, 1 370s, and 1 175s cm^{-1}; τ ($CDCl_3$) 1.57 (1 H, d, *J* 8 Hz, ArH), 2.24—2.62 (8 H, m, ArH), 2.66 (2 H, d, *J* 8 Hz, ArH), 2.88 (2 H, d, *J* 8 Hz, ArH), and 7.68 (3 H, s, ArMe); *m/z* 383, 381 (M^+, 14, 39%), 347 (6), 226 (82), and 193 (100) (Found: C, 66.1; H, 4.3; Cl, 8.9; N, 3.5; S, 8.0%. $C_{21}H_{16}ClNO_2S$ requires C, 66.1; H, 4.2; Cl, 9.3; N, 3.7; S, 8.4%).

1-*Methylsulphonyl*-2-*phenylindole* (6u).—To a vigorously stirred solution of 2-phenylindole (500 mg) in tetrahydrofuran (10 ml) containing tetra-n-butylammonium hydroxide solution (40%; 3 drops) was added sodium hydroxide solution (50%, 7 ml). After 4 min a solution of methanesulphonyl chloride (3 g) in tetrahydrofuran (20 ml) was added during 5 h. The mixture was partitioned between ethyl acetate and water and the organic phase dried and evaporated under reduced pressure to leave an orange oil. This was purified by chromatography over silica when toluene eluted pure N-*mesylindole* (6u) (72 mg), as off-white crystals, m.p. 105—106 °C (from ether), $\lambda_{max.}$ (EtOH) 216 and 272 nm (log ε 4.35 and 4.25); $\nu_{max.}$ (Nujol) 1 450s, 1 360s, and 1 175s cm^{-1}; τ ($CDCl_3$) 1.77 (1 H, d, *J* 8 Hz, ArH), 2.28—2.36 (3 H, m, ArH), 2.44—2.57 (5 H, m, ArH), 3.20 (1 H, s, indole-3-H), and 7.20 (3 H, s, $MeSO_2$); *m/z* 271 (M^+, 25%), 192 (100), and 165 (49) (Found: C, 66.8; H, 4.7; N, 4.9; S, 11.4. $C_{15}H_{13}NO_2S$ requires C, 66.4; H, 5.5; N, 5.2; S, 11.8).

1-*Benzoyl*-2-*phenylindole* (6v).—To a vigorously stirred solution of 2-phenylindole (300 mg) in tetrahydrofuran (10 ml) containing aqueous tetra-n-butylammonium hydroxide (40%; 3 drops) was added aqueous sodium hydroxide (50%; 7 ml). After 5 min benzoyl chloride (2.1 g) in tetrahydrofuran (20 ml) was added during 5 h. The mixture was partitioned between ethyl acetate and water and the organic phase separated, dried, and evaporated under reduced pressure. The resultant oil was crystallised from toluene and the mother liquor concentrated to give the N-*benzoylindole* (6w) as an unstable brown oil (50 mg), $\lambda_{max.}$ ($CHCl_3$) 264sh, 292sh, 306sh, and 334sh; $\nu_{max.}$ 1 680s cm^{-1}; τ ($CDCl_3$) 2.20—2.34 (3 H, m, ArH), 2.44—2.84 (11 H, m, ArH), and 3.17 (1 H, s, indole-3-H); *m/z* 297 (M^+, 18%), 208 (2), 193 (12), 165 (5), and 105 (100) [Found (by mass spectrometry): *M*, 297.115. $C_{21}H_{15}NO$ requires *M*, 297.115].

2-*Methyl*-1-*phenylsulphonylindole* (9a) *and* 3-*Chloro*-2-*methyl*-1-*phenylsulphonylindole* (9b).—2-Methylindole was treated with benzenesulphonyl chloride as described earlier; $a = 250$, $b = 10$, $c = 3$, $d = 7$, $f = 750$, $g = 452$ (mixture). The crude product was purified by chromatography over silica when toluene eluted 3-*chloro*-2-*methyl*-1-*phenylsulphonylindole* (9b) (60 mg), m.p. 100—102 °C (from methanol), $\lambda_{max.}$ (EtOH) 216, 257, and 290sh nm (log ε 4.4, 4.15, and 3.54); $\nu_{max.}$ (Nujol) 1 590m, 1 440s, 1 370s, and 1 180s cm^{-1}; τ ($CDCl_3$) 1.66 (1 H, d, *J* 9 Hz, ArH), 2.12 (2 H, d, *J* 9 Hz, ArH), 2.32—3.24 (6 H, m, ArH), and 7.31 (3 H, s, indole-2-Me); *m/z* 307, 305 (M^+, 9, 25%) 206 (1), 166, 164 (32, 100), 128 (14), and 101 (11) (Found: C, 59.25; H, 4.0; N, 4.5. $C_{15}H_{12}ClNO_2S$ requires C, 58.9; H, 3.9; N, 4.6%); and 2-*methyl*-1-*phenylsulphonylindole* (9a) (167 mg) as a yellow oil, $\lambda_{max.}$ (EtOH) 212, 252, and 284sh nm (log ε 4.33, 4.10, and 3.25), $\nu_{max.}$ 1 590m, 1 440s, 1 360s, and 1 170s cm^{-1}; τ ($CDCl_3$) 1.72 (1 H, d, *J* 9 Hz, ArH), 2.13 (2 H, d, *J* 9 Hz, ArH), 2.38—2.56 (4 H, m, ArH), 2.61—2.72 (2 H, m, ArH), 3.58 (1 H, s, indole-3-H), 7.34 (3 H, s, indole-2-Me); *m/z* 271 (M^+, 34%), 206 (2), 146 (10), 130 (100), and 103 (13) [Found (by mass spectrometry): *M*, 271.067. $C_{15}H_{13}NO_2S$ requires *M*, 271.066].

