α-Pyrones. Part 4.[1] Synthesis of 3-Benzoylamino-6-(indol-2-yl)pyran-2-ones and their Rearrangement to Substituted Azepino[1,2-*a*]indole-6-ones: Unusual Neighbouring Group Participation

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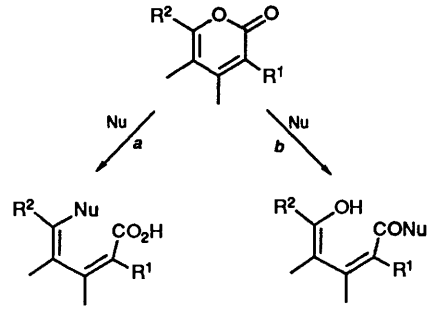
6-(2-Nitrostyryl)pyran-2-ones **3** are converted into 6-(indol-2-yl)pyran-2-ones **4** by reduction of the nitro group with triethyl phosphite and consequent addition of the nitrene intermediate to the styryl double bond. Compounds **4** undergo a rather unusual, base-catalysed, rearrangement leading to azepino[1,2-*a*]indol-6-ones **5**.

We are interested in developing new syntheses of nitrogen heterocycles through intramolecular rearrangements and/or condensations involving cyclization of nitrogen-functionalized chains on pyran-2-ones. The latter, highly reactive heterocycles, readily undergo nucleophilic attack, in some instances the attacking nucleophile giving rise to a variety of transformations as a result of reactive pyranone sites, which contain a doubly vinylogous lactone function, being present. Apart from the reaction possibilities offered by particular substituents, most nucleophiles react at the carbonyl group or at C-6, ring-opening being frequently associated with such reactions (Scheme 1).[2]

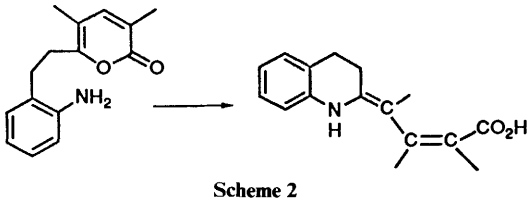


Scheme 1

The duality in action expressed by paths *a* and *b* is clearly absent when the nucleophile-containing group is part of the R^1 or R^2 substituent: in most instances, steric constraints are present which prevent more than one reactive site being involved. With a nitrogen atom as nucleophile such reactions give nitrogen-containing heterocycles.

By application of the strategy identified by path *a*, we recently developed a new synthesis of tetrahydroquinolines by generation *in situ* of 6-[2-(2-aminophenyl)ethyl]pyran-2-ones followed by nucleophilic addition of the amino group to the C-6 of the pyrone ring[3] (Scheme 2). The tetrahydroquinolines are, in turn, efficient starting materials for the synthesis of benzo[*c*]-quinolizin-1-ones.[1]

We now report that the 6-(2-nitrostyryl)pyran-2-ones can be transformed satisfactorily into 6-(indol-2-yl)pyran-2-ones which undergo an unusual, base-catalysed, rearrangement

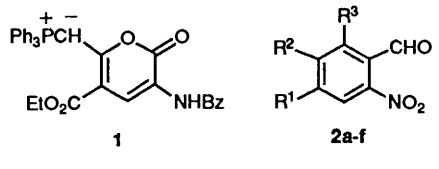


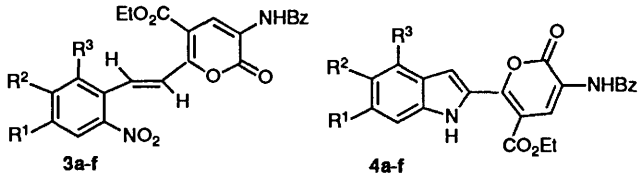
Scheme 2

eventually leading to azepino[1,2-*a*]indol-6-ones. This rearrangement entails the intramolecular cyclization of the 6-substituent on the lactone group, a cyclization which, sterically impossible as a direct reaction, is effected by participation of the 3-benzoylamino group. The azepino[1,2-*a*]indol-6-ones thus prepared represent a new family of compounds, their substitution pattern not being encountered earlier in the literature. Although such compounds are potentially interesting from both a theoretical and practical point of view (*e.g.* as seven-membered ring homologues of biologically active benzopyrrolizinones)[4] little effort has been devoted to their synthesis:[5] thus, low yields of azepino[1,2-*a*]indol-6-ones result from the photolysis of acridine *N*-oxides[6] or thermal rearrangement of 2-(2-methoxybenzyl)phenyl azides.[7]

