Indole β-Nucleophilic Substitution. Part 2.[1] Formation of a [2]Benzoxepino[4,3-*b*]indole and a Pyrido[4',3':5,6]oxepino[3,2-*b*]indole

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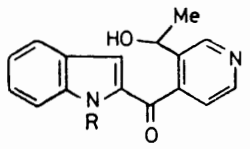
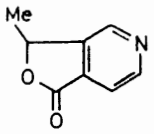
The syntheses are described of [2]benzoxepino[4,3-*b*]indol-11(6*H*,12*H*)-one, (12a) and 12-methylpyrido[4',3':3,4]oxepino[3,2-*b*]indol-5(6*H*,12*H*)-one, (5), by sequences involving the first examples of intramolecular nucleophilic substitution at an indole β-position, with departure of phenylsulphinate as leaving group from nitrogen. The spectroscopic and chemical evidence supporting the structures for these new heterocyclic systems, and thus by implication the operation of indole β-nucleophilic substitution, are detailed.

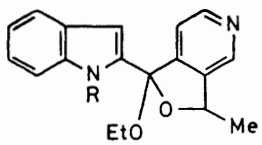
In the course of synthetic investigations [2] aimed at the indole alkaloid apparicine, we required the hydroxyketone (1a) as an intermediate, and had prepared [3] it by the α-acylation of the Grignard derivative of the pyrrole 4,7-dihydroindole with lactone (2) followed by dehydrogenation. With Sundberg's report [4] of the use of α-lithiated 1-phenylsulphonylindole for the introduction of substituents into the indole α-position with subsequent



(1)
a; R = H
b; R = SO_2Ph



(2)



(3)
a; R = SO_2Ph
b; R = H

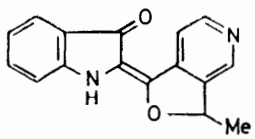
alkaline hydrolytic removal of the *N*-protecting group, a possible alternative route to (1a) presented itself.

RESULTS AND DISCUSSION

Condensation of 2-lithio-1-phenylsulphonylindole (2-LiPSI) with lactone (2) proceeded efficiently giving (1b); however subsequent treatment with alkali did not remove the phenylsulphonyl group cleanly (see below). The unexpected side-reaction, which in the alkaloid synthetic context was a complication but which proved (see below) to be of considerable intrinsic interest, could be avoided by conversion of (1b) to the acetal (3a) with ethanolic hydrogen chloride, after which straightforward alkaline hydrolysis led to (3b), identical with the derivative of (1a) which was utilised in our alkaloid synthetic studies.[3]

Treatment of the condensation product (1b) with aqueous ethanolic sodium hydroxide led, depending upon the concentration of base, either to a mixture of the anticipated hydrolysis product (1a) {at best [3M aqueous NaOH–MeOH (0.1 : 25)] 30% of the product} and a yellow material or, with 3M aqueous NaOH-MeOH (1 : 2) exclusively, cleanly and rapidly at reflux (*ca.* 2 min) to the yellow material which crystallised from the reaction mixture in high yield.

The high-melting yellow product proved to have two hydrogen atoms less than the anticipated hydrolysis product (1a) with u.v. absorption ($\lambda_{max.}$ 350, $\lambda_{infl.}$ 420 nm) indicating extensive conjugation. I.r. evidence showed the presence of NH and carbonyl groups, the absorption



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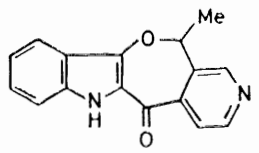
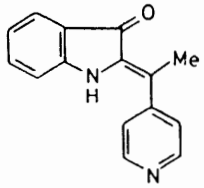


(5)



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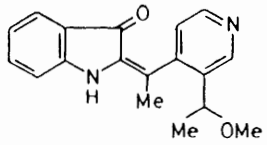

