Rearrangements of Pyrimido- and Diazepino-[1,2-*a*]indoles: Syntheses of 1,5-Benzodiazocines and 1,6-Benzodiazonines

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Rearrangements of the pyrimido[1,2-*a*]indoles **1** and **2** and the pyrimido[1,2-*a*]indolinium iodide **13** produce the 1,2,3,4,5,6-hexahydro-1,5-benzodiazocines **7–9**. The diazepino[1,2-*a*]indole **16** produces the 2,3,4,5,6,7-hexahydro-1,6-benzodiazonine **18**. Formation of compounds **7** and **8** is less facile than that of compounds **9** and **18**. The pyrimido[1,2-*a*]indoles **1** and **2** and the diazepino[1,2-*a*]-indole **16** undergo rearrangement with arenesulphonyl chlorides such as toluene-*p*-sulphonyl chloride but not with carboxylic acid chlorides to give the diazocines **10** and **12** and the diazonine **20**. Mechanisms for the rearrangements are discussed in terms of indole 2,3-oxide intermediates. The reduction of the pyrimido[1,2-*a*]indole **2** with lithium tetrahydroaluminate generates the bicyclic aminal **26**. The treatment of the bicyclic lactam **11** with lithium tetrahydroaluminate or with sodium methoxide results in ring-opening and formation of the 1,2,3,4-tetrahydro- and 1,2,3,4,5,6-hexahydro-1,5-benzodiazocines **27** and **28**.

2,3,4,10-Tetrahydropyrimido[1,2-*a*]indoles are orally active hypoglycaemic agents in warm-blooded animals [1] and Ciclazindol **1**, a representative of the class, improves the oral glucose tolerance of obese diabetic humans with an efficacy similar to that achieved with Metformin.[2] A by-product formed during routine preparations of Ciclazindol in small quantities was shown to be an isomer of Ciclazindol, formed by a novel yet general rearrangement of 2,3,4,10-tetrahydropyrimido[1,2-*a*]-indoles. This paper summarises our investigations into the chemistry of this ring system and the related 2,4,5,11-tetrahydro-3*H*-1,3-diazepino[1,2-*a*]indol-11-ols and demonstrates that their rearrangement products can be utilised in the syntheses of 1,2,3,4-tetrahydro-1,5-benzodiazocines and 2,3,4,-5,6,7-hexahydro-1,6-benzodiazonines, respectively.

Results and Discussion

Acid-catalysed dehydration of 1-(3-aminopropyl)indol-2(3*H*)-one **3** gives a high yield of the pyrimido[1,2-*a*]indole **1** and a low yield of the bridged isomer **7** [3] (Table 1, entry 1). The results of experiments in which the pyrimido[1,2-*a*]indoles **1** and **2** were subjected to the same reaction conditions (Table 1, entries 2, 3) indicate (*a*) that compound **7** is the thermodynamic product and compound **1** the kinetic product arising from dehydration of compound **3**, and (*b*) that compound **7** arises from rearrangement of compound **1**.

Rearrangement of the pyrimido[1,2-*a*]indolyl nucleus is a facile process after quaternisation. Thermolysis of the quaternary salt **13** or the ring-opened indol-2(3*H*)-one **4** in the absence of acid-catalysis affords good yields of the bicyclic lactam **9** (Table 1, entries 4, 5).

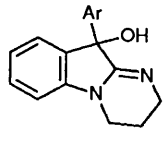
Treatment of the pyrimido[1,2-*a*]indole **1** with acetic anhydride or benzoyl chloride gives the esters **14** and **15**, respectively, whereas with benzenesulphonyl chloride or toluene-*p*-sulphonyl chloride, the rearrangement products **10** and **11** are formed (Table 1, entries 6, 7). The Ciclazindol analogue **2** reacts in a similar manner upon treatment with toluene-*p*-sulphonyl chloride to give the sulphonamide **12** (Table 1, entry 8).

Thermal rearrangements occur more easily for the diazepino[1,2-*a*]indole ring systems than for the smaller pyrimido[1,2-*a*]indoles (Table 1, entry 9 *vs.* entry 2). Acid-catalysed cyclohydration of the 1-(4-aminobutyl)indol-2(3*H*)-one **5** results in formation of the bicyclic lactam **19** and not the

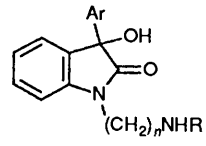
Table 1 Rearrangements

Entry No.	Starting material	Product	Reaction[a]	Time (h)	Temp.[b]	Yield (%)
1	**3**	**7**	**A**	4	R	0.6
2	**1**	**7**	**A**	168	R	14
3	**2**	**8**	**A**	72	R	4
4	**13**	**9**	**B**	24	R	>60
5	**4**	**9**	**B**	72	R	78
6	**1**	**10**	**C**	2	A	82
7	**1**	**11**	**D**	1	A	53
8	**2**	**12**	**D**	1	A	22
9	**16**	**18**	**A**	24	R	75
10	**5**	**19**	**A**	18	R	70
11	**16**	**20**	**D**	3	A	29

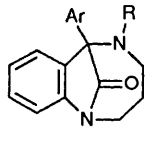
[a] **A** = xylene, TsOH (cat.); **B** = xylene; **C** = $PhSO_2Cl$, NEt_3, py; **D** = *p*-$MeC_6H_4SO_2Cl$, NEt_3, py. [b] R = reflux; A = ambient temperature.