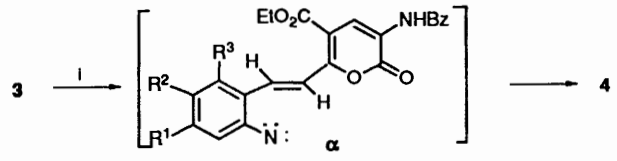
Results and Discussion

The preparation of 6-(2-nitrostyryl)pyran-2-ones **3a–f** by reaction of ethyl 3-benzoylamino-2-oxo-6-triphenylphosphoranylidenemethyl-2*H*-pyran-5-carboxylate **1** with the appropriate 2-nitrobenzaldehydes **2** has already been described.[3] Compounds **3a–c** are known and have the *E*-configuration which was also assigned to new products **3d**, **e** by analogy (superimposition of aromatic and vinyl signals made impossible a clear interpretation of the spectra) and confirmed for **3f** (which shows a NMR coupling constant of 15.1 Hz). With the aim of producing an electrophilic nitrogen species for intramolecular condensation, compounds **3a–f** were reduced with boiling triethyl phosphite (TEP), a reagent able, by reduction of nitro groups, to generate nitrenes *via* the nitroso function.[8–12] As depicted in Scheme 3, the 6-(indol-2-yl)pyran-2-ones **4a–f**





a, $R^1 = R^2 = R^3 = H$; **b**, $R^1 = R^2 = MeO$, $R^3 = H$; **c**, $R^1—R^2 = OCH_2O$, $R^3 = H$; **d**, $R^1 = R^2 = H$, $R^3 = C$:; **e**, $R^1 = F$, $R^2 = R^3 = H$; **f**, $R^1 = R^2 = H$, $R^3 = MeO$



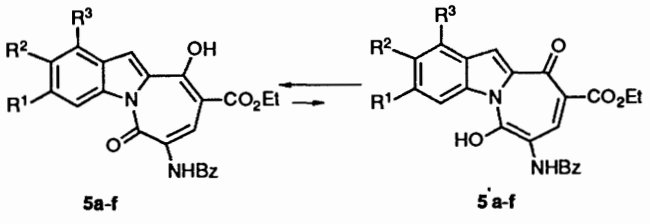
Scheme 3 *Reagents and conditions:* i, TEP, reflux

were formed (27–84%) by addition of nitrene to the styryl double bond.

The indolylpyranones **4a–f** were fully characterized on the basis of their analytical and spectroscopic data: carbonyl absorption in the IR region at 1670, 1690 and 1720 cm^{-1} was assigned to amide, ester and lactone groups, respectively. The correspondence with similar structures is good.[3] In the ^1H NMR spectra a doublet at δ *ca.* 7.2–7.5 (J 1.1–1.5 Hz, indolyl 3-H)[13] is coupled with an exchangeable proton signal at δ *ca.* 11.7–11.9 (indole NH); moreover, a singlet at δ 8.5–9.0 and an exchangeable proton signal at δ 8.5–9.8 are associated with the pyranone 4-H and NHCO.

Although nitrogen-containing heterocycles such as indoles are known to be formed in intramolecular reactions of nitrene and double bonds, the preparative value of such reactions is small because of the low product yields.[8–11] In our work however, for compounds **3**, classified as doubly vinylogous β-acyl-2-nitrostyrenes, low yields (27–29%) were obtained only for compounds **4a**, **b**, all the others being quite satisfactory.