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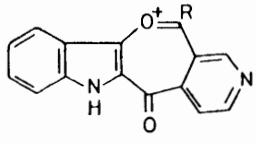
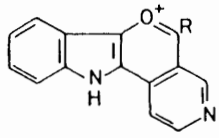


aa R = Me
ab R = H



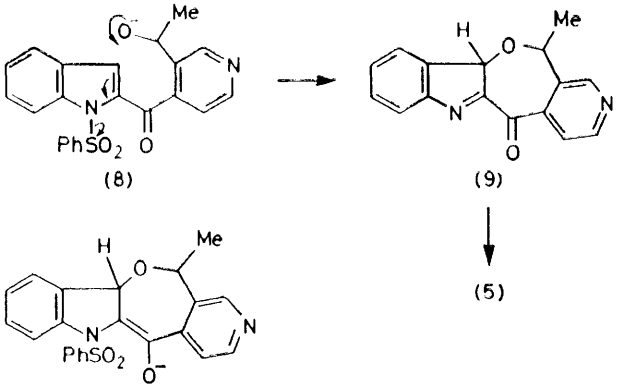
ba R = Me
bb R = H

of the latter at 1 620 cm^{-1} being at lower wave-number than that of the carbonyl group in (1a), suggesting its involvement in the conjugated system. Two structures, (4, or geometrical isomer) and (5), for the formation of which plausible mechanistic sequences can be drawn, seemed to be not inconsistent with these data but the ^1H n.m.r. spectrum of the yellow material, though unambiguously confirming the disubstituted pyridine, di-

substituted benzene, MeCH and NH functions, did not distinguish between (4) and (5).

Data which lead to the conclusion that the yellow material has structure (5) and not (4) include the carbonyl frequencies [5] of (6) and (7) (1 680 and 1 690 cm^{-1}) and their highest wavelength u.v. absorption maxima [5] (470 nm), each markedly different from the corresponding values for (5). Further, major mass spectral fragment ions shown by (5) and corresponding to $M^+ - H$, $M^+ - Me$, $M^+ - CHO$ and $M^+ - C_2H_3O$ are well accommodated by structures aa, ab, ba, and bb, respectively, rationally derived from $[(5)^+]$.

We envisage the formation of (5) as involving nucleophilic attack by alkoxide oxygen at the indole β-position with departure of phenylsulphinate from nitrogen either synchronously [arrows on (8)] or by way of a conjugate

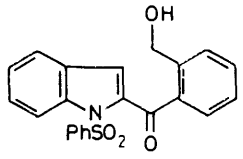


addition intermediate (10). The absence of the process in the treatment of acetal (3a) with base is incidental evidence for the intermediacy of (10), or at least for the requirement for a conjugated electron-withdrawing group at the indole α-position. Further comment on the mechanistic details of the process and comparison with related processes, as well as examples illustrating the scope, will be included in subsequent papers, but it was clear from this first adventitious synthesis that an excellent method for nucleophilic substitution at an indole β-position, a process of considerable novelty, had been discovered. It was considered necessary to add chemical evidence for structure (5), and thus by implication for the operation of intramolecular indole-β-nucleophilic substitution, to the spectroscopic data presented above. In particular we sought to establish the relationship between NH, carbonyl and ether groups [*cf.* structure (4)] and the continued presence of the aromatic indole unit.

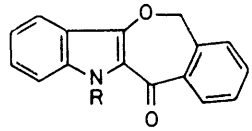
As a substrate for experimentation, chosen to avoid complications associated with the presence of the nucleophilic pyridine nitrogen in (5), a benzene analogue was prepared by condensation of 2-LiPSI with phthalide, [to give (11)] and then alcoholic alkali-induced ring closure to give (12a), in a synthesis just as easy and efficient as the formation of (5). The two oxepino-indoles had completely analogous spectral properties, in particular the u.v. absorptions of the two were very similar in shape and positions of absorption maxima.

The presence of the 3-alkoxyindole unit in (12a) was evidenced by reduction, in an u.v. cell with excess of $NaBH_4$: the absorption changed to one which overlay that of 3-methoxyindole [6] by removal of the carbonyl conjugation. Unfortunately attempts to isolate reduced material led to a complex mixture of products.

