Indole β-Nucleophilic Substitution. Part 3.[1] Synthesis of Four Isomeric Pyrido[*x'*,*y'*:5,6]oxepino[3,2-*b*]indolones

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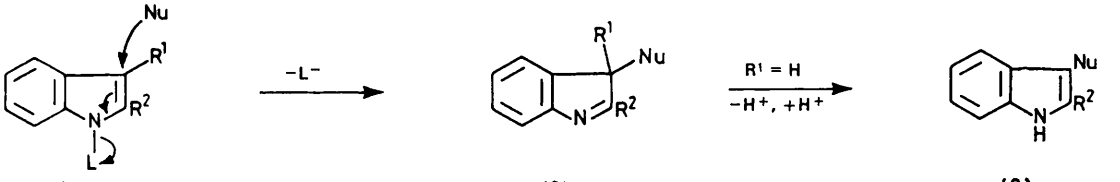
Condensations of 2-lithio-1-phenylsulphonylindole with the four pyridine analogues of phthalide gave 1-phenylsulphonylindol-2-yl *o*-hydroxymethylpyridyl ketones, from which on treatment with base were obtained the title compounds, by a process of intramolecular indole β-nucleophilic substitution. This new aspect of indole chemistry is discussed in the context of other related processes.

THE chemistry [2] of indoles is dominated by reactions illustrating their susceptibility to electrophilic attack in the pyrrole ring at the β-position. In reactions with bases or nucleophiles the formation and reactions of indolyl anions produced by abstraction of *N*-hydrogen or of the α-proton of *N*-substituted indoles are also well represented.[2] Only isolated reports [3,4] of nucleophilic *addition* have appeared, and then only where the indole carried an electron-withdrawing group; thus Grignard reagents added [3] to the 4-position of 5-nitroindole and to the α-position of β-benzoylindoles,[4a] though not to the β-position of α-aroylindoles.[4b]

A few examples [5-10] of the introduction of a nucleophile at the indole β-position have been recorded: the simplest of these is the displacement of iodine in the reaction of 3-iodoindole with silver acetate in acetic acid to give 3-acetoxyindole,[5] presumably assisted by the silver ions. In all other reported examples the indolic substrate has carried a leaving group on nitrogen and the overall nucleophilic substitution can be summarised by the sequence (1) ⟶ (2) ⟶ (3), though it may not necessarily be synchronous as implied by the arrows on (1), nor involve an intermediate (2).



(1)

	R¹	R²	L
a;	H	H	I
b;	H	H	Cl
c;	alkyl	alkyl	Ph(OAc)I
d;	alkyl	alkyl	$(AcO)_3Pb$
e;	H	Ph	HO
f;	H	Ph	TsO
g;	H	Ph	p-$O_2NC_6H_2CO_2$
h;	NC	EtO_2C	

(2)

	R¹	R²	Nu
a;	alkyl	alkyl	RO
b;	alkyl	alkyl	$(AcO)_3Pb$
c;	alkyl	alkyl	AcO
d;	NC	EtO_2C	TsO

(3)

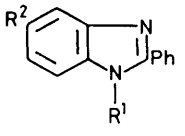
	R²	Nu
a;	H	I
b;	H	Cl
c;	Ph	TsO
d;	Ph	p-$O_2NC_6H_4CO_2$
e;	Ph	p-$O_2NC_6H_4SO_2O$
f;	Ph	$PhCO_2$
g;	Ph	AcO
h;	Ph	2-oxocyclohexyl
i;	Ph	$EtO_2C(NC)CH$
j;	Ph	$EtO_2C(Ac)CH$