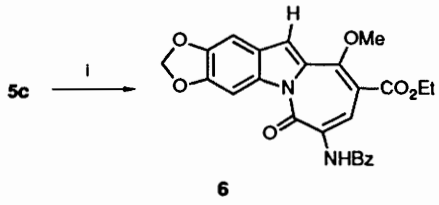
That compounds **4** would undergo intramolecular condensation upon treatment with base seemed likely because of the presence of a nucleophilic centre, the readily deprotonable indole NH, in close proximity to the electrophilic pyran-2-one moiety. The geometrical constraints of the molecule being taken into account, it appeared that a 5-ethoxycarbonyl substituted compound would be likely to give benzopyrrolizinones. It was, therefore, surprising that on reaction with anhydrous potassium carbonate in refluxing acetonitrile compounds **4a–f** were smoothly converted into the corresponding azepino[1,2-*a*]indoles **5a–f** (50–80%).



a, $R^1 = R^2 = R^3 = H$; **b**, $R^1 = R^2 = MeO$, $R^3 = H$; **c**, R^1—$R^2 = OCH_2O$, $R^3 = H$; **d**, $R^1 = R^2 = H$, $R^3 = Cl$; **e**, $R^1 = F$, $R^2 = R^3 = H$; **f**, $R^1 = R^2 = H$, $R^3 = MeO$

The products were identified spectroscopically (ν_{max}/cm^{-1} 1620–1640 and 1660–1680 corresponding to the amide, ester and the lactam carbonyl groups, respectively; 3400–3380 and 3580–3570 cm^{-1} NH and OH groups). The ^1H NMR spectra show singlets at δ 7.9–8.1 and 9.4 corresponding to 11-H and 8-H, respectively, a signal at δ 8.5–9.0 associated with 4-H (in fair agreement with the literature)[6,7] and two exchangeable signals at δ 9.4 and 14.3 (NH and OH). All these spectroscopic data are consistent with the proposed structure. Further structural confirmation was offered by a NOESY experiment on **5d** in which the close spatial proximity of 11-H to the OH group was demonstrated. This result rules out, at least when the compound is in solution, the tautomeric structure **5'**.

As expected, compound **5c** reacted with diazomethane in tetrahydrofuran to afford the 10-methoxy derivative **6** (Scheme 4) whose structure was confirmed from its ^1H NMR spectrum: this lacked the exchangeable proton signal at δ 14.3 which was, instead, replaced by a new singlet at δ 4.0. A NOESY experiment substantiated the proximity of the methoxy group both to 11-H and to the ethoxycarbonyl group.



Scheme 4 *Reagent and conditions:* i, CH_2N_2, THF

As far as the mechanism of the rearrangement of compounds **4** into **5** is concerned, the following applies. The formation of the final products is formally the result of amidation between the indole NH and the pyranone lactone group. Direct reaction being sterically prevented (see above), the sequence depicted in Scheme 5 provides a reasonable reaction mechanism. Under the action of the base (producing the anion **I**) the lactone moiety rearranges, with participation of the neighbouring benzoylamino group, to an oxazolone ring (intermediate **II**) which is actively involved in the translactonization. Clearly, the final outcome of the rearrangement is made possible by the conformational mobility of the newly formed chain linked to C-2 of the indole ring and facilitated by the greater reactivity of the oxazolone ring with respect to the pyranone. Protonation of **IV** affords the final products. We were unable to isolate the intermediate azalactone, although this is not surprising because intermediate **II** is highly reactive and its equilibrium with the more stable pyranone structure **I** is shifted in its favour only as a consequence of the transfomation into the final product. Indeed, by IR monitoring of the reaction a labile intermediate was detected by absorption at 1740 cm^{-1} (conjugated oxazolones).[14] The same intermediate was detected by TLC in the form of a red spot, a colour generally associated with highly conjugated oxazolones.[1,14] Isolation of this intermediate failed since it reverts to starting material during work-up.

Few translactonization involving neighbouring acylamino groups are known to us.[15,16] A new and characterizing feature of the present rearrangement is that the first step, although not favoured in itself, is brought to completion by an irreversible cyclization of the labile intermediate. As far as the competition between the expected condensation involving the ester group and the observed reaction course is concerned, two factors may be responsible, *i.e.* the greater reactivity of the lactone group with respect to ester and the likely greater acidity of the benzoylamino group (which is essentially a vinylogous imide) over that of the indole hydrogen.