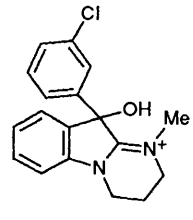
1 Ar = *m*-ClC_6H_4
2 Ar = Ph



3 *n* = 3, R = H, Ar = *m*-ClC_6H_4
4 *n* = 3, R = CH_3, Ar = *m*-ClC_6H_4
5 *n* = 4, R = H, Ar = *m*-ClC_6H_4
6 *n* = 3, R = H, Ar = Ph



7 R = H, Ar = *m*-ClC_6H_4
8 R = H, Ar = Ph
9 R = Me, Ar = *m*-ClC_6H_4
10 R = $PhSO_2$, Ar = *m*-ClC_6H_4
11 R = *p*-$MeC_6H_4SO_2$, Ar = *m*-ClC_6H_4
12 R = *p*-$MeC_6H_4SO_2$, Ar = Ph



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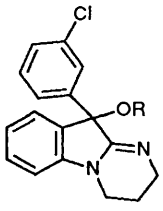
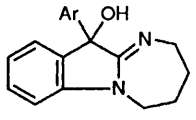
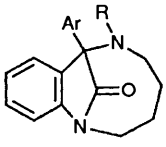
alcohol **17** (Table 1, entry 10). It appears that the lactam **19** is both the kinetic and thermodynamic product arising from the cyclisation of the aminobutylindol-2(3*H*)-one **5**, unlike the case with the compound **3**. The diazepino[1,2-*a*]indole **16**, like the pyrimido[1,2-*a*]indoles **1** and **2**, undergoes rearrangement with toluene-*p*-sulphonyl chloride to form the sulphonamido product **20** (Table 1, entry 11).



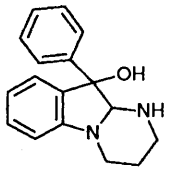
14 R = Ac
15 R = Bz



16 Ar = Ph
17 Ar = *m*-ClC$_6$H$_4$



18 R = H, Ar = Ph
19 R = H, Ar = *m*-ClC$_6$H$_4$
20 R = *p*-MeC$_6$H$_4$SO$_2$, Ar = Ph



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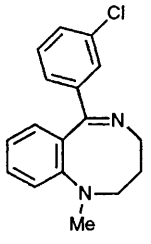

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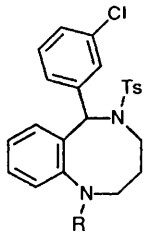
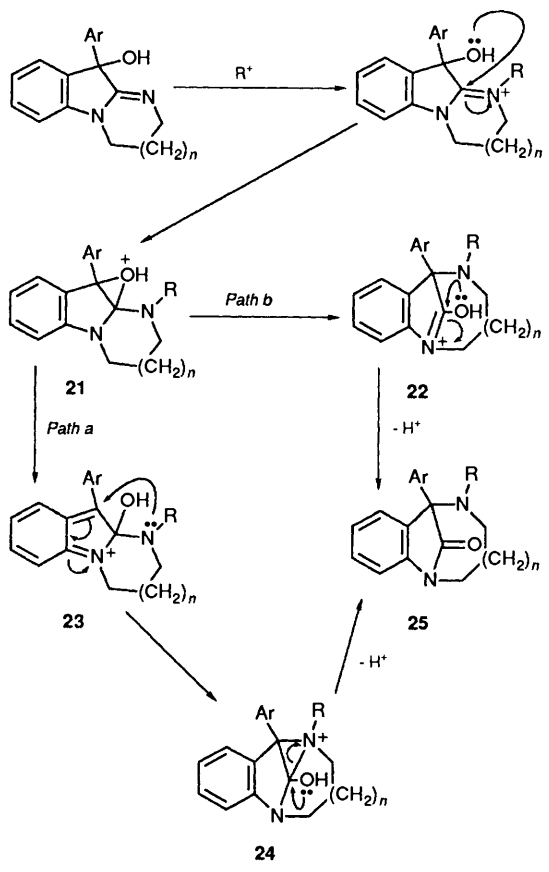


28 R = AcO
29 R = Me

The rearrangement mechanism may involve formation of an indole 2,3-oxide such as **21** * (Scheme 1), which is converted *via* the 2*H*-indolinium cation **23** (path *a*) to an aziridinium cation **24**. An alternative mechanism requires a direct 1,2-shift of the alkylamino group (path *b*) in the epoxide **21** to give the 2-hydroxy-3*H*-indolinium cation **22**. The subsequent loss of a proton from either of the two cationic species **22** or **24** creates the lactam **25**.

A study of the reactions of the pyrimido[1,2-*a*]indole **2** and the bicyclic lactam **11** with nucleophilic reagents was undertaken. Treatment of compound **2** with aqueous base results in rapid formation of the ring-opened indol-2(3*H*)-one **6**. This outcome contrasts with the report[6] that a 10-methyl (instead of 10-phenyl) analogue of compound **2** is stable in aqueous solution at pH 9, albeit at room temperature. Reduction of compound **2** with lithium tetrahydroaluminate generates the aminal **26**.[7] It is of interest to note that the dissolving metal reductions of pyrimido[1,2-*a*]indol-10-ols generally produce 1-(3-aminopropyl)indoles.[6]

Treatment of the bicyclic lactam **11** with lithium tetrahydroaluminate gives rise to the 1,5-benzodiazocine **27** by a mechanism which presumably involves hydride attack at the



Scheme 1 Mechanisms for the formation of the bicyclic lactam **25**. n = 1 or 2, R = H, Me, PhSO$_2$ or *p*-MeC$_6$H$_4$SO$_2$, Ar = Ph or *m*-ClC$_6$H$_4$.

amide carbonyl group followed by elimination of sulphinate anion. The stability of diaryl imines such as compound **27**[8–11] to complex metal hydrides arises from steric hindrance to reaction.[12] Reaction of the bicyclic lactam **11** with sodium methoxide results in unusual C–C bond cleavage with formation of the urethane **28**.

Treatment of the urethane **28** with lithium tetrahydroaluminate in boiling tetrahydrofuran produces the amine **29**. The lack of reduction of the sulphonamido group in the latter lends strength to the mechanistic argument for an intramolecular displacement of sulphinate anion in the preparation of the 1,5-benzodiazocine **27**.

Experimental

M.p.s were determined on a Kofler hot stage and are uncorrected. IR spectra were recorded on a Perkin-Elmer 983G spectrophotometer and band positions are reported in wavenumbers. ^{1}H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded using a Bruker WP-200SY spectrometer. ^{1}H (60 MHz) NMR spectra were recorded on a Varian EM360 spectrometer. Chemical shifts (δ) are reported in ppm downfield from Me$_4$Si as internal standard. Mass spectra (*m*/*z*) were determined by Dr. A. Crawshaw (York University). Elemental analyses were performed under the supervision of Dr. K. Heatherington.