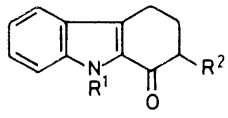
The possibility of forming a ring between carbonyl



(11)



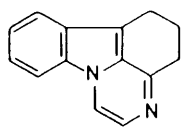
(12)
a; R = H
b; R = $CH_2CH(OEt)_2$



(13)
a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = CH_2Ph$
c; $R^1 = CH_2CH(OEt)_2$, $R^2 = H$

carbon and indolic nitrogen seemed a good way of establishing their relationship [*cf.* the quite different relative positions of carbonyl and NH groups in (4)]; 1-oxo-1,2,3,4-tetrahydrocarbazole [7] (13a) was utilised as a model to elaborate a sequence.

Plans to attach a chain initially at the carbonyl group were set aside when it was found that the carbonyl group in (12a), conjugated to two aromatic rings and vinylogously with oxygen, did not react with Brady's reagent, malononitrile–piperidine acetate, semicarbazide, or hydroxylamine.[8] The formation of a pyrazine ring



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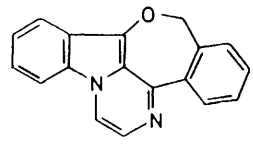

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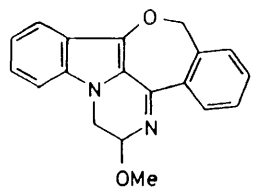

(16)

by the introduction of two carbons and nitrogen between the carbonyl group and NH in (13b) was reported [9] by Russian workers; viability of the sequence involving *N*-alkylation of (13a) with bromoacetal [to give (13a)] and then reaction with dilute acid followed by ammonium acetate to give (14) was verified.

Turning to the benzoxepinoindole (12a), alkylation with sodium hydride as base gave the acetal (12b), which displayed the same u.v. absorption as starting material but which i.r. and ^1H n.m.r. showed lacked NH. Hydrolysis with aqueous hydrochloric acid and reaction, without purification of the aldehyde, with methanolic ammonium acetate gave a mixture of the anticipated pyrazine (15) and a methanol adduct (16), readily identified by its u.v. absorption, which was similar to starting material (12a), and ^1H n.m.r. signals for a CH_2CH system and a methoxy group.

EXPERIMENTAL

1-*Phenylsulphonylindol-2-yl* 3-(1-*Hydroxyethyl*)-4-*pyridyl Ketone* (1b).—1-Phenylsulphonylindole [10] (7.2 g) in dry THF (200 ml) under N_2 was lithiated by the addition of n-BuLi (15 ml, 15% solution in hexane) at −78 °C during 1 min, followed by allowing the temperature to rise to room temperature for 0.5 h. After re-cooling to −78 °C the lactone [3] (2) (4.2 g) in THF was added and the mixture once again allowed to warm to room temperature. After 0.25 h *ca.* half the solvent was removed from the dark red solution by evaporation and the residue added to water and ether. The brown oil (9.8 g) resulting contained traces of 1-phenylsulphonylindole, indole, and the ether (5) and was purified by chromatography over silica; the *hydroxyketone* (1a) (6.6 g) was eluted with Et_2O and obtained as a colourless foam; $\lambda_{max.}$ (EtOH) 224 and 305 nm, $\lambda_{infl.}$ 249 nm; $\nu_{max.}$ ($CHCl_3$) 1 670s cm^{-1}; τ($CDCl_3$) 1.00 (1 H, s, pyridine-α-H), 1.20—2.91 (11 H, m, Ar-H), 2.98 (1 H, s, indole-β-H), 4.76 [1 H, q, *J* 7 Hz, C*H*(OH)Me], 6.7 (1 H, br s, OH), and 8.39 [3 H, d, *J* 7 Hz, C*H*$_3$CH(OH)]; *m/e* 406 (M^+, 20%), 388 (20), 265 (35), 248 (100), 247 (90), and 148 (90) (Found: M^+, 406.097 51. $C_{22}H_{18}N_2O_4S$ requires *M*, 406.098 73).

