Umpoled Vilsmeier reagents. The chemistry of aminochlorocarbenes derived from Vilsmeier reagents by the action of bases[1]

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Vilsmeier reagents such as *N*-methyl-*N*-phenylchloroiminium chloride are readily deprotonated by *tert*-amines even in $POCl_3$ solution. The resulting transient intermediates, aminochlorocarbenes, are nucleophilic (*i.e.* umpoled Vilsmeier reagents) and are trapped with electrophiles. In this way dimers [1,2-bis(*N*-methylanilino)-1,2-dichloroethanes] 3, 'trimers' (indolo[3,2-*b*]quinolininium chlorides) 4 and 5, 'tetramers' (2,2′-bis-indoles) 11 and isatins 9 and 10 are accessible in one-pot processes from the formanilide.

Introduction

Vilsmeier reagents have been used extensively in organic synthesis for over 70 years.[2] These electrophilic chloromethyleneiminium salts are efficient and powerful reagents for the formylation of electron-rich compounds such as anilines, enols (tautomers of the corresponding ketones) and enamines and alkenes. Furthermore they serve as versatile building blocks in constructing a wide variety of heterocyclic rings.[3] In past publications, for example, we have shown that Vilsmeier reagents derived from *N*-substituted formanilides are valuable precursors to quinolines using both the 'Vilsmeier approach' and the 'reverse Vilsmeier approach'.[3,4] More recently, the synthesis of 1,5-diazocines was effected unexpectedly by the formylation of *tert*-anilines with *N*-alkylformanilide-derived iminium species.[5,6] It was this study of the applications of the Vilsmeier reagents in the synthesis of medium-sized heterocycles that lead to our current discovery of their considerable acidity and ready deprotonation to give aminochlorocarbenes, in effect, the umpolung of Vilsmeier reagents.

Results and discussion

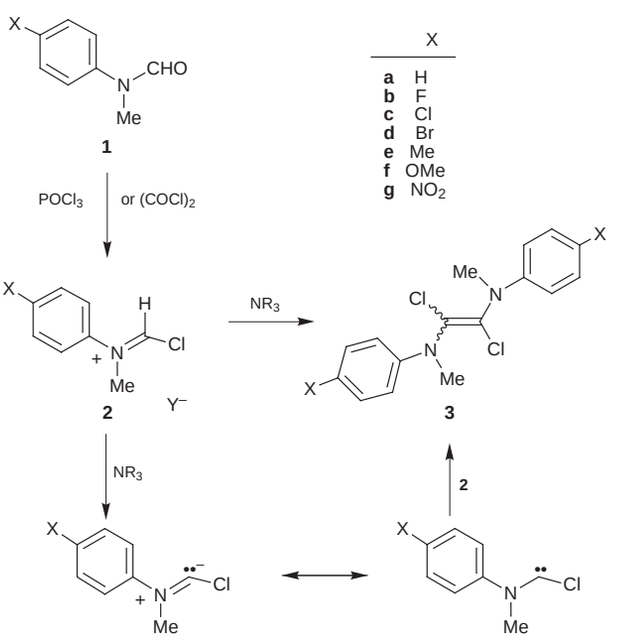
During the above mentioned study, which involved the Vilsmeier formylation of a *tert*-aniline, minor amounts of by-products were noticed that could best be explained by deprotonation of the Vilsmeier reagent to give an aminochlorocarbene. In other words, the *tert*-aniline was acting as a base, even in $POCl_3$ solution! As a result, we examined the effect of various bases upon different varieties of Vilsmeier reagents **2** derived from *N*-methylformanilides **1**. Products derived from interaction of two (dimers), three (trimers) or four molecules (tetramers) of the Vilsmeier reagent were observed in specific cases. We therefore undertook a systematic study of the chemistry of Umpoled Vilsmeier reagents as a function of base used, substituent and reaction conditions.