3-(3-Chlorophenyl)-3-hydroxy-1-(3-methylaminopropyl)indol-2(3H)-one **4**.—The methiodide **13** (2.0 g, 4.5 mmol) in aqueous NaOH (1 mol dm^3; 25 ml) was heated under reflux for 45 min, after which the mixture was cooled to room temperature and treated with ammonium chloride (1.6 g, 30 mmol). It was then

* Similar intermediates have been proposed in the preparation of 3,3-diaryl-1-methylindol-2(3*H*)ones.[4,5]

extracted with chloroform (2 × 30 ml) and the extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was dissolved in propan-2-ol (5 ml) and acidified with ethereal hydrogen chloride to give the *dioxindole hydrochloride* **4** (1.6 g, 96%), m.p. 255–257 °C (decomp.) (Found: C, 58.65; H, 5.6; N, 7.7. $C_{18}H_{19}ClN_2O_2$·HCl requires C, 58.9; H, 5.5; N, 7.6%); ν_{max}(Nujol)/cm^{-1} 3221, 2780, 1721 (C=O), 1610 and 1354; δ_H[200 MHz, $(CD_3)_2SO$] 1.99 (2 H, m, $MeNCCH_2$), 2.50 (3 H, s, Me), 2.8–3.1 (2 H, m, $MeNCH_2$), 3.80 (2 H, t, $OCNCH_2$), 6.98 (1 H, s, OH), 7.0–7.5 (8 H, complex, aromatic protons) and 9.09 (2 H, s, $\overset{+}{N}H_2$).

1-3-(*Aminopropyl*)-3-*hydroxy*-3-*phenylindol*-2(3H)-*one* **6**.—A solution of the amidine **2** (2.9 g, 11 mmol) in NaOH (2 mol dm^{-3}; 50 ml) and methanol (40 ml) was heated under reflux for 3 h and then cooled to room temperature. The methanol was removed by evaporation under reduced pressure and the acidity of the aqueous residue adjusted to pH 8 with HCl (2 mol dm^{-3}). The mixture was extracted with chloroform (3 × 50 ml) and the extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the *amine* **6**[3] as a solid. The hydrochloride of the product was isolated from propan-2-ol with ethereal hydrogen chloride as a colourless solid (2.82 g, 81%), m.p. 228–230 °C (decomp.) (Found: C, 63.8; H, 6.3; N, 8.6. $C_{17}H_{18}N_2O_2$·HCl requires C, 64.0; H, 6.0; N, 8.8%); ν_{max}(Nujol)/cm^{-1} 3237, 2900, 2048, 1691 (C=O) and 1610; δ_H[200 MHz, $(CD_3)_2SO$] 1.92 (2 H, m, $NCCH_2$), 2.84 (2 H, t, $HNCH_2$), 3.78 (2 H, t, $OCNCH_2$), 6.77 (1 H, s, OH), 7.06 (1 H, td, 6-H), 7.15 (1 H, dd, 7-H), 7.2–7.4 (7 H, complex, other aromatic protons) and 8.03 (3 H, s, $\overset{+}{N}H_3$).

6-(3-*Chlorophenyl*)-1,2,3,4,5,6-*hexahydro*-1,6-*methano*-1,5-*benzodiazocin*-11-*one* **7**.—(*a*) *Preparation from* 1-(3-*aminopropyl*)-3-(3-*chlorophenyl*)-3-*hydroxyindol*-2(3H)-*one* **3**. A mixture of the amine **3**[3] (270 g, 0.85 mol) and toluene-*p*-sulphonic acid (10 g) in xylene (5 l) was heated under reflux and stirred in an apparatus fitted with a water separator for 4 h. The mixture was then cooled to room temperature and filtered to give the pyrimido[1,2-*a*]indole **1**, m.p. 190–192 °C (lit.,[1] 193–195 °C) in nearly quantitative yield. The filtrate was evaporated under reduced pressure and the residue purified by chromatography (alumina–toluene) to give a yellow gum. The hydrochloride salt was obtained by dissolving the gum in propan-2-ol, acidifying the solution to pH 1 with hydrogen chloride and filtering off the precipitate. The solid on drying *in vacuo* furnished the *product hydrochloride* **7** (1.4 g, 0.6%) as a yellow solid, m.p. 230–235 °C (decomp.) (Found: C, 60.8; H, 5.0; N, 8.0. $C_{17}H_{15}ClN_2O$·HCl requires C, 60.9; H, 4.8; N, 8.4%); ν_{max}(Nujol)/cm^{-1} 2600, 1712 (C=O), 1611, 1315 and 1176; δ_H[200 MHz, $(CD_3)_2SO$] 1.72 (1 H, dm, *J* 14) and 1.8–2.1 (1 H, m) (3-H_2), 2.90 (1 H, dt, *J* 14, 3) and 3.35 (1 H, m) (4-H_2), 3.35 (1 H, m) and 4.28 (1 H, dd, *J* 14, 5) (2-H_2), 6.89 (1 H, t, 8-H), 7.29 (1 H, d, 10-H), 7.72 (1 H, t, 9-H), 7.82 (1 H, m, ClCCHCCN), 7.5–7.7 (4 H, complex, other aromatic protons) and 10.7 (2 H, s, $\overset{+}{N}H_2$).