Experimental

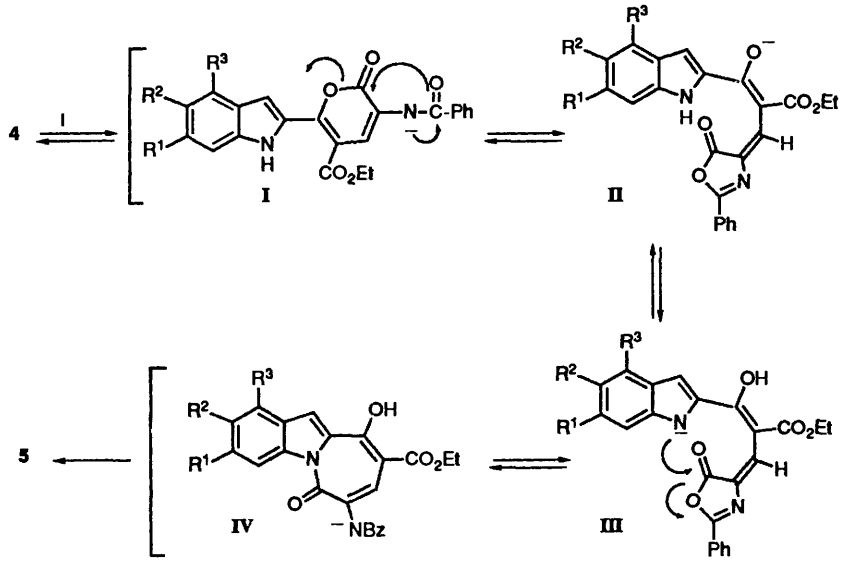
M.p.s were determined with Büchi 510 (capillary) apparatus. The IR spectra were recorded on a SP Pye Unicam SP3-200S Philips spectrophotometer. NMR spectra were performed on Bruker AC 200 instrument with the solvent indicated. *J*-Values are given in Hz. Mass spectra data were performed on a Varian MAT IH COS 50 instrument using electron-impact ionization techniques. Column chromatography was performed on silica gel using Kieselgel 60 (Merk).

2-Nitrobenzaldehydes **2a–d** were commercial products. 4-Fluoro-2-nitrobenzaldehyde **2e**,[17] 2-methoxy-6-nitrobenzaldehyde **2f**,[18] ethyl 3-benzoylamino-2-oxo-6-triphenylphosphoranylidenemethyl-2*H*-pyran-5-carboxylate **1**[19] and ethyl 3-benzoylamino-6-(2-nitrostyryl)-2-oxo-2*H*-pyran-5-carboxylates **3a–c**[3] are known compounds.

