Nucleophilic Substitutions at an Indole β-position

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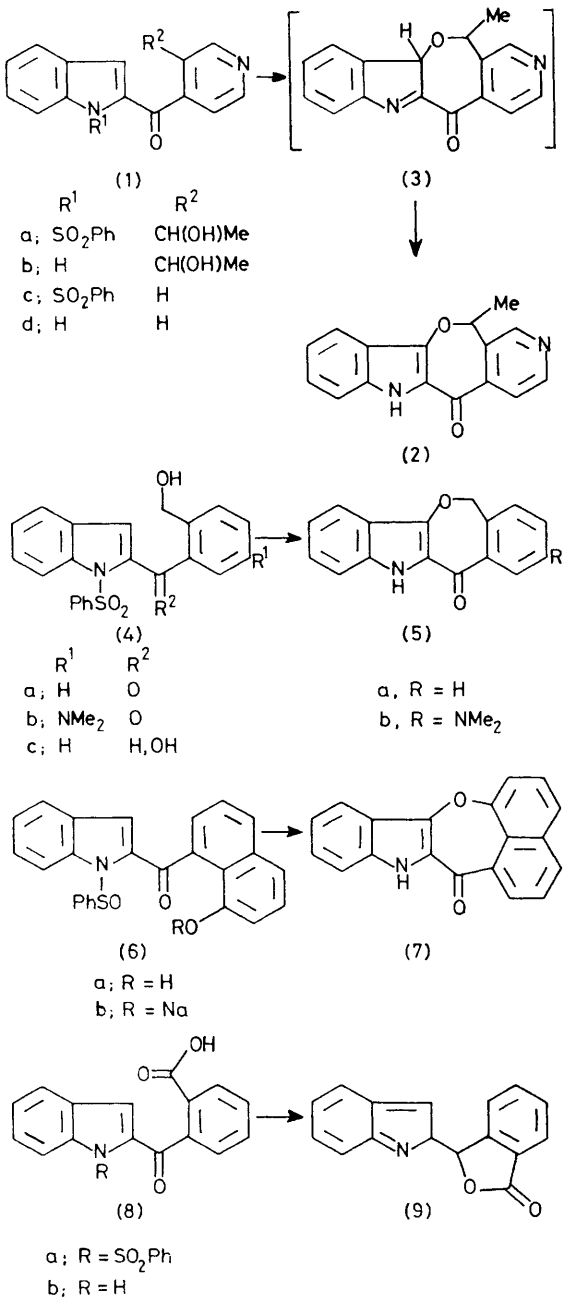
Summary Intramolecular substitution by oxygen nucleophiles at *N*-benzenesulphonylindole β-positions, with loss of benzene sulphinate, and the use of this novel process for the synthesis of oxepino[2,3:*b*]indoles are described.

THE characteristic chemistry[1] of indoles centres on their susceptibility to electrophilic attack at the β-position. There seems to be only one example[2] of the introduction of a nucleophile at the β-position, this being the silver ion-assisted displacement of iodide by acetate. The rearrange-

ments of *N*-tosyloxy-2-phenylindole,[3a] *N*-*p*-nitrobenzoyloxy-2-phenylindole,[3b] and *N*-chloroindole[3c] to their corresponding β-substituted isomers represent, at least formally, S_N2' type indole β-nucleophilic substitutions by tosylate, *p*-nitrobenzoate, and chloride, with departure of these groups as anions from nitrogen. Directly analogous processes occur when *N*-chloro-,[4a] *N*-dialkylsulphonio-[4b] or



N-hydroxy-anilines[4c] are substituted, by nucleophiles, at the *ortho*- or *para*-positions of the ring, with departure of the nitrogen substituent.

Although nucleophilic addition of phenyl Grignard reagent at the α-position of a β-acylindole has been reported,[5a] the analogous β-addition to α-acylindoles apparently does not occur.[5b] A similar process has been suggested[5c] as a key step in the biosynthesis of the echitamine group of indole alkaloids but model studies[5d] aimed at achieving such an addition were unsuccessful.