(*b*) *Preparation from pyrimido*[1,2-a]*indole* **1**. The pyrimido-[1,2-*a*]indole **1**[1] (5 g, 16.8 mmol) and a catalytic quantity of toluene-*p*-sulphonic acid (0.01 g) in xylene (50 ml) was heated under reflux for 7 d, cooled to room temperature and the unchanged starting compound **1** (4.2 g) filtered off. The filtrate was evaporated under reduced pressure and the residue purified by chromatography (alumina–toluene) to afford the amine **7** (0.7 g, 14%) as a pale yellow solid, m.p. 128–130 °C; λ_{max}(95% EtOH)/nm 216 (ε 21 400 dm^3 mol^{-1} cm^{-1}), 238 (30 800), 260 (7900) and 425 (3200); ν_{max}(Nujol)/cm^{-1} 3365 (NH) and 1700 (C=O); δ_H(60 MHz, $CDCl_3$) 1.2–1.9 (2 H, m, CCH_2C), 2.1 (1 H, s, NH), 2.75–4.2 (4 H, m, 2 × CH_2), 6.6–7.0 (2 H, m, ArH) and 7.2–7.7 (6 H, m, ArH); δ_C(50 MHz, $CDCl_3$) 25.4 (1 C, t, C-3), 40.0 (1 C, t, C-2 or C-4), 40.3 (1 C, t, C-4 or C-2), 79.6 (1 C, s, C-6), 109.5–160.2 (12 C, ArC) and 197.3 (1 C, s, C=O); *m/z* 300, 298 (M$^+$, 5%, 13%), 272, 270 (M$^+$ − CO, 11, 30), 271, 269 (M$^+$ − H − CO, 33, 100), 243, 241 (M$^+$ − H − CO − C_2H_4, 11, 30), 206 (M$^+$ − H − CO − C_2H_4 − Cl, 17) and 187 (M$^+$ − C_6H_4Cl, 8); *m** 216 (269 ⟶ 241) and 176 (241 ⟶ 206). The hydrochloride salt was isolated from propan-2-ol as a bright yellow solid, m.p. 230–235 °C (decomp.).

6-*Phenyl*-1,2,3,4,5,6-*hexahydro*-1,6-*methano*-1,5-*benzodiazocin*-11-*one* **8**.—A stirred suspension of the amidine **2**[1] (1.71 g, 6.5 mmol) and toluene-*p*-sulphonic acid (0.07 g) in xylene (50 ml) was heated under reflux for 3d and then cooled to room temperature. The unchanged amidine **2** (1.52 g) was filtered off and the filtrate was evaporated under reduced pressure and the residue purified by chromatography (silica–ether). The resulting red oil was dissolved in propan-2-ol (5 ml) and acidified with ethereal hydrogen chloride to give the *diazocine hydrochloride* **8** (0.079 g, 4%) as a yellow solid, m.p. 273–275 °C (decomp.) (Found: C, 68.2; H, 5.8; N, 9.2. $C_{17}H_{16}N_2O$·HCl requires C, 67.9; H, 5.7; N, 9.3%); ν_{max}(Nujol)/cm^{-1} 2910, 1713 (C=O), 1610, 1459 and 1376; δ_H[200 MHz; $(CD_3)_2SO$] 1.74 (1 H, dm, *J* 13) and 1.97 (1 H, qt, *J* 13, 4) (3-H_2), 2.88 (1 H, td, *J* 13, 3) and 3.35 (1 H, m) (4-H_2), 3.27 (1 H, m) and 4.27 (1 H, dd, *J* 14, 4) (2-H_2), 6.67–7.8 (9 H, complex, ArH) and 10.7 (2 H, s, $\overset{+}{N}H_2$).

6-(3-*Chlorophenyl*)-5-*methyl*-1,2,3,4,5,6-*hexahydro*-1,6-*methano*-1,5-*benzodiazocine*-11-*one* **9**.—(*a*) *Preparation from indol*-2(3H)-*one* **4**. The dioxindole **4** (0.56 g, 1.7 mmol) in xylene (20 ml) was boiled under reflux in an apparatus fitted with a water separator for 3 d, evaporated under reduced pressure and the residue purified by chromatography (silica–chloroform) to afford the *lactam* **9** (0.415 g, 78%) as a yellow solid, m.p. 146–148 °C [from toluene–light petroleum (b.p. 60–80 °C)] (Found: C, 69.2; H, 5.7; N, 8.5. $C_{18}H_{17}ClN_2O$ requires C, 69.1; H, 5.5; N, 9.0%); λ_{max}(95% EtOH)/nm 217 (ε 22 100 dm^3 mol^{-1} cm^{-1}), 243 (29 700), 265sh (7300), 318 (900) and 443 nm (3400); ν_{max}(Nujol)/cm^{-1} 1687 (C=O), 1610, 1318, 1013 and 752; δ_H(200 MHz, $CDCl_3$) 1.19 (1 H, dm *J* 14) and 2.15 (1 H, qdd, *J* 14, 6, 4) (3-H_2), 2.42 (3 H, s, Me), 2.79 (1 H, dt, *J* 14, 3) and 3.07 (1 H, td, *J* 14, 4) (4-H_2), 3.39 (1 H, td, *J* 14, 4) and 3.99 (1 H, dd, *J* 14, 6) (2-H_2), 6.65 (1 H, t, 8-H), 6.80 (1 H, d, 10-H) and 7.2–7.6 (6 H, complex, other ArH); δ_C[50 MHz, $(CD_3)_2SO$] 17.2 (1 C, t, C-3), 35.4 (1 C, q, Me), 38.7 (1 C, t, C-4), 47.6 (1 C, t, C-2), 83.7 (1 C, s, C-6), 107.6–160.6 (12 C, ArC) and 196.7 (1 C, s, C-11); *m/z* 314, 312 (M$^+$, 5%, 13%), 286, 284 (M$^+$ − CO, 17, 45), 285, 283 (M$^+$ − H − CO, 43, 100), 258, 256 (M$^+$ − CO − C_2H_4, 3, 8), 257, 255 (M$^+$ − H − CO − C_2H_4, 9, 24) and 91 ($C_7H_7^+$, 50); *m** 230 (283 ⟶ 255).

(*b*) *Preparation from pyrimido*[1,2-a]*indolinium iodide* **13**. A stirred suspension of the salt **13** (10 mg, 0.02 mmol) in xylene (5 ml) was heated under reflux for 24 h to give a straw coloured solution which was cooled to room temperature and evaporated under reduced pressure. The residue was dissolved in dichloromethane (25 ml) and the solution washed with 3% aqueous ammonia (50 ml) and water (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give an oil (10 mg). Analysis of this by ^{1}H NMR spectrometry showed that the bulk of this material (>60%) was the benzodiazocine **9**.