12-*Methylpyrido*[4′,3′:3,4]*oxepino*[3,2-b]*indol*-5(6H,12H)-*one* (5).—The keto-alcohol (1b) (3.0 g) in MeOH (100 ml) was treated with aqueous NaOH (3 N, 50 ml) and the mixture refluxed for 5 min. The cooled mixture was filtered to give the *oxepino-indole* (5) (1.8 g), m.p. 259—261 °C; $\lambda_{max.}$ 225 and 350 nm (log ε 4.46 and 4.09); $\lambda_{infl.}$ 285 and 420 nm (log ε 3.89 and 3.57); $\nu_{max.}$ (Nujol) 3 440m and 1 620s cm^{-1}; τ ([$^2H_6$]DMSO) −1.30 (1 H, br s, NH), 1.11 (1 H, s, pyridine-α-H), 1.21 (1 H, d, *J* 5 Hz, pyridine-α-H), 2.19 (1 H, d, *J* 5 Hz, pyridine-β-H), 2.30—3.10 (4 H, m, Ar-H), 4.42 [1 H, q, *J* 7 Hz, C*H*(O)Me], and 8.15 [3 H, d, *J* 7 Hz, (O)CHC*H*$_3$]; *m/e* 264 (M^+, 45%), 263 (100), 249 (67), 235 (30), and 221 (21) (Found: C, 72.5; H, 4.6; N, 10.3. $C_{16}H_{12}N_2O_2$ requires C, 72.7; H, 4.6; N, 10.6%).

1-*Ethoxy*-3-*methyl*-(1-*phenylsulphonylindol*-2-*yl*)-1H,3H-*furano*[3,4-c]*pyridine* (3a).—The ketone (1b) (40 mg) in dry EtOH was treated with HCl gas. After 24 h at room temperature the solvent was removed and the residue partitioned between aqueous K_2CO_3 and Et_2O to give, after preparative t.l.c. on silica (eluting with EtOAc), the stereoisomers of the *compound* (3a), as a foam, in a ratio of *ca.* 5 : 3; τ($CDCl_3$) exemplified by 3.22 and 3.28 (2 : 5, 1 H, 2 × indole-β-H); *m/e* 434 (M^+, 14%), 389 (90), 293 (15), 248 (90), 247 (65), 233 (100), and 178 (50) (Found: M^+, 434.1302. $C_{24}H_{22}N_2O_4S$ requires M^+, 434.1300).

Hydrolysis of Compound (3a).—The stereoisomeric mixture (3a) (20 mg) was heated with aqueous 2M NaOH (1 ml) in refluxing MeOH (5 ml) for 24 h. After partitioning between water and ether, and preparative t.l.c. on silica eluting with Et_2O, the stereoisomers (3b) (5 mg) were obtained, identical in all respects with the mixture obtained previously.[3]

1-*Phenylsulphonylindol*-2-*yl* 2-*Hydroxymethylphenyl Ketone* (11).—2-LiPSI prepared as described above using 1-phenylsulphonylindole (10 g) in THF (100 ml) was treated with phthalide (5.2 g) as a slurry in THF (50 ml). As the mixture came to room temperature with stirring the lactone dissolved and after 0.5 h the reaction was completed by warming at 40 °C for 10 min. Approximately half the solvent was removed from the dark brown solution under reduced pressure and the residue partitioned between water and Et_2O to give a crystalline solid (11.3 g); traces of indole and 1-phenylsulphonylindole were removed by crystallisation from methanol to give pure *ketone* (11) (5.2 g), m.p. 129—133 °C; $\lambda_{max.}$ (EtOH) 251 and 298 nm (log ε 4.16 and 4.08); $\lambda_{infl.}$ 256 and 268 nm (log ε 4.12 and 3.98); $\nu_{max.}$ (Nujol) 3 560m and 1 660s cm^{-1}; τ($CDCl_3$) 1.85—2.80 (14 H, m, Ar-H), 3.05 (1 H, s, indole-β-H), 5.25 (2 H, s, CH_2O), and 7.65 (1 H, br s, OH); *m/e* 391 (M^+, 20%), 262 (27), 261 (100), 203 (23), and 202 (17) (Found: C, 67.8; H, 4.5; N, 3.4; S, 8.2%. $C_{22}H_{17}NO_4S$ requires C, 67.5; H, 4.4; N, 3.5; S, 8.1%).