Dimer formation

Vilsmeier reagents **2** (Y = Cl) generated by the action of oxalyl chloride on an *N*-methylformanilide in THF solution, react with Hünig's base to give 1,2-dichloro-1,2-diaminoethenes **3** (dimers), often in good yield. Indeed, Böhme and Sutoyo[7] noted this reaction for simple formamides some years ago in an uncited but significant note. Some examples are collected in Table 1. This reaction is best explained by deprotonation of the Vilsmeier reagent to give the nucleophilic aminochlorocarbene

Table 1 The formation of dimers **3** from formanilides **1**

X	Base	Yield **3** (%)
H	Hünig's	56
F	Hünig's	81
Cl	Hünig's	54
Cl	Et_3N	17
Cl	Bu^n_3N	23
Cl	pyridine	22
Br	Hünig's	49



Scheme 1

followed by further reaction at the nucleophilic carbon by another molecule of Vilsmeier reagent (Scheme 1).

The same reaction occurs when a formanilide **1** in $POCl_3$ solution is treated with a *tert*-amine, though a mixture of products results. When a bulky base was used, the dimer **3** was formed optimally. Bulky bases are probably slower in the deprotonation step and are less reactive towards both the solvent and the Vilsmeier reagent and are thus more selective for dimer formation. Since the dimers **3** react efficiently with further Vilsmeier reagent (see below) the selectivity is made more significant. The dimers **3** are unstable compounds that decompose slowly on storage. Indeed, when electron-releasing groups were present (*e.g.* X = Me or OMe) the products rapidly

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Table 2 The formation of trimers **4** and **5** from formanilides **1** and dimers **3**

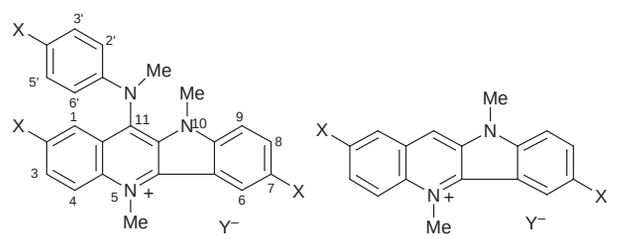
ArNMeCHO **1** (X)	Extra amide	Dimer **3** (X)	*t*/h	Yield **4** (%)	Yield **5** (%)
H	DMF	—			8
F	—	—		38	
F	DMF	—	5		30
F	DMF	—	24		75
F	MFA[a]	—	22	30	17
F	FMFA[b]	—	2	30	6
F	MeOMFA[c]	—	24	34	23
F	DEF[d]	—	24		20
F	NFM[e]	—	24		68
—	DMF	F	6		54
Cl	—	—		36	6
Cl	—	—	16	40	
Cl	—	—	23	31	
—	DMF	Cl	6		49
Me	DMF	—	24	8	
MeO	DMF	—	24		28

[a] MFA = *N*-methylformanilide. [b] FMFA = 4-fluoro-*N*-methylformanilide. [c] MeOMFA = 4-methoxy-*N*-methylformanilide. [d] DEF = diethylformamide. [e] NFM = *N*-formylmorpholine.

decomposed. Both ^{1}H and ^{13}C NMR spectroscopy showed a mixture of both *E*- and *Z*-isomers in similar ratios in the case of **3b** and **3c**.

'Trimer' formation

When a Vilsmeier reagent generated from an *N*-alkylformanilide in $POCl_3$ solution, is treated with a *tert*-amine, a red colour develops and on chromatographic work-up, this red-coloured compound is firmly retained on silica after removal of other products such as the dimer **3**. Elution with methanol yielded a crystalline red salt which proved to be the indolo[3,2-*b*]-quinoline 'trimer' **4** or **5**. We found that these products were



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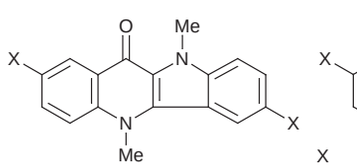
5



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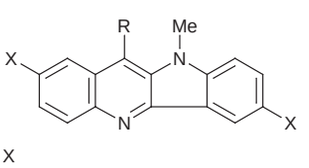
a H
b F
c Cl
d Br
e Me
f OMe
g NO_2