The synthesis [5] of 3-iodoindole (3a) from indole, iodine, and sodium hydroxide is likely to involve initial electrophilic *N*-iodination of the indolyl anion to give (1a), for in the analogous chlorination of indole with aqueous sodium hypochlorite *N*-chloroindole (1b) was a demonstrable [6] intermediate *en route* to 3-chloroindole (3b). Recently,[7] iodosobenzene diacetate in alcoholic solution has been used for the preparation of 3-alkoxy-3*H*-indoles from 2,3-disubstituted indoles; this, it was suggested,[7] involved intermediates (1c) in which nucleophilic attack at the β-position was made possible by the departure of acetate and iodobenzene from indolic nitrogen, the product being the 3*H*-indole (2a). Awang and Vincent speculate [7] that the β-acetoxylation of 2,3-disubstituted indole (alkaloid)s with lead(IV) acetate proceeds not as had been previously suggested [11] by initial β-electrophilic attack to give (2b), but *via* electrophilic *N*-attack with the formation presumably of (1d) followed by acetate attack at the β-position and the departure of acetate and lead(II) acetate from nitrogen, giving (2c).

In the remaining recorded [8-10] examples of β-nucleophilic substitution, the indolic substrate also carried a phenyl or (in one instance [9]) an ethoxycarbonyl group in conjugation at the indole α-position. 1-Hydroxy-2-phenylindole (1e) gave 2-phenyl-3-tosyloxyindole (3c) amongst other products when the hydroxy-group was tosylated, giving (1f), which rearranged in the presence of pyridine at room temperature; [8] here leaving group and attacking nucleophile are identical. In extension of this rearrangement, it was found [9] that the *p*-nitrobenzoate (1g) could be isolated, to be later rearranged to 3-*p*-nitrobenzoyloxy-2-phenylindole (3d) on refluxing in methanol. In a more recent study [10] the chemistry of (1e) was extended to include the parallel formation of 3-

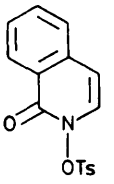
p-nitrophenylsulphonyloxy- (3e), 3-benzoyloxy- (3f), and 3-acetoxy- (3g) 2-phenylindoles, and, perhaps most interestingly, by reaction of the hydroxyindole with tosyl chloride in the presence of a carbon nucleophile, to produce 3-(2-oxocyclohexyl)- (3h) (from the morpholine enamine of cyclohexanone), 3-cyano(ethoxycarbonyl)methyl- (3i) (from ethyl cyanoacetate), and 3-(1-ethoxycarbonyl)acetonyl- (3j) (from ethyl acetoacetate) 2-phenylindoles. 3-Cyano-2-ethoxycarbonyl-1-hydroxyindole (1h) gave [9] the 3*H*-indole (2d) on tosylation in triethylamine. Of relevance also is the result of tosylation of the benzimidazole analogue (4a) of (1e) followed by treatment with pyridine, which gave [12] the product (4b) of nucleophilic attack by pyridine on the benzenoid ring with departure of the *N*-substituent.

Whether, in any of these examples, departure of the *N*-leaving group precedes nucleophilic *C*-attack, a sequence which would imply the intermediacy of a nitrenium ion, is not known. Certainly such intermediates are believed to intervene in reactions of *N*-chloroanilines [13] and arylhydroxylamines [14] when a nucleophile attacks the ring while chloride or protonated hydroxyl leaves from nitrogen. No comment on intermediates was made in a report [15] of the comparable departure of acetate from *N*-(arylcarbonyl)arylhydroxylamine acetates with concomitant nucleophilic attack on the ring. An intermediate nitrenium ion was postulated for the rearrangement of *N*-(tosyloxy)indol-2-one [16]



(4)

R¹	R²
a; HO	H
b; H	$C_5H_5N^+$



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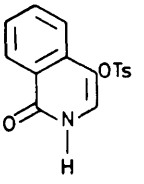
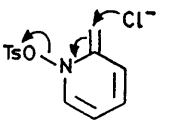