[2]*Benzoxepino*[4,3-b]*indol*-11(6H,12H)-*one* (12a).—The keto-alcohol (11) (1 g) in MeOH (30 ml) was treated with aqueous NaOH (3 M, 15 ml) and the mixture refluxed for 5 min. On cooling the *benzoxepinoindole* (12a) (0.56 g) was filtered off, m.p. 136—143 °C, $\lambda_{max.}$ (EtOH) 255 and 335 nm (log ε 4.13 and 4.14); $\lambda_{max.}$ 393 nm (log ε 3.67); $\nu_{max.}$ (Nujol) 3 300m and 1 640s cm^{-1}; τ($CDCl_3$) 0.80 (1 H, s, NH), 1.75—3.00 (10 H, m, Ar-H), and 4.66 (2 H, s, CH_2); *m/e* 249 (M^+, 100%), 248 (28), 232 (38), 221 (31), 220 (50), 193 (25), and 165 (19) (Found: C, 75.9; H, 4.45; N, 4.1. $C_{16}H_{11}NO_2$·0.5-MeOH requires C, 75.2; H, 3.8; N, 5.3%).

9-(2,2-*Diethoxyethyl*)-3,4-*dihydrocarbazol*-1(2H)-*one* (13c).—The ketone [7] (13a) (3.4 g) in dry DMF (50 ml) under N_2 with stirring was treated at room temperature successively with NaH (1.2 g, 50% dispersion in oil) for 0.5 h and then with bromoacetal (10 ml) for 15 h. The mixture was poured into water and extracted with Et_2O to give a brown oil (10 g) which was purified by chromatography over alumina: eluting with toluene gave the acetal (13c) (1.85 g) as a yellow oil; $\lambda_{max.}$ 240 and 310 nm; $\lambda_{infl.}$ 345 nm; $\nu_{max.}$ (film) 1 660s cm^{-1}; τ($CDCl_3$) 2.33—2.97 (4 H, m, Ar-H), 5.20—5.45 (3 H, m, NCH_2CH), 6.10—6.75 (4 H, m, 2 × OCH_2Me), 6.97 (2 H, d, *J* 7 Hz, $ArCH_2$), 7.32 (2 H, d, *J* 7 Hz, $COCH_2$), 7.74 (2 H, m, $CH_2CH_2CH_2$), and 8.91 (6 H, d, *J* 8 Hz, 2 × OCH_2Me); *m/e* 301 (M^+, 10%), 257 (30), 255 (15), 166 (20), and 198 (100) (Found: M^+ 301.1673. $C_{18}H_{23}NO_3$ requires *M*, 301.1678).

5,6-*Dihydro*-4H-*pyrazino*[3,2,1-j,k]*carbazole* (14).—The acetal (13c) (1.5 g) was heated in aqueous 2M HCl–MeOH for 4 h after which ammonium acetate (2 g) was added and reflux was continued for a further 2 h. Addition of potassium carbonate and extraction with EtO gave the pyrazine (14) (0.83 g) as a yellow oil; $\lambda_{max.}$ 223, 262, 313, 326, and 408 nm; $\lambda_{infl.}$ 290, 430, and 450 nm; τ($CDCl_3$) 2.10—2.82 (6 H, m, Ar-H), 6.80—7.10 (4 H, m, $CH_2CH_2CH_2$), and 7.75 (2 H, m, $CH_2CH_2CH_2$); *m/e* 208 (M^+, 100%) and 207 (100) (Found: M^+, 208.1003. $C_{14}H_{12}N_2$ requires *M*, 208.1000).