7 R = -$NMeC_6H_4$-4-X
8 R = H

more readily isolated by precipitation of the beautifully crystalline PF_6^- salts from aqueous quenched reaction mixtures by addition of ammonium hexafluorophosphate. Furthermore, when a preformed dimer was treated with a Vilsmeier reagent in $POCl_3$ solution, the trimer was formed more efficiently, the whole process being potentially a one-pot process, carried out directly from the *N*-alkylformanilide (Table 2). However, a closer examination of the NMR spectral data of the crude salt revealed that on some occasions, a mixture of the two indoloquinolinium salts **4** and **5** was formed. In the majority of cases,

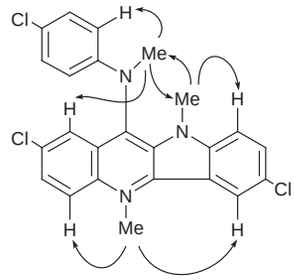


Fig. 1

treatment of an *N*-methylarylamide with $POCl_3$ and base gave mostly trimer **4** with minor amounts of the analogue **5**, recrystallisation or chromatography yielding the pure major product. When 4-methoxy-*N*-methylformanilide was converted into the trimer, however, the product proved to be solely the 11-unsubstituted analogue **5**.

The structure of the trimers **4** was evident from their spectroscopy and from subsequent chemistry. Thus electrospray mass spectroscopy confirmed the molecular ion masses, while ^{1}H and ^{13}C NMR spectroscopy defined the overall indoloquinoline structure, showing the three formanilide-derived units, with one low field methyl resonance, characteristic of the quinolinium salt. Two of the three aryl groups also showed extra substitution. Difference nOe spectroscopy by irradiation of the methyl groups confirmed the contiguity of the units (Fig. 1). Finally, hydrolysis of a typical salt **4e** with aqueous sodium hydroxide removed the pendant methylanilino group in the indoloquinolinium 11-position to give the corresponding quinolone **6e** in high yield.

As the Vilsmeier reagent used for dimer formation can be different from that used to convert the dimer to the trimer, the potential for mixed structures is evident. Thus, for example, the dimer **3c** on reaction with an aliphatic Vilsmeier salt such as the DMF-derived reagent might be expected to form the 11-dimethylamino analogue of the trimer **4c**. To our surprise, while the reaction is effective, irrespective of the aliphatic Vilsmeier reagent used, the product proved in all cases studied to be the 11-unsubstituted indoloquinoline **5**, in this case **5c** (Table 2).

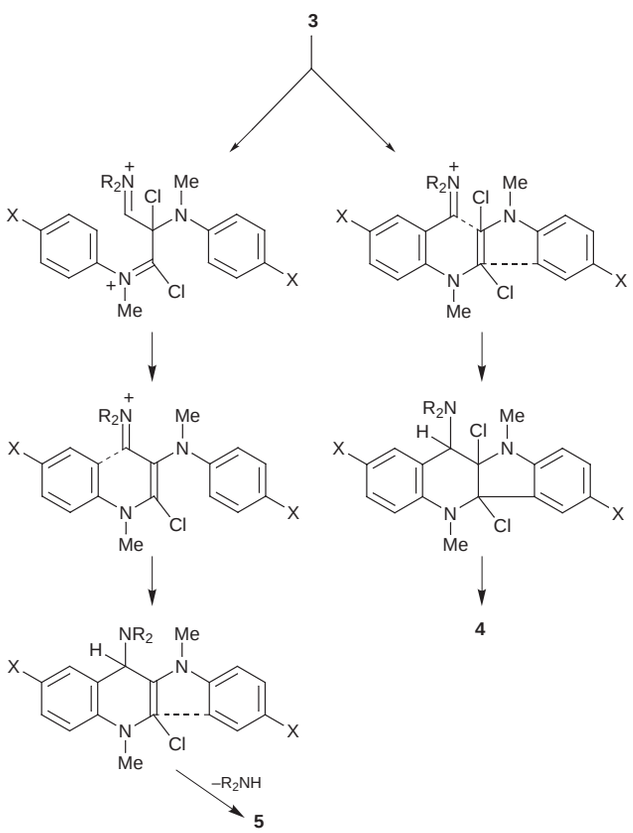
Since this indoloquinoline ring system is both known as a natural product (*e.g.* cryptolepine[8] is the 10-desmethyl derivative of **5**, X = H) and has considerable pharmaceutical interest, as an antihypoglycemic agent, an antimalarial and particularly as a potential anti-cancer agent by DNA intercalation,[9] we sought a method for dealkylation to allow generation of the parent derivatives **7** and **8**. Such methods are known utilising triphenylphosphine and sodium iodide[10] and were effective. However, a very recent demethylation method utilising refluxing pyridinium chloride[11] proved optimally effective. The compounds **4**, **5** and **7** as iodides and **8** as the hydrochloride were tested (see below) by DNA titration as potential intercalators, proving to be very effective.