(6)

in methanol at room temperature to give a mixture of 7-(tosyloxy)indol-2-one and 5-methoxyindol-2-one. In an example [17] of closer similarity to the 1-hydroxy-2-phenylindole rearrangements, tosylation of *N*-hydroxyisoquinolin-1-one [giving first (5)] led to a rearranged product (6) by a process which tracer studies showed proceeded *via* a solvent-separated ion pair and *not either* by intermolecular attack by tosylate with synchronous departure of tosylate from nitrogen *or* intermolecular tosylate attack on a nitrenium ion. Similar treatment of *N*-hydroxyquinolin-2-one gave [17] 8-tosyloxyquinolin-2-one and of isoquinoline *N*-oxide, *via* a presumed 1,2-adduct, 4-tosyloxyisoquinoline.[18] Comparable are the conversions [19] of 2-picoline *N*-oxide into 2-chloromethylpyridine with tosyl chloride, said [19a] to proceed *via* (7), and of steroid nitrones [19b] with, for example, tosyl chloride, *via* part structure (8) to (9). Finally, 1,4-dinitropyrazoles are attacked [20] by secondary amines at carbon with nitrite as *N*-leaving group, the process



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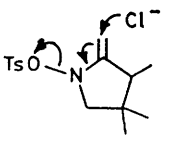

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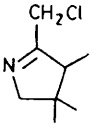

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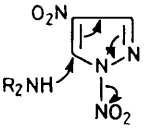
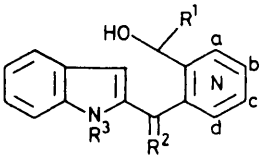


(10)

indicated by the arrows on structure (10) being favoured for the mechanism.

RESULTS AND DISCUSSION

When the oxo-alcohol (11a) was boiled briefly in ethanolic aqueous sodium hydroxide in expectation of simply removing the *N*-protecting group,[21] extremely smooth conversion into the pyrido-oxepino-indole (12a)



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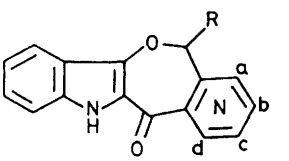


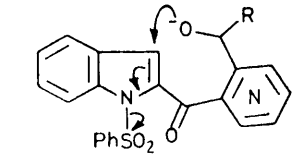
(12)

R¹	R²	R³	R
a; CH_3; N at b	O	$PhSO_2$	a; Me; N at b
b; H; N at a	O	$PhSO_2$	b; H; N at a
c; H; N at b	O	$PhSO_2$	c; H; N at b
d; H; N at c	O	$PhSO_2$	d; H; N at c
e; H; N at d	O	$PhSO_2$	e; H; N at d
f; H; no N	O	$PhSO_2$	f; H; no N
g; H; no N	H,HO	$PhSO_2$	
h; H; no N	H,HO	H	

occurred.[1] This, the first example [1] of a process involving intramolecular indole β-nucleophilic substitution with departure of benzenesulphinate from indolic nitrogen,[22] may proceed synchronously [arrows on (13)] or *via* the conjugate addition enolate (14); we believe it less likely that the process involves a nitrenium ion. The presence of the carbonyl group was shown to be essential, for although (11f) smoothly cyclised [1] to (12f), when the diol (11g) was similarly treated with base only hydrolysis occurred, to give (11h). The presence of the carbonyl group, intrinsically necessary for the S_NAr-like pathway *via* (14) would also aid passage *via* the synchronous route by reducing the electron density at the indole β-carbon, though in a superficially similar cyclisation [23] of (15) to (16) there was no carbonyl conjugation. We believe the process bears a closer resemblance to the intramolecular nucleophilic substitution observed in the Sommelet–Hauser rearrangement,[24] or especially to the

processes exemplified by the transformation [25] of the sulphonium ylide (17) into (19) *via* (18).