In the course of our synthetic studies we utilised Sundberg's method[6] for the introduction of substituents at an indole α-position, *viz.* acylation of 2-lithiobenzenesulphonylindole, preparing (**1a**) by reaction with 3-(1-hydroxyethyl)-pyridine-4-carboxylic acid lactone.[7] In anticipation of removing[8] the *N*-protecting group, (**1a**) was treated with aqueous 3N NaOH–MeOH (1:2). A smooth conversion into a yellow, highly crystalline product took place on heating at reflux for 10 min [83%, m.p. 259—261 °C, ν_{max} (Nujol) 1620 cm^{-1}; λ_{max} (EtOH) 345 and 400 nm (log ε 4·36 and 3·88); τ {$(CD_3)_2SO$} −1·3 (1H, s, HN), 1·1—3·1 (7H, m, ArH), 4·42 (1H, q, *J* 7 Hz, OC*H*Me), and 8·15 (3H, d, *J* 7 Hz, OCH*Me*); *m/e* 264 (M^+, 45%), 263 (100), 249 (67), 235 (30), and 221 (21)]. The novel structure (**2**) of the yellow product follows from its molecular weight, two hydrogens less than that of (**1b**), the lack of OH i.r. stretching or an indole β-proton n.m.r. signal coupled with the presence of indole NH signal, extended wavelength u.v. absorption and highly conjugated carbonyl i.r. stretching. We interpret the formation of the oxepinoindole (**2**) as involving intramolecular β-nucleophilic attack by alcoholate with concurrent or subsequent departure of benzenesulphinate followed by the tautomerism of initial 3*H*-indolic product (**3**) to (**2**). The straightforward hydrolysis product (**1b**) could be obtained using dilute alkali.

We have found it possible to extrapolate this new process; thus both (**4a**) and (**4b**), derived similarly using phthalide and 3-dimethylaminophthalide,[9] were cyclised, just as cleanly and simply to give (**5a**) [90%; m.p. 139—143 °C; ν_{max} (Nujol) 3300 and 1640 cm^{-1}; λ_{max} (EtOH) 255, 335, and 393sh nm (log ε 4·11, 4·14, and 3·67, respectively); τ ($CDCl_3$) 0·8 (1H, s, HN), 2·2—3·0 (7H, m, ArH), and 4·66 (2H, s, CH_2); *m/e* 249 (M^+, 100%), 248 (28), 232 (38), 221 (31), 220 (50), 193 (25), and 165 (19)], and (**5b**) [m.p. 225—228 °C; ν_{max} (Nujol) 3280 and 1620 cm^{-1}; λ_{max} (EtOH) 220, 257, 333, and 383 nm (log ε 4·34, 4·52, 4·32 and 3·9, respectively); τ ($CDCl_3$) 1·31 (1H, s, HN), 2·3—3·25 (7H, ArH), 4·75 (7H, s, CH_2), and 6·96 (6H, s, NMe_2); *m/e* 292 (M^+, 100%), 291 (75), 275 (100), and 263 (30)], respectively.

The phenol (**6a**), which resulted from the acylation of 2-lithiobenzenesulphonylindole with 8-hydroxy-1-napthoic acid lactone,[10] could not be cyclised in the same way, due to rapid hydrolysis of the benzenesulphonyl group. However, heating the dry sodium salt (**6b**), caused cyclisation to occur, with the formation of (**7**) [75%; m.p. 280—282 °C; ν_{max} (Nujol) 3300 and 1625 cm^{-1}; λ_{max} (EtOH) 235sh, 260sh, 275sh, 330, and 430 nm (log ε 4·51, 4·28, 4·16, 4·2, and 3·7, respectively); τ ($CDCl_3$) 1·45 (1H, s, HN), and 1·25—2·85 (10H, m, ArH); *m/e* 285 (M^+, 100%), 238 (21), and 237 (29)].

Even comparably vigorous conditions were unsuccessful in attempts to cyclise (**8a**), prepared from phthalic anhydride, the simple solution conditions having again led to hydrolysis [→ (**8b**)]. Although a yellow product was obtained by heating the sodium salt to higher temperatures, [40%; m.p. 158—180 °C; ν_{max} (Nujol) 1690 cm^{-1}; λ_{max} (EtOH) 241, 265sh, and 372 nm (log ε 4·38, 4·14, and 3·89, respectively); *m/e* 247 (M^+, 100%, 219 (20), and 190 (20)] its structure is (**9**) or a geometrical isomer, on the basis of above data and its transformation by very mild aqueous base into (**8b**).

Preliminary studies suggest that, as well as the obvious requirement for benzenesulphonyl as a leaving group from nitrogen, the α-acyl substituent is a prerequisite for the operation of the novel process here described, since the alcohol (**4c**) was merely hydrolysed under the same conditions which successfully cyclise the ketone (**4a**). Further, it seems that intramolecularity is also important, for the ketone (**1c**), on treatment with methoxide, gave only the methanolysed product (**1d**), no intermolecular methoxide attack at the β-position being observed.

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