What is the mechanism of formation of these interesting indoloquinolines? Why are 11-substituted derivatives formed in some cases but 11-unsubstituted or mixed products in others? Both electronic and steric factors appear to influence the course of the reactions. We suggest that as regards electrophilic attack, the dimers **3** are bidentate, bearing both an enamine and a dialkylaniline moiety and that the initial site of formylation is critical in determining the ultimate product formed (Scheme 2). When ring attack initiates the process then trimer **4** is formed while enaminic attack leads to trimer **5**. The nature of the ring substituents exerts a delicate balance upon this dichotomy. Thus, a 4-OMe group in the aryl rings of the dimer **3** is electron withdrawing (inductively) at the 2-position where electrophilic attack by Vilsmeier reagent would occur, but electron-releasing at the enaminic position (mesomerically). This should lead *via* enamine attack to the 11-unsubstituted indoloquinolines. The

Table 3 Formation of isatins **9**, **10** and others from *N*-methylformanilides

N-Methylformanilide	Electrophile	Isatin	Yield (%)	Mp (°C)	Lit. mp (°C)	Ref.
1a	Br_2	**9a**	62	133–135	134	15
1b		**9b**	62	148–149	151	16
1b	TFA		48[a]			
1c	Br_2	**9c**	65	169–170	170–171	17
			78[b]			
			70[c]			
	TFA		45[d]			
	$SOCl_2$		55			
	$POCl_3$		34[e]			
	PhN_2PF_6		59[f]			
1d	Br_2	**9d**	71	167–168	170–172	18
1e		**9e**	58	150–152	152	18
1f		**9f**	66	168–170	170–171	18
1g		**9g**	34	201–202	202–203	19
2-$ClC_6H_4NMeCHO$		1-Me-7-Cl-isatin	20	156	155	18
			40[g]			
3-$ClC_6H_4NMeCHO$		1-Me-6-Cl-isatin	11	165–168	167	20
N-formylindoline		**10**	79	205–206	206–208	21

[a] Conditions: 90 min at 50 °C. [b] 2 h at RT. [c] 24 h at RT. [d] 90 min at 50 °C. [e] 3 h at RT. [f] 2.5 h at RT. [g] From isolated dimer.

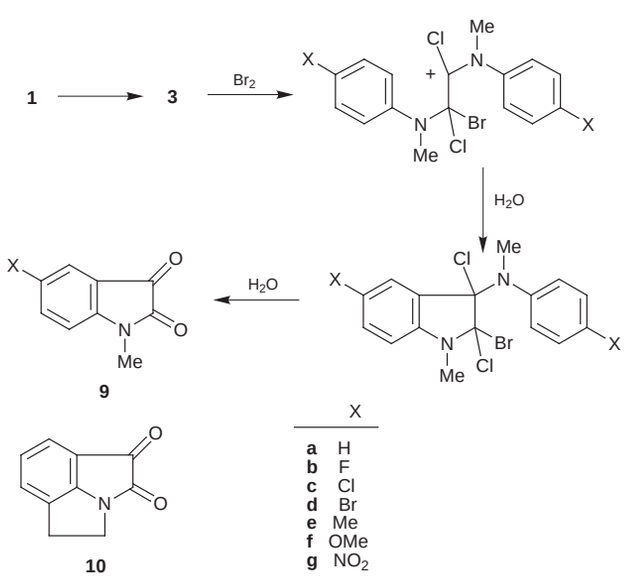


Scheme 2

halo-substituents would however not show the latter activation. Steric factors may be critical in the apparent difference between aliphatic and aromatic Vilsmeier reagent behaviour upon the dimers **3**. We have found elsewhere that *N*-methylformanilide-based Vilsmeier reagents are much more sterically demanding in regioselective formylations compared to their aliphatic analogues.[6]