The more exact definition of the sequence of events will be dealt with in later papers; the work reported here represents the first stage of a broad experimental survey of the scope and limitations of intramolecular



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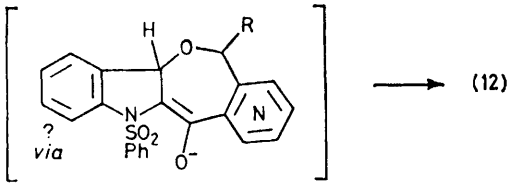

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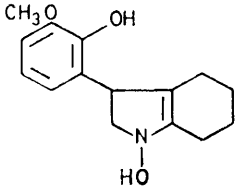

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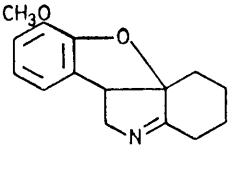

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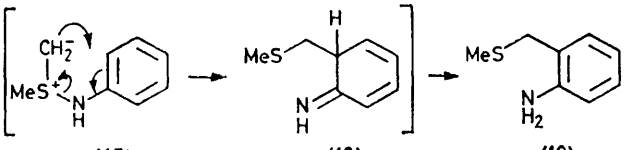
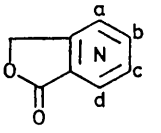


(17) (18) (19)

indole β-nucleophilic substitution processes for the construction of new heterocyclic systems, here the synthesis of pyrido-oxepino-indoles.

The preparation of the substrates for the intramolecular indole β-nucleophilic substitution was based on the use of 2-lithio-1-phenylsulphonylindole.[26] The lithiation was conveniently effected with commercial n-butyllithium initially at −78 °C and then at room temperature. For the condensations, the solution was returned to −78 °C for the addition of the pyridine lactone [27] (20a—d) and the reaction was completed at room temperature. Each condensation produced a mixture of the desired oxo-alcohol (11b—e), together with small amounts of phenylsulphonylindole and indole, the latter formed we assume by butyl-lithium attack at sulphur; the desired basic products were readily separated from the non-basic indoles with acid.

In no instance did we observe any double addition products and this, we speculate, shows the anticipated single-addition intermediate to exist in cyclic form (21) till work-up. It is interesting then that none of the hydroxy-ketones (11b—e) showed any sign of existing as or even being in equilibrium with a corresponding



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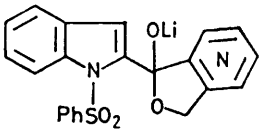
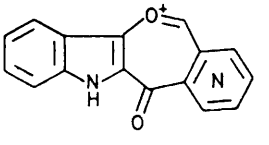


(21)

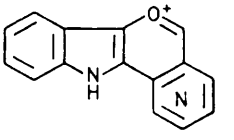
a; N at a
b; N at b
c; N at c
d; N at d

cyclic hemi-acetal. Thus each compound had u.v. absorption characteristic of 2-arylcarbonyl-1-phenylsulphonylindoles with $\lambda_{max.}$ *ca.* 310 nm, in contrast with the absorption of the isolated 1-phenylsulphonylindole chromophore, $\lambda_{max.}$ 255 nm. In addition each had strong i.r. carbonyl stretching in the range 1 655—1 670 cm^{-1}.

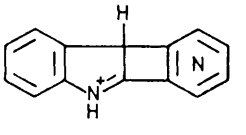
In working out conditions for the base-catalysed ring closures we sought to define the minimum conditions and found that, in each case, reaction was so efficient that it was complete within 2—5 min at reflux in methanol–aqueous 3M-sodium hydroxide; in fact more prolonged reflux was deleterious. The pyrido-oxepino-indoles (12b—e) were highly crystalline, yellow materials isolable in effectively pure form simply either by filtration from the cooled reaction mixtures or after pouring into water. Each had effectively the same, characteristic u.v. absorption, changes in the position of the pyridine nitrogen causing only small differences. All other spectral data were similar too; in particular each ether gave major mass spectral fragment ions (which may be taken as characteristic of the system) corresponding to M − H, M − CHO, and M − C_2HO_2, which seem to be well rationalised in terms of structures (A), (B), and (C), respectively.