12-(2,2-*Diethoxyethyl*)-[2]*benzoxepino*[4,3-b]*indol*-11(6H,12H)-*one* (12b).—The ether (12a) (450 mg) in dry DMF (10 ml) was treated successively with NaH (170 mg) under N_2,

which generated a dark red solution, and then bromoacetal (1 ml) and the mixture was heated at 110 °C for 7 h. After cooling, adding to water, and extraction with ether a brown oil was obtained; purification by chromatography over silica (eluant toluene) gave the *acetal* (12b) (90 mg) as a yellow oil; $\lambda_{max.}$ 256 and 336 nm; $\lambda_{infl.}$ 395 nm; $\nu_{max.}$ (film) 1 620s cm^{-1}; $\tau(CDCl_3)$ 1.90—3.30 (8 H, m, Ar-H), 4.75 (2 H, s, CH_2O), 5.15 (1 H, d, *J* 6 Hz, $CHCH_2$), 5.39 (2 H, d, *J* 6 Hz, $CHCH_2$), 6.20—6.74 [4 H, m, $(OCH_2Me)_2$], and 8.79—9.01 [6 H, m, $(OCH_2Me)_2$]; *m/e* 365 (M^+, 10%), 262 (11), and 103 (100) (Found: M^+, 365.1631. $C_{22}H_{23}NO_4$ requires *M*, 365.1627).

Pyrazinobenzoxepinoindole (15) and *Dihydropyrazinobenzoxepinoindole* (16).—The acetal (12b) (0.5 g, crude alkylation product) was hydrolysed in 2M HCl–THF at reflux for 0.5 h. After dilution with water Et_2O extracted the corresponding aldehyde (12c) (340 mg), which was not purified but treated with ammonium acetate in MeOH at reflux for 0.5 h. After pouring into dilute aqueous ammonia and extraction with Et_2O, basic material was extracted from the ethereal solution with 2M HCl and then regenerated by basification and extraction to give a red oil (280 mg), the components of a portion (80 mg) of which were separated by preparative t.l.c. on silica eluting with petroleum ether–triethylamine (1 : 1), to give the *pyrazine* (15) (15 mg) as a red amorphous solid; $\lambda_{max.}$ (EtOH) 223, 290, 330, and 343 nm; $\lambda_{infl.}$ 275 nm; $\tau(CDCl_3)$ 1.63—2.80 (10 H, m, Ar-H) and 4.70 (2 H, s, CH_2O); *m/e* 272 (M^+, 95%), 244 (90), 181 (25), 166 (70), and 151 (100) (Found: M^+, 272.0944. $C_{18}H_{12}N_2O$ requires *M*, 272.0950); and the *dihydropyrazine* (16) (33 mg) as a yellow amorphous solid; $\lambda_{max.}$ (EtOH) 236 and 343 nm; $\lambda_{infl.}$ 255 and 380 nm; $\tau(CDCl_3)$ 1.75—3.05 (8 H, m, Ar-H), 4.68—4.89 (1 H, m, CHOMe), 4.77 (2 H, s, CH_2O), 5.47—5.66 (1 H, m, CHN), 6.20 (3 H, s, OMe), and 6.18—6.60 (1 H, m, CHN); *m/e* 304 (M^+, 80%), 272 (100), and 244 (80) (Found M^+, 304.1207. $C_{19}H_{16}N_2O_2$ requires *M*, 304.1212).

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[2] For a review see M. S. Allen, D. I. Bishop, M. Harris, G. J. Hignett, D. I. C. Scopes, N. D. V. Wilson, and J. A. Joule in 'Indole and biogenetically related alkaloids,' eds. J. D. Phillipson and M. H. Zenk, Academic Press Inc., New York, 1980, ch. 13.

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