6-(3-*Chlorophenyl*)-5-*phenylsulphonyl*-1,2,3,4,5,6-*hexahydro*-1,6-*methano*-1,5-*benzodiazocin*-11-*one* **10**.—A solution of Ciclazindol **1** (5.33 g, 17.8 mmol) in pyridine (25 ml) and triethylamine (2.78 ml, 20 mmol) was treated dropwise with benzenesulphonyl chloride (3.43 g, 19.6 mmol) with water-bath cooling. The solution was stirred at room temperature for 2 h,

poured onto ice–water (100 g) and the solid filtered off and washed with water (3 × 20 ml). A solution of the solid in toluene (100 ml) was washed with HCl (2 mol dm^3; 2 × 50 ml), water (50 ml) and brine (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give the *sulphonamide* **10** (6.4 g, 82%) as pale pink crystals, m.p. 173–175 °C (from ethanol) (Found: C, 62.9; H, 4.4; N, 6.2. $C_{23}H_{19}ClN_2O_3S$ requires C, 62.9; H, 4.4; N, 6.4%); ν_{max}(Nujol)/cm^{-1} 1758 (C=O), 1333 (SO_2), 1162 (SO_2), 1007 and 847; δ_H(200 MHz, $CDCl_3$) 1.44 (1 H, dm, *J* 14) and 1.70 (1 H, qm, *J* 14) (3-H_2), 3.53 (1 H, dd, *J* 16, 10) and 3.77 (1 H, ddd, *J* 16, 6, 2) (4-H_2), 3.62 (1 H, dd, *J* 14, 5) and 3.91 (1 H, td, *J* 14, 4) (2-H_2), 7.18 (1 H, dd, 10-H), 7.98 (1 H, dd, 7-H) and 7.3–7.6 (11 H, complex, other ArH); δ_C[50 MHz, $(CD_3)_2SO$] 27.3 (1 C, t, C-3), 49.4 (1 C, t, C-4), 52.4 (1 C, t, C-2), 74.8 (1 C, s, C-6), 115.8–147.0 (18 C, ArC) and 183.0 (1 C, s, C-11); *m/z* 299, 297 ($M^+ - SO_2Ph$, 8%, 14%), 285, 283 (8, 17), 258, 256 (6, 17), 230, 228 (8, 22), 216, 214 (10, 24), 165 (50), 166 (28), 141 (SO_2Ph^+, 17) and 77 (Ph^+, 100).

6-(3-*Chlorophenyl*)-5-(p-*tolylsulphonyl*)-1,2,3,4,5,6-*hexahydro*-1,6-*methano*-1,5-*benzodiazocin*-11-*one* **11**.—A solution of Ciclazindol **1** (29.5 g, 0.1 mol) in pyridine (270 ml) and triethylamine (14 ml, 0.1 mol) was treated portionwise with toluene-*p*-sulphonyl chloride (19.06 g, 0.1 mol) at 0 °C. The mixture was stirred for 1 h and then evaporated under reduced pressure. The solid residue was dissolved in dichloromethane (200 ml) and the solution washed with water (2 × 200 ml), HCl (0.1 mol dm^3; 2 × 200 ml) and water (200 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The solid was recrystallised from water–dimethylformamide–methanol (2:1:1) to give the *sulphonamide* **11** (24.0 g, 53%), m.p. 180–181 °C (Found: C, 63.8; H, 4.8; Cl, 8.0; N, 6.1. $C_{24}H_{21}ClN_2O_3S$ requires C, 63.6; H, 4.7; Cl, 7.8; N, 6.2%); ν_{max}(Nujol)/cm^{-1} 1760 (C=O), 1596, 1343 (SO_2), 1150 (SO_2) and 1063; δ_H(200 MHz, $CDCl_3$) 1.72 (1 H, qm, *J ca.* 15) and 1.84 (1 H, dt, *J* 14, 5) (3-H_2), 2.38 (3 H, s, Me), 3.49 (1 H, dd, *J* 16, 12) and 3.74 (1 H, ddd, *J* 16, 5, 2) (4-H_2), 3.63 (1 H, dd, *J* 14, 5) and 3.92 (1 H, td, *J* 14, 5) (2-H_2), 7.09 (1 H, m, 10-H), 7.16 (2 H, d, 2 × MeCC*H*), 7.31 (2 H, d, 2 × SO_2CCH), 7.32 (1 H, m, 8-H), 7.4–7.5 (3 H, m, ClCCHCHCH), 7.46 (1 H, m, 9 H) and 7.97 (1 H, m, 7 H); *m/z* 299, 297 ($M^+ - Ts$, 10%, 18%), 285, 283 (4, 10), 271, 269 (6, 13), 230, 228 (5, 14), 165 (12), 155 (Ts^+, 8), 125 (13), 91 ($C_7H_7^+$, 100), 77 (Ph^+, 17) and 65 ($C_5H_5^+$, 21).