(A)



(B)



(C)

The operation of the intramolecular indole β-nucleophilic substitution process for the synthesis of oxepinoindoles was insensitive to changes in the relative position (or presence) of pyridine ring nitrogen in precursors (11a—f). The preparation of oxepinoindoles (see also ref. 1) provides a good illustration of the potential versatility of intramolecular indole β-nucleophilic substitution for the construction of hetero polycyclic systems; further examples will be given in future papers.

EXPERIMENTAL

General Procedure for Synthesis of 1-*Phenylsulphonylindol*-2-*yl* o-*Hydroxymethylpyridyl Ketones* (11b—e).—To a solution of 1-phenylsulphonylindole (2.0 g) in dry tetrahydrofuran (THF) (100 ml) at −78 °C was added n-butyllithium (4.9 ml of 1.6M-solution in hexane) in one portion. The mixture was allowed to warm to room temperature during 1 h, and then warmed to 40 °C for 5 min. After recooling to −78 °C the lactone (20a—d) (1.0 g) in dry THF (100 ml) was added rapidly in one portion. The cooling bath was removed and the mixture allowed to warm to room temperature, then brought to 40 °C for 5 min. The solvent was then removed in vacuum at 20 °C. The residue was partitioned between water (30 ml) and ether (4 × 100 ml) and the product extracted from the organic layer with 2M-hydrochloric acid [(11d) required 6M-hydrochloric acid] (in some cases a gummy hydrochloride partly separated from solution and was combined with the aqueous layer). Basification of the aqueous extract with solid potassium carbonate, extraction with chloroform, and evaporation gave the ketone (11). *Ketone* (11b) (1.12 g, 39%) had m.p. 139—140 °C (from MeOH), $\lambda_{max.}$ (EtOH) 208, 244, and 306 nm (log ε 4.53, 4.18, and 4.05); $\nu_{max.}$ ($CHCl_3$) 3 450br and 1 670s cm^{-1}; τ($CDCl_3$) 1.30 (1 H, dd, *J* 2 and 6 Hz, pyridine α-H), 1.9—2.8 (11 H, m, ArH), 3.10 (1 H, s, indole β-H), 4.90 (2 H, s, CH_2O), and 5.4 (1 H, brs, OH); *m/z* 392 (M^+, 2%), 251 (100), 233 (64), 221 (15), 205 (27), 135 (45), 134 (28), and 77 (31) (Found: C, 64.1; H, 4.2; N, 7.05. S, 8.4. $C_{21}H_{16}N_2O_4S$ requires C, 64.3; H, 4.1; N, 7.1; S, 8.2%). *Ketone* (11c) (1.68 g, 58%) was amorphous, $\lambda_{max.}$ (EtOH) 205, 240sh, and 318 nm (log ε 4.43, 4.04, and 3.92); $\nu_{max.}$ ($CHCl_3$) 3 450br and 1 660s cm^{-1}; τ($CDCl_3$) 1.20 (1 H, s, pyridine α-H), 1.40 (1 H, d, *J* 6 Hz, pyridine α-H), 1.80—2.80 (10 H, m, ArH), 2.95 (1 H, s, indole β-H), 5.2 (2 H, s, CH_2O), and 6.8 (1 H, br, s, OH); *m/z* 392 (M^+, 3%), 251 (80), 233 (61), 205 (36), 149 (25), 134 (72), 94 (100), and 77 (31) (Found: M^+, 392.0822. Required: *M*, 392.0831). *Ketone* (11d) (1.14 g, 49%) had m.p. 169—171 °C (from MeOH); $\lambda_{max.}$ (EtOH) 212, 245sh, and 308 nm (log ε 4.42, 4.16, and 3.93); $\nu_{max.}$ ($CHCl_3$) 3 500br and 1 655s cm^{-1}; τ($CDCl_3$) 1.30 (1 H, d, *J* 6 Hz, pyridine α-H), 1.35 (1 H, s, pyridine α-H), 1.80—2.80 (10 H, m, ArH), 3.0 (1 H, s, indole β-H), 5.1 (2 H, s, CH_2O), and 6.6 (1 H, br, s, OH); *m/z* 392 (M^+, 5%), 374 (20), 257 (30), 251 (94), 233 (74), 221 (18), 205 (22), 134 (100), 116 (48), 106 (35), 89 (32), and 77 (88) (Found: C, 64.0; H, 4.1; N, 7.3; S, 8.2%). *Ketone* (11e) had m.p. 186—187 °C (from MeOH); $\lambda_{max.}$ (EtOH) 202, 245, and 309 nm (log ε 4.56, 4.21, and 4.02); $\nu_{max.}$ ($CHCl_3$) 3 500br and 1 665s cm^{-1}; τ($CDCl_3$) 1.50 (1 H, d, *J* 6 Hz, pyridine α-H), 1.80—2.80 (11 H, ArH), 2.82 (1 H, s, indole β-H), 5.12 (2 H, s, CH_2O), and 7.10 (1 H, br, s, OH); *m/z* 392 (M^+, 0.7%), 374 (2), 251 (100), 233 (12), 205 (10), 134 (16), 106 (15), 94 (24), and 77 (28) (Found: C, 64.1; H, 4.1; N, 6.9; S, 8.0%).