Isatin formation

The above mechanisms (Scheme 2) require that either a quinoline or else an indole ring (equally feasible as a first cyclisation) is first formed in the above trimer **4/5** formation. We have frequently observed the former but the latter is not a common process.[3] In order to explore the possibility of forming an indole from a formanilide derivative we examined the action of various electrophiles upon the alkenes **3**. To our satisfaction, isatins **9** and **10** were formed when the dimers were treated with various non-carbon electrophiles including acid (TFA), bromine and aliphatic acid chlorides ($SOCl_2$, $POCl_3$) and benzendiazonium hexafluorophosphate, the best yields being observed utilising bromine. The reaction appears to be general insofar as the dimers are available and can be conducted as a simple, rapid (~2 h) one-pot process from the formanilide without dimer isolation. In many cases this process is the optimal route to these pharmaceutically[12] and synthetically[13] important derivatives, being more efficient and better yielding than the old Sandmeyer methods.[14] Some examples are collected in Table 3 and the proposed mechanism of isatin formation is shown in Scheme 3. Although not fully optimised,



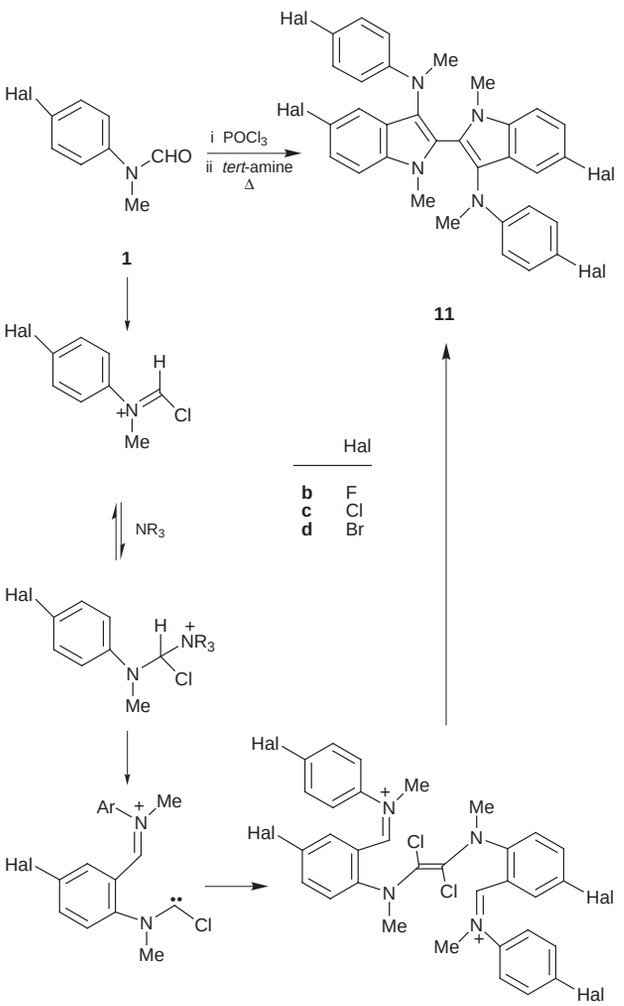
Scheme 3

ortho- and *meta*-substituted formanilides appear to be less effective than *para*-substituted isomers, possibly due to the dimer not being formed efficiently.