6-*Phenyl*-5-(p-*tolylsulphonyl*)-1,2,3,4,5,6-*hexahydro*-1,6-*methano*-1,5-*benzodiazocin*-11-*one* **12**.—The reaction of 10-phenyl-2,3,4,10-tetrahydropyrimido[1,2-*a*]indol-10-ol[1,3] **2** (1.88 g, 7.1 mmol) in pyridine (50 ml) and triethylamine (1.1 ml, 7.9 mmol) with toluene-*p*-sulphonyl chloride (2.0 g, 10.5 mmol) gave by the method used for the compound **11** a red foam which was crystallised from ethyl acetate (1 ml) to give the *sulphonamide* **12** (0.67 g, 22%), m.p. 189–191 °C (Found: C, 69.0; H, 5.4; N, 6.3. $C_{24}H_{22}N_2O_3S$ requires C, 68.9; H, 5.3; N, 6.7%); ν_{max}(Nujol)/cm^{-1} 1764 (C=O), 1606, 1332 (SO_2), 1148 (SO_2) and 850; δ_H(200 MHz, $CDCl_3$) 1.39 (1 H, ddd, *J* 16, 5, 1) and 1.6 (1 H, m) (3-H_2), 2.36 (3 H, s, Me), 3.53 (1 H, ddd, *J* 16, 11, 1) and 3.76 (1 H, ddd, *J* 16, 6, 3) (4-H_2), 3.61 (1 H, dd, *J* 14, 5) and 3.92 (1 H, ddd, *J* 14, 13, 4) (2-H_2), 7.08 (1 H, d, 10-H), 7.12 (2 H, d, 2 × MeCC*H*), 7.27 (2 H, d, 2 × SO_2CCH), 7.32 (1 H, td, 8-H), 7.4–7.5 (4 H, complex, 9-H and 2 × *meta* and 1 × *para* protons of phenyl substituent), 7.60 (2 H, m, 2 × *ortho* protons of phenyl substituent) and 7.99 (1 H, dd, 7 H).

10-(3-*Chlorophenyl*)-10-*hydroxy*-1-*methyl*-2,3,4,10-*tetrahydropyrimido*[1,2-a]*indolium Iodide* **13**.—A solution of Ciclazindol **1** (9.0 g, 30 mmol) in absolute ethanol (70 ml) was treated with methyl iodide (6 ml, 96 mmol), heated under reflux for 45 min, and cooled to room temperature. After 18 h, the precipitate was filtered off and dried *in vacuo* to furnish the *methiodide* **13** (12.0 g, 90%), m.p. 254–256 °C (decomp.) (Found: C, 49.3; H, 4.2; N, 6.4. $C_{18}H_{18}ClIN_2O$ requires C, 49.1; H, 4.1; N, 6.4%); ν_{max}(Nujol)/cm^{-1} 3156, 1670, 1612, 1605 and 1421; δ_H[200 MHz, $(CD_3)_2SO$] 2.20 (1 H, m) and 2.33 (1 H, m) (3-H_2), 3.12 (3 H, s, Me), 3.72 (2 H, t, 4-H_2), 3.97 (1 H, m) and 4.07 (1 H, m) (2-H_2), 7.10–7.63 (8 H, complex, ArH) and 7.95 (1 H, s, OH).

10-*Acetoxy*-10-(3-*chlorophenyl*)-2,3,4,10-*tetrahydropyrimido*[1,2-a]*indole* **14**.—Ciclazindol **1** (3 g, 10 mmol) was dissolved in acetic anhydride (100 ml). After 48 h, the solution was evaporated under reduced pressure and any residual acetic anhydride removed as an azeotrope with toluene. The resulting foam was dissolved in ethanol (5 ml) and the solution acidified with ethereal hydrogen chloride. The precipitate was filtered off and dried *in vacuo* to give the *product hydrochloride* **14** (3.24 g, 90%), m.p. 213–216 °C (decomp.) (Found: C, 60.4; H, 4.8; N, 7.3. $C_{19}H_{17}ClN_2O$·HCl requires C, 60.5; H, 4.8; N, 7.4%); ν_{max}(Nujol)/cm^{-1} 2600, 1747 (C=O), 1679, 1612 and 1318; δ_H[200 MHz, $(CD_3)_2SO$] 1.9–2.3 (2 H, m, 3-H_2), 2.27 (3 H, s, Me), 3.55 (2 H, m, 4-H_2), 3.9–4.2 (2 H, m, 2-H_2), 7.20–7.60 (7 H, m) and 7.72 (1 H, t) (ArH and ClCCHCCO) and 12.2 (1 H, s, $\overset{+}{N}H$).

10-*Benzoyloxy*-10-(3-*chlorophenyl*)-2,3,4,10-*tetrahydropyrimido*[1,2-a]*indole* **15**.—A solution of Ciclazindol **1** (5.96 g, 20 mmol) in pyridine (60 ml) at 0–5 °C was treated dropwise with benzoyl chloride (3 g, 21 mmol) and stirred for 3 h at room temperature. A precipitate of the amidine hydrochloride **1** (1.95 g) was filtered off and the filtrate evaporated under reduced pressure. The residue was suspended in toluene and the mixture re-evaporated to remove residual benzoyl chloride. The remaining material upon suspension in propan-2-ol, acidification with ethereal hydrogen chloride and evaporation under reduced pressure afforded the *benzoate hydrochloride* **15** as a hemihydrate salt (5.1 g, 58%), m.p. 195–197 °C (decomp.) (from propan-2-ol–ether) (Found: C, 64.2; H, 4.75; N, 6.4. $C_{24}H_{19}ClN_2O_2$·HCl·$\frac{1}{2}H_2O$ requires C, 64.3; H, 4.7; N, 6.25%); ν_{max}(Nujol)/cm^{-1} 2600, 1724 (C=O), 1679, 1610 and 1316; δ_H[200 MHz, $(CD_3)_2SO$] 2.0–2.3 (2 H, m, 3-H_2), 3.6 (2 H, m, 4-H_2), 4.0–4.3 (2 H, m, 2-H_2), 7.25 (1 H, td) and 7.4–7.9 (10 H, m) and 8.11 (2 H, dd) (8-H, ArH and 2 × O=CCCH) and 11.5 (1 H, s, $\overset{+}{N}H$).