Table 1 Reaction conditions and analytical data for compounds **4–5**

Reagent	Conditions		Column chromatography[a] eluent (ratio)	Product (formula)	Yields (%)	M.p. (°C) (solvent)	Found % (Required)		
	Time (h)	Base (mmol)					C	H	N
3a	10	—	a (2:3)	**4a** ($C_{23}H_{18}N_2O_5$)	27	190–192 (CH_2Cl_2–Pr^i_2O)	68.4 (68.64)	4.66 4.50	6.75 6.96)
3b	8	—	a (2:3)	**4b** ($C_{25}H_{22}N_2O_7$)	29	226 (decomp.) (TEP)	64.7 (64.93	4.69 4.79	6.01 6.06)
3c	2	—	b (1:4)	**4c** ($C_{24}H_{18}N_2O_7$)	66	233 (decomp.) (TEP)	64.6 (64.57	4.01 4.06	6.09 6.27)
3d	4	—	b (1:9)	**4d** ($C_{23}H_{17}ClN_2O_5$)	68	205–206 (TEP)	63.0 (63.23	3.92 3.92	6.68 6.41)
3e	3	—	b (1:9)	**4e** ($C_{23}H_{17}FN_2O_5$)	43	199–200 (CH_2Cl_2–Pr^i_2O)	65.85 (65.79	4.26 4.08	6.38 6.66)
3f	4	—	a (1:2.5)	**4f** ($C_{24}H_{20}N_2O_6$)	84	210–211 (TEP)	66.55 (66.80	4.47 4.67	6.68 6.48)
4a	24	10	—	**5a** ($C_{23}H_{18}N_2O_5$)	50	205–206 (CH_2Cl_2–Pr^i_2O)	68.5 (68.64	4.28 4.50	6.72 6.96)
4b	16	10	b (1:4)	**5b** ($C_{25}H_{22}N_2O_7$)	50	229–231 (CH_2Cl_2–Pr^i_2O)	64.6 (64.93	4.56 4.79	5.95 6.06)
4c	10	2.5	—	**5c**[b] ($C_{24}H_{18}N_2O_7$)	59	227–229 (CH_2Cl_2–Pr^i_2O)	64.6 (64.57	4.31 4.06	6.42 6.27)
4d	13	2.5	—	**5d** ($C_{23}H_{17}ClN_2O_5$)	80	234–236 (CH_2Cl_2–Pr^i_2O)	63.0 (63.23	3.78 3.92	6.33 6.41)
4e	12	2.5	a (1:2.5)	**4e** ($C_{23}H_{17}FN_2O_5$)	60	191–193 (CH_2Cl_2–Pr^i_2O)	65.9 (65.79	3.93 4.08	6.57 6.66)
4f	28	2.5	b (1:4)	**5f** ($C_{24}H_{20}N_2O_6$)	40	230–231 (CH_2Cl_2–Pr^i_2O)	66.6 (66.80	4.85 4.67	6.70 6.48)

[a] a, AcOEt–C_6H_{12}; b, AcOEt–C_6H_6. [b] *m/z* **5c**: 446 (M^+, 28.5), 400 (14.1), 341 (2.81), 295 (9.41) and 105 (100).



Scheme 5 *Reagent and conditions:* i, K_2CO_3, MeCN, heat

Ethyl 3-*Benzoylamino*-6-(2-*chloro*-6-*nitrostyryl*)-2-*oxo*-2H-*pyran*-5-*carboxylate* **3d**.—Compound **3d** was prepared as described for **3a**;[3] reaction time 2 h; yield 91%; m.p. 211 °C (Found: C, 58.95; H, 3.6; N, 5.8. $C_{23}H_{17}ClN_2O_7$ requires C, 58.91; H, 3.65; N, 5.97%); ν_{max}(Nujol)/cm^{-1} 3400 (NH), 1730 (CO pyrone), 1705 (CO_2Et) and 1690 (CONH); δ_H($CDCl_3$) 1.4 (3 H, t, *J* 7.1, Me), 4.4 (2 H, q, *J* 7.1, CH_2), 7.4–7.9 (10 H, m, H arom. and CH=CH), 8.7 (1 H, s, NH D_2O-exchangeable) and 8.9 (1 H, s, 4-H).

Ethyl 3-*Benzoylamino*-6-(4-*fluoro*-6-*nitrostyryl*)-2-*oxo*-2H-*pyran*-5-*carboxylate* **3e**.—Compound **3e** was prepared as described for **3a**;[3] reaction time 10 h; yield 90%; m.p. 192 °C (Found: C, 60.8; H, 3.6; N, 6.1. $C_{23}H_{17}FN_2O_7$ requires C, 61.13; H, 3.79; N, 6.19%); ν_{max}(Nujol)/cm^{-1} 3400 (NH), 1730 (CO pyrone), 1700 (CO_2Et) and 1680 (CONH); δ_H($CDCl_3$) 1.4 (3 H, t, *J* 7.2, Me), 4.4 (2 H, q, *J* 7.2, CH_2), 7.3–8.0 (10 H, m, H arom. and CH=CH), 8.7 (1 H, s, NH D_2O-exchangeable) and 8.9 (1 H, s, 4-H).