Tetramer formation

The 4-halo-*N*-methylformanilides in $POCl_3$ solution on treatment with bases gave, in addition to the trimer, a beautifully fluorescent, yellow product in low (5–28%) yield. Spectroscopic analysis showed the compounds to be 2,2′-bis-indoles **11**,

analogues of indigo. Indeed, these compounds in solution slowly developed a purple colour, though attempted acid hydrolysis was ineffective. DABCO appears to be the most effective base for tetramer formation (see Experimental) and a mechanism is proposed (Scheme 4) which invokes further

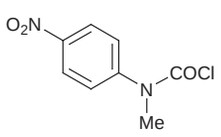


Scheme 4

involvement of an umpoled Vilsmeier reagent. 2-Formylation of the 4-halo-*N*-methylformanilides followed by proton abstraction to give a carbene, which then dimerises and cyclises appears to underlie this intriguing reaction.

Other reaction pathways

4-Nitro-*N*-methylformanilide does not give an isolable dimer and no trimer in the above reactions. It does however yield an isatin in the one-pot method (Table 3). In $POCl_3$ solution, however the only significant products on base treatment were the corresponding isatin **9** (20%) and the *N*-methyl-*N*-(4-nitrophenyl)carbamoyl chloride **12** (14%), clearly a derivative of the deprotonated Vilsmeier reagent.



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Attempts to react the dimers **3** with various dienes (tetraphenylcyclopentadienone and tetrachlorothiophene dioxide) were ineffective.

DNA intercalation studies

The potential for intercalation into DNA is easily measured by titrating a solution of the potential intercalator with buffered calf thymus DNA solution, and observing the UV spectrum after addition of each aliquot.[22] Water soluble salts are optimally used and for this purpose we converted the PF_6^- salts into the corresponding iodides with sodium iodide in acetone. The 11-unsubstituted indoloquinolinium iodides proved highly effective as intercalators and full details will be published elsewhere.

Conclusion

Vilsmeier reagents are readily deprotonated with *tert*-amines giving nucleophilic aminochlorocarbenes, the reaction even being effective in $POCl_3$ solution. From these carbenes under appropriate conditions can be made dimers [1,2-dichloro-1,2-bis(*N*-aryl-*N*-methylamino)ethenes], trimers (indolo[3,2-*b*]-quinolinium salts), isatins and tetramers [2,2′-bis-indoles]. The trimers are effective DNA intercalators, being analogues of natural products.

Experimental

Melting points, which are uncorrected, were determined using a Reichert Kofler hot-stage apparatus. Infrared spectra were obtained on a Unicam Research Series 1 FTIR instrument as KBr discs or liquid films. NMR spectra were recorded in $CDCl_3$ or [$^2H_6$]DMSO solution with $SiMe_4$ as internal standard on JEOL 270 or Varian Unity 200 spectrometers. Chemical shifts are reported in ppm while the coupling constant *J* values are in Hz. Mass spectra were measured on a Kratos MS8ORF mass spectrometer and microanalyses were carried out at Newcastle University, UK and at the Institute of Chemistry, Academia Sinica, Beijing. Thin layer chromatography (TLC) was performed with Merck silica $60F_{254}$ plates and Janssen silica (35–70 μm) was used for flash chromatography. Light petroleum refers to that of bp 60–80 °C.

General procedure for the reaction of *para*-substituted *N*-methylformanilides 1 with a base in $POCl_3$

A mixture of *para*-substituted *N*-methylformanilides **1** (20 mmol) and phosphorus oxychloride (10 cm^3) was heated at 80 °C for 10 min and then cooled in ice. To the mixture was added a base (20 mmol) dropwise with stirring. The reaction mixture was kept at 80 °C for a period of time as specified in Table 2, and was then poured into ice (*ca.* 100 g). The mixture was neutralised with aqueous NaOH (10%) to pH *ca.* 8 and extracted with chloroform (3 × 100 cm^3). After drying ($MgSO_4$) and removal of the solvent the residue was chromatographed to give the products indicated in Tables 1, 2 and 3. 1,2-Dichloro-1,2-bis(*N*-aryl-*N*-methylamino)ethene **3** was eluted with a mixture of light petroleum and ethyl acetate (10–7 : 1) and pyrroloindole **10** and 2,2′-bis-indole **11** with light petroleum and ethyl acetate (4 : 1). Indolo[3,2-*b*]quinolinium salts **4** and **5** were finally obtained by washing the column with methanol. The resulting residue was converted into the hexafluorophosphate salt by addition of NH_4PF_6 (20 mmol).