3-*Chloro*-1-*phenylsulphonyl*-2-(2-*pyridyl*)*indole* (10e), 1-*Phenylsulphonyl*-2-(2-*pyridyl*)*indole* (10f), *and* 1,3-*Diphenylsulphonyl*-2-(2-*pyridyl*)*indole* (12g).—Using the general method, the 2-(2-pyridyl)indole (10a) (1.94 g) in benzene (30 ml) with benzenesulphonyl chloride (10.6 g) for 15 h gave a mixture which was separated by chromatography over silica, with toluene–ether (2 : 1) as eluant to give first the *chloro-indole* (10e) (2.36 g), m.p. 146—148 °C (from methanol), $\lambda_{max.}$ (EtOH) 277sh, 235sh, 306sh, and 325 nm (log ε 4.12, 4.03, 3.95, and 4.04); τ ($CDCl_3$) 1.24 (1 H, d, *J* 6 Hz, py-α-H), 1.76 (1 H, d, *J* 8 Hz, ArH), and 2.18—2.68 (11 H, m, ArH); *m/z* 371, 369 (M^+, 9%), 304 (45), 269 (13), 277 (100), and 192 (63) (Found: C, 62.3; H, 3.6; Cl, 8.7; N, 7.4, S, 8.5. $C_{19}H_{14}ClN_2O_2S$ requires C, 61.9; H, 3.6; Cl, 9.6; N, 7.6; S, 9.7%); secondly the 1-*phenylsulphonylindole* (10f) (90 mg), m.p. 148—149 °C (from methanol) $\lambda_{max.}$ (EtOH) 215sh, 268, 274, and 290 nm (log ε 4.18, 4.86, 3.86, and 3.86); τ ($CDCl_3$), 1.32 (1 H, d, *J* 6 Hz, py-α-H), 1.67 (1 H, d, *J* 8 Hz, ArH), 2.24—2.76 (11 H, m, ArH), and 3.13 (1 H, s, indole-3-H); *m/z* 334 (M^+, 9%), 270 (79), and 193 (100) (Found: C, 67.9; H, 4.2; N, 8.1; S, 9.2%. $C_{19}H_{14}N_2O_2S$ requires C, 68.2; H, 4.2; N, 8.3; S, 9.6%); and lastly the *diphenylsulphonyl*-

indole (10g) (43 mg), m.p. 208—210 °C (from methanol), $\lambda_{max.}$ (EtOH) 213sh, 260, 267, 274, and 294 nm (log ε 4.41, 4.25, 4.23, 4.30); τ ($CDCl_3$) 1.23 (1 H, d, *J* 6 Hz, py-α-H), 1.80 (1 H, d, *J* 8 Hz, ArH), and 2.13—2.84 (16 H, m, ArH); *m/z* 458 (M^+, 20%), 381 (5), 317 (91), 269 (100), and 241 (33) [Found (by mass spectrometry): *M*, 474.071. $C_{25}H_{18}N_2O_4S_2$ requires *M*, 474.070].

Acknowledgements

L. D., G. L. H., and M. M. C. thank the S.E.R.C. for maintenance grants. Part of the work (G. L. H. and M. M. C.) was undertaken as part of S.E.R.C. CASE Awards and we thank Glaxo Group Research Ltd., Ware for their interest and support.

References

1 Part 6, G. L. Humphrey, L. Dalton, and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1983, preceding paper.
2 For a fuller discussion see M. G. Beal, W. R. Ashcroft, M. M. Cooper, and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1982, 435.
3 M. M. Cooper, G. J. Hignett, and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3008.
4 P. G. Gassman, G. A. Campbell, and G. Mehta, *Tetrahedron*, 1972, **28**, 2749.
5 T. Hino, M. Endo, M. Tonozuka, and Y. Hashimoto, *Chem. Pharm. Bull.*, 1977, **25**, 2350.
6 K. Ogino, S. Kozuka, and S. Oae, *Tetrahedron Lett.*, 1969, 3559.
7 R. J. Sundberg, *J. Org. Chem.*, 1965, **30**, 3604.
8 T. Nagayoshi, S. Saeki, and M. Hamana, *Heterocycles*, 1977, **6**, 1666.
9 M. De Rosa and J. L. T. Alonsa, *J. Org. Chem.*, 1978, **43**, 2639.
10 M. De Rosa, L. Carbognani, and A. Febres, *J. Org. Chem.*, 1981, **46**, 2054.
11 D. V. C. Awang and A. Vincent, *Can. J. Chem.*, 1980, **58**, 1589.
12 T. Ithara, *Synthesis*, 1979, 151.
13 H. B. MacPhillamy, R. L. Dziemian, R. A. Lucas, and M. E. Kuehne, *J. Am. Chem. Soc.*, 1958, **80**, 2172.
14 A. H. Jackson, D. N. Johnston, and P. V. R. Shannon, *J. Chem. Soc., Chem. Commun.*, 1975, 911.
15 E. v. Meyer, A. Friessner, and Th. v. Findeisen, *J. Prakt. Chem.*, 1902, **65**, 528.
16 J. Caixach, R. Capell, C. Galvez, A. Gonzalez, and N. Roca, *J. Heterocycl. Chem.*, 1979, **16**, 1631.

Received 13*th April* 1983; *Paper* 3/587