Ethyl 3-*Benzoylamino*-6-(2-*methoxy*-6-*nitrostyryl*)-2-*oxo*-2H-*pyran*-5-*carboxylate* **3f**.—Compound **3f** was prepared as described for **3a**;[3] reaction time 10 h; yield 89%; m.p. 170 °C (Found: C, 62.3; H, 4.1; N, 5.8. $C_{24}H_{20}N_2O_8$ requires C, 62.06; H, 4.34; N, 6.02%); ν_{max}(Nujol)/cm^{-1} 3400 (NH), 1730 (CO pyrone), 1700 (CO_2Et) and 1670 (CONH); δ_H($CDCl_3$) 1.4 (3 H, t, *J* 7.1, Me), 4.0 (3 H, s, OMe), 4.4 (2 H, q, *J* 7.1, CH_2), 7.1–8.0 (9 H, m, H arom. and CH=), 8.1 (1 H, d, *J* 16.1, CH=), 8.7 (1 H, s, NH D_2O-exchangeable) and 8.9 (1 H, s, 4-H).

Table 2 Spectroscopic data for compounds **4**

	ν_{max}/cm^{-1} [a]		$\delta_H(CDCl_3)$, (*J*/Hz)					
Product	NH	C=O	NH_{ind}	4-H_{pyr}	NHCO	Aromatic protons	3-H_{ind}	Other protons
4a	3370, 3250	1720, 1690, 1660	11.7	9.0	8.6	8.0–7.1	*b*	4.5 (2 H, q, *J* 7.1, CH_2), 1.5 (3 H, t, *J* 7.1, Me)
4b	3400, 3270	1720, 1690, 1670	11.75[c]	9.0	8.5	7.9–7.5, 7.0, 6.9	7.48[c]	4.5 (2 H, q, *J* 7.1, CH_2), 3.95, 3.92 (6 H, two s, OMe), 1.5 (3 H, t, *J* 7.1, Me)
4c	3450, 3250	1720, 1690, 1670	11.7[c,d]	8.5	9.8	8.0–7.5, 7.1, 7.0	7.2[c]	4.4 (2 H, q, *J* 7.1, CH_2), 6.0 (2 H, s, OCH_2O), 1.3 (3 H, t, *J* 7.1, Me)
4d	3400, 3250	1710, 1690, 1670	11.9	9.0	8.6	8.0–7.1	*b*	4.5 (2 H, q, *J* 7.1, CH_2), 1.5 (3 H, t, *J* 7.1, Me)
4e	3350, 3300	1720, 1690, 1670	11.7	9.0	8.6	8.0–6.8	*b*	4.5 (2 H, *q*, *J* 7.1, CH_2), 1.5 (3 H, t, *J* 7.1, Me)
4f	3380, 3280	1710, 1680, 1670	11.8[d]	8.5	9.8	8.0–6.5	7.27	4.3 (2 H, q, *J* 7.2, CH_2), 3.9 (3 H, s, OMe), 1.3 (3 H, t, *J* 7.2, Me)

[a] Nujol. [b] Overlapped with aromatic protons. [c] **4b**: d, *J* 1.1; **4c**: d, *J* 1.5. [d] [$^2H_6$]-DMSO.

Table 3 Spectroscopic data for compounds **5**

	ν_{max}/cm^{-1} [a]		$\delta_H/(CDCl_3)$ (*J*/Hz)						
Product	OH, NH	C=O	OH	8-H	NHCO	4-H	11-H	Aromatic	Other protons
5a	3580, 3390	1680, 1630	14.3	9.42	9.39	9.01[b]	8.0	8.0–7.5	4.5 (2 H, q, *J* 7.1, CH_2), 1.5 (3 H, t, *J* 7.1, Me)
5b	3570, 3380	1660, 1620	14.3	9.37	9.31	8.56	7.8	8.0–7.5, 7.09 (s, 1-H)	4.5 (2 H, q, *J* 7.1, CH_2), 4.04, 3.98 (6 H, two s, OMe), 1.5 (3 H, t, *J* 7.1, Me)
5c	3580, 3380	1670, 1640	14.3	9.40	9.32	8.50	7.8	8.0–7.5, 7.09 (s, 1-H)	4.5 (2 H, q, *J* 7.1, CH_2), 6.1 (2 H, s, OCH_2O), 1.5 (3 H, t, *J* 7.1, Me)
5d	3570, 3400	1670, 1630	14.3	9.44	9.33	8.94–8.89[c]	8.1	8.0–7.5	4.5 (2 H, q, *J* 7.1, CH_2), 1.5 (3 H, t, *J* 7.1, Me)
5e	3580, 3380	1660, 1640	14.3	9.40	9.30	8.74[d]	8.0	8.0–7.2	4.5 (2 H, q, *J* 7.1, CH_2), 1.5 (3 H, t, *J* 7.1, Me)
5f	3580, 3390	1680, 1630	14.3	9.41	9.37	8.57[e]	8.1	8.0–6.8	4.5 (2 H, q, *J* 7.1, CH_2), 4.0 (3 H, s, OMe), 1.5 (3 H, t, *J* 7.1, Me)