General Procedure for Synthesis of Pyrido[x′,y′ : 5,6]-*oxepino*[3,2-b]*indolones* (12b—e). A solution of the ketone (11b—e) (*W* g) in methanol (100*W* ml) and aqueous *X*M-sodium hydroxide (50*W* ml) was heated on a steam-bath for *Y* min, then the whole was poured into water (*Z* ml) and the precipitate collected by filtration [no precipitate formed in the case of (12e), which was accordingly isolated by extraction with chloroform]. 6H-*Pyrido*[3′,2′ : 5,6]*oxepino*[3,2-b]*indol*-5(12H)-*one* (12b) (0.44 g, 63%) (*W* = 1.1, *X* = 0.36, *Y* = 2, *Z* = 800) had m.p. 207—208 °C (from MeOH); $\lambda_{max.}$ (EtOH) 216, 248, 267, 340, and 390sh nm (log ε 4.52, 4.01, 3.87, 4.25, and 3.76); $\nu_{max.}$ ($CHCl_3$) 3 460 and 1 615s cm^{-1}; τ[$(CD_3)_2SO$] − 1.40 (1 H, s, NH), 1.12 (1 H, d, *J* 5 Hz, pyridine α-H), 1.55 (1 H, d, *J* 7 Hz, pyridine γ-H), 2.25 (2 H, m, pyridine β-H and indole 4-H), 2.55—2.85 (4 H, m, ArH), and 4.53 (2 H, s, CH_2O); δ_C[$(CD_3)_2SO$] 177.71(s), 152.77(s), 152.04(d), 146.86(s), 136.49(s), 136.06(d), 132.41(s), 127.53(d), 124.24(d), 121.76(s), 119.72(d), 119.36(d), 117.02(s), 112.49(d), and 77.78(d); *m/z* 250 (M^+, 100%), 249 (28), 221 (52), 194 (26), 193 (62), 192 (12), and 76 (31) (Found: C, 72.05; H, 3.9; N, 11.3. $C_{15}H_{10}N_2O_2$ requires C, 72.0; H, 4.0; N, 11.1%). 6H-*Pyrido*[4′,3′ : 5,6]*oxepino*[3,2-b]*indol*-5(12H)-*one* (12c) (0.73 g, 83%) (*W* = 1.37, *X* = 2, *Y* = 5, *Z* = 1 400) had m.p. 246—247 °C (from MeOH); $\lambda_{max.}$ (EtOH) 223, 278, 347, and 410 nm (log ε 4.41, 3.81, 4.15, and 3.64); $\nu_{max.}$ ($CHCl_3$) 3 440m and 1 620s cm^{-1}; τ[$(CD_3)_2SO$]—1.4 (1 H, s, NH), 1.02 (1 H, s, pyridine α-H), 1.11 (1 H, d, *J* 5 Hz, pyridine α-H), 2.07 (1 H, d, *J* 5 Hz, pyridine β-H), 2.26 (1 H, d, *J* 7 Hz, indole 4-H), 2.55—2.90 (3 H, m, ArH), and 6.48 (2 H, s, CH_2O); δ_C[$(CD_3)_2SO$] 178.22(s), 150.94(d), 150.21(d), 147.44(s), 142.85(s), 136.94(s), 127.96(d), 127.82(s). 