General procedure for the reaction of *para*-substituted *N*-methylformanilides 1 with oxalyl chloride and then a base

Oxalyl chloride (1.74 cm^3, 20 mmol) was added slowly to an *N*-methylformanilide (20 mmol) at ambient temperature under nitrogen with stirring. When gas evolution ceased, dry THF was added (10 cm^3) and the suspension cooled to 0–5 °C and Hünig's base (2.59 g, 20 mmol) was added dropwise. The mixture was heated at 35 °C for 1.5 h, diluted with light petroleum (~50 cm^3), filtered through a pad of silica gel, washing with light petroleum and ethyl acetate (95 : 5), and the washings evaporated to give dimer **3**.

General procedure for the reaction of *para*-substituted *N*-methylformanilides 1 with oxalyl chloride and then another Vilsmeier reagent and base

Oxalyl chloride (1.74 cm^3, 20 mmol) was added slowly to an *N*-methylformanilide (20 mmol) at ambient temperature under nitrogen with stirring. When gas evolution ceased, dry THF was added (10 cm^3) and the suspension cooled to 0–5 °C and Hünig's base (2.59 g, 20 mmol) was added dropwise. The THF was removed *in vacuo* and an amide (DMF, MFA = *N*-methylformanilide, DEF = diethylformamide or NFM = *N*-formylmorpholine) (20 mmol) and $POCl_3$ (10 cm^3) was added and the mixture heated at 80 °C for 24 h. The cooled mixture was poured onto ice and ethyl acetate (~25 cm^3) and ammonium hexafluorophosphate (3.26 g, 20 mmol) added. The red–orange precipitate of indoloquinolinium salt **5** was filtered, washed with water and diethyl ether and dried.

1,2-Dichloro-1,2-bis(*N*-methyl-*N*-phenylamino)ethene 3a. Isolated as a white solid; ν_{max}(KBr)/cm^{-1} 1596, 1496, 1110, 746, 686; δ_H($CDCl_3$) 7.17–7.30 (4H, m, ArH), 6.82–6.92 (6H, m, ArH), 3.12 (6H, s, Me).

1,2-Dichloro-1,2-bis(*N*-4-fluorophenyl-*N*-methylamino)ethene 3b. Isolated as a white solid; ν_{max}/cm^{-1} 1506, 1467, 1108, 829, 763; δ_H($CDCl_3$) 6.99–7.11 (4H, m, ArH), 6.80–6.87 (4H, m, ArH), 2.90/3.16 (6H, s, Me); δ_C($CDCl_3$) 143.3, 133.6, 129.2, 125.9, 116.0 and 37.1.

1,2-Dichloro-1,2-bis(*N*-4-chlorophenyl-*N*-methylamino)ethene 3c. Isolated as a white solid; ν_{max}/cm^{-1} 1592, 1490, 1108, 971, 891; δ_H($CDCl_3$)‡ 7.20/7.29 (4H, d, *J* 8.9, ArH), 6.72/6.79 (4H, d, *J* 8.9, ArH), 3.17/2.89 (6H, s, Me); δ_C($CDCl_3$)‡ 144.2/143.2, 133.5/135.85, 129.15/129.0, 125.7/125.5, 115.8/116.2 and 37.1/37.7.

1,2-Dichloro-1,2-bis(*N*-4-bromophenyl-*N*-methylamino)ethene 3d. Isolated as a white solid; ν_{max}/cm^{-1} 1587, 1488, 1257, 1110, 811; δ_H($CDCl_3$) 7.28–7.42 (4H, m, ArH), 6.86–94 (4H, m, ArH), 3.16 (6H, s, Me).