7-*Phenyl*-2,3,4,5,6,7-*hexahydro*-1H-1,7-*methano*-1,6-*benzodiazonine*-12-*one* **18**.—A stirred suspension of 11-phenyl-2,4,5,11-tetrahydro-3*H*-1,3-diazepino[1,2-*a*]indol-11-ol[13] **16** (0.89 g, 3.2 mmol) and toluene-*p*-sulphonic acid (0.07 g) in xylene (40 ml) was heated under reflux for 24 h, cooled to room temperature and evaporated under reduced pressure. The residual oil was purified by chromatography (silica–ether) and crystallisation from ether to give the *diazonine* **18** (0.67 g, 75%) as yellow crystals, m.p. 140–142 °C (Found: C, 77.8; H, 6.55; N, 9.7. $C_{18}H_{18}N_2O$ requires C, 77.7; H, 6.5; N, 10.1%); ν_{max}(Nujol)/cm^{-1} 3329, 1718 (C=O), 1616, 1319 and 981; δ_H(200 MHz, $CDCl_3$) 1.3–1.5 (1 H, m) and 1.6–1.9 (3 H, m) (NHCCH_2CH_2), 2.20 (1 H, t, *J* 15) and 3.03 (1 H, dm, *J* 15) (5-H_2), 2.26 (1 H, br s, NH), 3.28 (1 H, td, *J* 15, 3) and 3.93 (1 H, dm, *J* 15) (2-H_2) and 6.70–7.5 (9 H, complex ArH).

7-(3-*Chlorophenyl*-2,3,4,5,6,7-*hexahydro*-1H-1,7-*methano*-1,6-*benzodiazonin*-12-*one* **19**.—A mixture of 1-(4-aminobutyl)-3-(3-chlorophenyl)indol-2(3*H*)-one[3] **5** (8.5 g, 25.7 mmol) and a catalytic quantity of toluene-*p*-sulphonic acid (0.1 g) in xylene (100 ml) was heated under reflux for 18 h with continuous removal of water *via* a Dean–Stark trap, cooled to room temperature and evaporated under reduced pressure to give an

oil. A solution of this in the minimum quantity of propan-2-ol (< 10 ml) on acidification with ethereal hydrogen chloride furnished the *product hydrochloride* **19** (6.32 g, 70%) as yellow crystals, m.p. 189–191 °C (decomp.) (Found: C, 62.0; H, 5.35; Cl, 10.5; N, 7.8. $C_{18}H_{17}ClN_2O$·HCl requires C, 61.9; H, 5.2; Cl, 10.25; N, 8.0%); ν_{max}(Nujol)/cm^{-1} 2600, 1721 (C=O), 1611, 1323 and 956; δ_H[200 MHz, $(CD_3)_2SO$] 1.6–2.2 (4 H, complex, 3-H_2, 4-H_2), 2.45 (1 H, m) and 3.25 (1 H, m) (5-H_2), 3.4 (1 H, m) and 4.2 (1 H, m) (2-H_2), 6.90 (1 H, t, 9-H), 7.25 (1 H, d, 11-H), 7.5–7.8 (6 H, complex, other ArH) and 10.5 (2 H, s, $\overset{+}{N}H_2$).

7-*Phenyl*-6-(p-*tolylsulphonyl*)-2,3,4,5,6,7-*hexahydro*-1H-1,7-*methano*-1,6-*benzodiazonin*-12-*one* **20**.—Toluene-*p*-sulphonyl chloride (0.191 g, 1 mmol) was added to the amidine **16** (0.278 g, 1 mmol) in pyridine (5 ml) and triethylamine (0.14 ml, 1 mmol) at 10 °C and the solution stirred at room temperature for 3 h. Evaporation of the mixture gave a red gum which on treatment with toluene, re-evaporation *in vacuo* and crystallisation from propan-2-ol furnished the *diazonine* **20** (0.124 g, 29%) as a pink solid, m.p. 202–204 °C (from acetonitrile) (Found: C, 69.3; H, 5.7; N, 6.3. $C_{25}H_{24}N_2SO_3$ requires C, 69.4; H, 5.6; N, 6.5%); ν_{max}(Nujol)/cm^{-1} 1735 (C=O), 1607, 1325 (SO_2), 1152 (SO_2) and 857; δ_H(200 MHz, $CDCl_3$) 0.89 (1 H, m), 1.47 (1 H, m), 1.70 (1 H, m) and 2.25 (1 H, m) (3-H_2, 4-H_2), 2.35 (3 H, s, Me), 3.48 (1 H, ddd, *J* 14, 9, 7) and 4.06 (1 H, ddd, *J* 14, 7, 3) (2-H_2), 3.63 (1 H, ddd, *J* 17, 8, 2) and 3.78 (1 H, ddd, *J* 17, 9, 2) (5-H_2), 6.89 (1 H, m, 11-H), 7.09 (2 H, d, 2 × SCCH), 7.23 (2 H, d, 2 × MeCC*H*), 7.93 (1 H, m, 8-H) and 7.1–7.6 (7 H, complex, other ArH).

1,2,3,4,10,10a-*Hexahydro*-10-*phenylpyrimido*[1,2-a]*indole*-10-*ol* **26**.—A stirred solution of lithium tetrahydroaluminate (0.4 g, 10.5 mmol) in tetrahydrofuran (20 ml) was treated with a slurry of the amidine **2** (1.32 g, 5 mmol) in tetrahydrofuran (50 ml). After the initial exothermic reaction, the mixture was heated under reflux for 3 h, cooled to room temperature, treated with water (0.5 ml) and NaOH (2 mol dm^3; 0.5 ml), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give an oil which crystallised from ether as the *product* **26** (0.73 g, 55%), m.p. 145–147 °C (Found: C, 76.25; H, 7.0; N, 10.4. $C_{17}H_{18}N_2O$ requires C, 76.7; H, 6.8; N, 10.5%). The hemifumarate of the product was prepared from propan-2-ol as needles, m.p. 157 °C (decomp.) [Found: C, 70.3; H, 6.2; N, 8.4. Calc. for $C_{17}H_{18}N_2O$·½($C_4H_4O_4$): C, 70.35; H, 6.2; N, 8.6%]; ν_{max}(Nujol)/cm^{-1} 3100, 2500–1800, 1610, 1585 and 1354; δ_H[200 MHz, $(CD_3)_2SO$] 1.5 (2 H, m, 3-H_2), 2.63 (1 H, ddd, *J* 14, 9, 7) and 2.98 (1 H, dt) (4-H_2), 2.77 (1 H, ddd, *J* 14, 8, 6) and 3.77 (1 H, dt) (2-H_2), 4.16 (1 H, s, 10a-H), 6.60 (1 H, s, OH), 6.66 (1 H, d, 6-H), 6.72 (1 H, t, 8-H), 7.03 (1 H, d, 9-H) and 7.1–7.3 (6 H, complex, other ArH).