[a] Nujol. [b] d, *J* 7.3. [c] m. [d] dd, *J* 2.2, 11.3. [e] d, *J* 8.7.

General Procedure for the Preparation of Ethyl 3-Benzoylamino-6-(indol-2-yl)-2-oxo-2H-pyran-5-carboxylates **4**.—6-(2-Nitrostyryl)pyran-2-one **3** (4.3 mmol) was refluxed in anhydrous TEP (30 cm^3) under nitrogen for the time indicated in Table 1. After cooling of the reaction mixture, compounds **4b–d, f** separated as pure yellow–orange products. In the case of **4a, e** after solvent evaporation the crude mixture was recrystallized from CH_2Cl_2–Pr^i_2O to yield pure products. The mother liquor of crystallized compound **4** was chromatographed on a silica gel column to afford a further crop of pure **4** after recrystallization from CH_2Cl_2–Pr^i_2O. Reaction conditions and analytical data are given in Table 1, and spectroscopic data in Table 2.

General Procedure for the Preparation of Ethyl 7-Benzoylamino-10-hydroxy-6-oxo-6H-azepino[1,2-a]indole-9-carboxylate **5**.—The indole **4** (2.5 mmol) and anhydrous K_2CO_3 (2.5–10 mmol) were stirred, under nitrogen, in anhydrous MeCN (50 cm^3) and then heated under reflux when the mixture turned red. The reaction was monitored by TLC: the initially formed red spot turned yellow, the colour of the final product, in the time indicated in Table 1. After cooling, the reaction mixture was acidified with AcOH to pH 3–4, the solvent removed and the crude sticky product taken up in water (15 cm^3) and extracted with CH_2Cl_2 (3 × 15 cm^3). The combined extracts were washed with water (20 cm^3), dried (Na_2SO_4) and concentrated, and the residue either crystallized or chromatographed on a silica gel column to give a pure yellow solid. Reaction conditions and analytical data are given in Table 1, and spectroscopic data in Table 3.

Ethyl 7-Benzoylamino-10-methoxy-2,3-methylenedioxy-6-oxo-6H-azepino[1,2-a]indole-9-carboxylate **6**.—Azepino[1,2-*a*]indole **5c** (100 mg, 2.23 mmol) was stirred in anhydrous THF (15 cm^3) and the solution cooled to 0 °C. Addition of a solution of CH_2N_2 in Et_2O (10.66 g dm^{-3}, 5 cm^3) gave immediate formation of the title compound **6**. The solvent was removed and recrystallization of the residue from CH_2Cl_2–C_5H_{12} gave the product **6** (85 mg, 83%) as red crystals; m.p. 110 °C (Found: C, 65.45; H, 4.1; N, 5.9. $C_{25}H_{20}N_2O_7$ requires C, 65.35; H, 4.35; N, 6.10%); ν_{max}(Nujol)/cm^{-1} 3370 (NH), 1720 (CO_2Et), 1690 (CON) and 1660 (CONH); $\delta_H(CDCl_3)$ 1.5 (3 H, t, *J* 7.1, Me), 4.0 (3 H, s, OMe), 4.4 (2 H, q, *J* 7.1, OCH_2), 6.1 (2 H, s, OCH_2O), 7.1 (1 H, s, 1-H), 7.48 (1 H, s, 11-H), 7.5–8.0 (5 H, m, H arom.), 8.5 (1 H, s, 4-H), 9.1 (1 H, s, 8-H) and 9.5 (1 H, s, NH D_2O-exchangeable).

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