121.84(s), 120.45(d), 119.94(d), 119.50(d), 117.09(s), 112.65(d), and 72.59(t); *m/z* 250 (M^+, 100%), 249 (22), 221 (65), 194 (33), 193 (27), and 94 (38) (Found: C, 71.8; H, 4.0; N, 11.05%). 11H-*Pyrido*[3′,4′ : 5,6]*oxepino*[3,2-b]*indol*-12(5H)-*one* (12d) (0.73 g, 83%) (*W* = 1.4, *X* = 0.36, *Y* = 1.5, *Z* = 800) had m.p. 239 °C (from MeOH); $\lambda_{max.}$ (EtOH) 232, 268sh, 310, and 405 nm (log ε 4.44, 3.89, 3.49, and 3.19); $\nu_{max.}$ ($CHCl_3$) 3 420m and 1 620s cm^{-1}; τ[$(CD_3)_2SO$] − 1.4 (1 H, s, NH), 0.85 (1 H, s, pyridine α-H), 1.10 (1 H, d, *J* 5 Hz, pyridine α-H), 2.30—2.90 (5 H, m, ArH), and 4.50 (2 H, s, CH_2O); δ_C[$(CD_3)_2SO$] 178.29(s), 153.49(d), 148.90(d), 146.93(s), 141.97(s), 136.49(s), 131.68(s), 127.67(d), 123.59(d), 122.20(s), 119.79(d), 119.50(d), 117.09(s), 112.65(d), 74.20(t); *m/z* 250 (M^+, 100%), 249 (24), 233 (20), 221 (34), 194 (22), and 193 (15) (Found: C, 71.5; H, 3.9; N, 10.8%). 11H-*Pyrido*[2′,3′ : 5,6]*oxepino*[3,2-b]*indol*-12(5H)-*one* (12e) (0.56 g, 81%) (*W* = 1.1, *X* = 2, *Y* = 5, *Z* = 1 500) had m.p. 275—277 °C (from MeOH); $\lambda_{max.}$ 205, 228, 267, 276, 347, and 400sh nm (log ε 4.26, 4.30, 3.87, 3.79, 3.69, and 3.35); $\nu_{max.}$ ($CHCl_3$) 3 440m and 1 620s cm^{-1}; τ($CDCl_3$) 1.10 (1 H, d, *J* 4 Hz, pyridine α-H), 1.30 (1 H, br, s, NH), 2.10 (1 H, dd, *J* 7 Hz, pyridine γ-H), 2.25—2.85 (5 H, m, ArH), and 4.63 (2 H, s, CH_2O); δ_C[$(CD_3)_2SO$] 178.29(s), 152.83(s), 149.78(d), 146.42(s), 138.10(d), 136.43(s), 130.26(s), 127.38(d), 126.43(d), 121.84(s), 119.65(d), 119.28(d), 117.02(s), 112.49(d), and 73.91(t); *m/z* 250 (M^+, 100%), 249 (85), 221 (59), 194 (18), 193 (34), 192 (19), and 83 (36) (Found: C, 71.6; H, 4.0; N, 10.8%).

M. G. B., W. R. A., and M. M. C. thank the S.R.C. for maintenance grants. Part of this work (M. G. B. and M. M. C.) was undertaken as part of S.R.C. CASE awards;

we thank Glaxo Group Research Ltd., Ware, for their interest and support.

[1/1019 *Received*, 25*th June*, 1981]

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