6-(3-*Chlorophenyl*)-1-*methyl*-1,2,3,4-*tetrahydro*-1,5-*benzodiazocine* **27**.—A solution of lithium tetrahydroaluminate (3.0 g, 79 mmol) and the lactam **11** (2.26 g, 5 mmol) in tetrahydrofuran (100 ml) was heated under reflux for 30 h. The work-up procedure employed for the compound **26** and chromatography [silica, toluene–ethyl acetate (9:1)] afforded the *imine* **27** (0.42 g, 30%) as a colourless oil (Found: C, 71.9; H, 6.2; N, 9.6. $C_{17}H_{17}ClN_2$ requires C, 71.7; H, 6.0; N, 9.8%); λ_{max}(95% EtOH)/nm 211 (ε 37 600 dm^3 mol^{-1} cm^{-1}), 242 (20 300), 262sh (12 000) and 365 (2700); ν_{max}(Nujol)/cm^{-1} 1610 (C=N); δ_H(60 MHz, $CDCl_3$) 1.2–2.2 (2 H, m, CCH_2C), 2.6–4.2 (4 H, m, 2 × CH_2), 3.9 (3 H, s, Me) and 6.3–7.8 (8 H, m, ArH); *m*/*z* 286, 284 (M^+, 27%, 70%), 271, 269 (M^+ − Me, 6, 17), 257, 255 (M^+ − H − C_2H_4, 35, 100), 244, 242 (10, 50) and 173 (M^+ − C_6H_4Cl, 15).

6-(3-*Chlorophenyl*-1-*methoxycarbonyl*-5-(p-*tolylsulphonyl*)-1,2,3,4,5,6-*hexahydro*-1,5-*benzodiazocine* **28**.—A solution of sodium methoxide [from sodium (1.38 g, 0.06 mol) and methanol (60 ml)] was added to the sulphonamide **11** (13.5 g, 0.03 mol) in methanol (150 ml) and the solution boiled under reflux for 0.5 h. On cooling to room temperature a precipitate was formed which was filtered off and recrystallised from acetonitrile to give the *urethane* **28** (12.78 g, 88%), m.p. 149–150 °C (Found: C, 62.2; H, 5.3; N, 6.1. $C_{25}H_{25}ClN_2O_4S$ requires C, 61.9; H, 5.2; N, 5.8%); λ_{max}(95% EtOH)/nm 231sh (ε 16 600 dm^3 mol^{-1} cm^{-1}); ν_{max}(Nujol)/cm^{-1} 1702 (C=O), 1594, 1344 (SO_2), 1163 (SO_2) and 1052 (CO); δ_H(200 MHz, $CDCl_3$) 1.9–2.3 (2 H, m, 3-H_2), 2.44 (3 H, s, CMe), 2.9 (1 H, m) and 3.47 (1 H, ddd, *J* 14, 6, 2) (4-H_2), 3.0 (1 H, m) and 3.97 (1 H, dd, *J* 13, 5) (2-H_2), 3.56 (3 H, s, OMe), 6.23 (1 H, s, 6-H), 6.57 (1 H, s, NCCCHCCl), 6.62 (1 H, d, ClCCCCH), 7.07 (1 H, m, ClCCCH), 7.31 (2 H, d, 2 × MeCC*H*), 7.77 (2 H, d, 2 × SCCH) and 7.1–7.5 (5 H, complex, other ArH); δ_C[50 MHz, $(CD_3)_2SO$] 21.0 (1 C, q, CMe), 27.0 (1 C, t, C-3), 42.3 (1 C, t, C-2), 49.5 (1 C, t, C-4), 52.4 (1 C, q, OMe), 64.4 (1 C, d, C-6), 126.1–143.7 (18 C, ArC) and 155.1 (1 C, s, C=O); *m*/*z* 331, 329 (M^+ − Ts, 30%, 100%), 302, 300 (5, 12), 242 (70), 206 (60), 125 (60) and 91 ($C_7H_7^+$, 85).

6-(3-*Chlorophenyl*)-1-*methyl*-5-(p-*tolylsulphonyl*)-1,2,3,4,5,6-*hexahydro*-1,5-*benzodiazocine* **29**.—A solution of lithium tetrahydroaluminate (0.5 g, 13 mmol) and the urethane **28** (4.85 g, 10 mmol) in dry tetrahydrofuran (20 ml) was boiled under reflux for 1 h. The work-up procedure employed for compound **26** gave an oil which on crystallisation from toluene–light petroleum (b.p. 60–80 °C) yielded the *amine* **29** (2.25 g, 51%), m.p. 148–150 °C (Found: C, 65.6; H, 5.8; Cl, 8.0; N, 6.3; S, 7.2. $C_{24}H_{25}ClN_2O_2S$ requires C, 65.4; H, 5.7; Cl, 8.0; N, 6.35; S, 7.3%); λ_{max}(95% EtOH)/nm 229sh (ε 16 600 dm^3 mol^{-1} cm^{-1}); ν_{max}(KBr disc)/cm^{-1} 1325 (SO_2) and 1160 (SO_2); δ_H(200 MHz, $CDCl_3$) 1.2–1.45 (1 H, m) and 1.5–1.7 (1 H, m) (3-H_2), 2.41 (3 H, s, NMe), 2.43 (3 H, s, CMe), 2.58 (1 H, ddd, *J* 12, 8.5, 5) and 2.73 (1 H, dt, *J* 12, 5) (2-H_2), 3.24 (1 H, ddd, *J* 15, 8.5, 3) and 3.77 (1 H, ddd, *J* 15, 6, 3) (4-H_2), 6.25 (1 H, s, 6-H), 6.63 (1 H, s, ClCCHCCN), 6.65 (1 H, m, ClCCCCH), 7.28 (2 H, d, 2 × MeCC*H*), 7.76 (2 H, d, 2 × SCCH) and 7.1–7.45 (6 H, complex, other ArH).

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