2,7-Difluoro-5,10-dimethyl-11-(*N*-4-fluorophenyl-*N*-methylamino)-10*H*-indolo[3,2-*b*]quinolinium hexafluorophosphate 4b (Y = PF_6). Mp 254–257 °C (from methanol) (Found: C, 52.4; H, 3.2; N, 7.4. $C_{24}H_{19}F_9N_3P$ requires C, 52.3; H, 3.5; N, 7.6%); ν_{max}/cm^{-1} 1635, 1608, 1592, 1502 and 840; δ_H([$^2H_6$]DMSO) 8.96 (1H, dd, *J* 9.9 and 4.6, H-4), 8.75 (1H, dd, *J* 8.1 and 2.7, H-6), 7.9–8.15 (3H, m, ArH), 7.78 (1H, dd, *J* 9.2 and 2.6, H-1), 7.08 (2H, t, *J* 8.6, H-3′ and 5′), 6.72 (2H, m, H-2′ and 6′), 5.10 (3H, s, Me-5), 3.94 (3H, s, Me-10) and 3.64 (3H, s, Me); δ_C([$^2H_6$]DMSO) 161.8, 158.9, 158.2, 155.4, 154.2, 144.3, 144.2, 143.1, 140.6, 139.0, 138.9, 134.4, 133.9, 127.3, 127.2, 122.8, 122.6, 122.5, 122.4, 122.3, 121.9, 116.1, 115.7, 114.7, 114.6, 114.5, 114.1, 113.9, 113.2, 113.0, 111.6, 111.2, 108.1, 107.7, 40.7, 40.1 and 31.3; *m*/*z* (electrospray) 406 (M^+, 5%), 391 (100), 376 (60) and 107 (50).

2,7-Dichloro-5,10-dimethyl-11-(*N*-4-chlorophenyl-*N*-methylamino)-10*H*-indolo[3,2-*b*]quinolinium hexafluorophosphate 4c (Y = PF_6). Mp 268–269 °C (from methanol) (Found: C, 47.4; H, 3.1; N, 6.6. $C_{24}H_{19}Cl_3F_6N_3P$ requires C, 48.1; H, 3.2; N, 7.0%); ν_{max}/cm^{-1} 1633, 1596, 1585, 1494 and 842; δ_H([$^2H_6$]-DMSO) 8.95 (1H, d, *J* 2.0, H-6), 8.93, (1H, d, *J* 9.9, H-4), 8.20 (1H, dd, *J* 9.9, 2.6, H-3), 8.0–8.15 (3H, m, H-1, 8 and 9), 7.29 (2H, d, *J* 8.1, H-3′ and 5′), 6.7 (2H, br, H-2′ and 6′), 5.18 (3H, s, Me-5), 3.99 (3H, s, Me-10) and 3.73 (3H, s, Me); δ_C([$^2H_6$]DMSO) 146.5, 145.1, 140.5, 138.1, 136.0, 134.2, 133.6, 133.0, 132.4, 129.1, 126.6, 126.5, 125.2, 123.1, 122.6, 121.5, 114.9, 114.8, 113.3, 40.9, 40.1 and 31.3; *m*/*z* (electrospray) 460/458/456/454 (M^+).

2,7-Dibromo-5,10-dimethyl-11-(*N*-4-bromophenyl-*N*-methylamino)-10*H*-indolo[3,2-*b*]quinolinium hexafluorophosphate 4d (Y = PF_6). Mp 278–279 °C (from methanol) (Found: C, 38.9; H, 2.3; N, 5.4. $C_{24}H_{19}Br_3F_6N_3P$ requires C, 39.4; H, 2.6; N, 5.75%); ν_{max}/cm^{-1} 1629, 1594, 1581, 1490 and 842; δ_H([$^2H_6$]-DMSO) 6.71–9.05 (10H, m, ArH), 5.08 (3H, s, Me-5), 3.88 (3H, s, Me-10) and 3.63 (3H, s, Me); δ_C([$^2H_6$]DMSO) 146.9, 145.3, 140.4, 137.9, 136.8, 136.2, 135.0, 133.3, 132.0, 128.0, 126.9, 125.8, 121.5, 121.4, 115.5, 115.3, 114.1, 113.5, 110.8, 40.8, 40.1 and 31.3; *m*/*z* (electrospray) 592/590/588/586 (M^+).

2,5,7,10-Tetramethyl-11-(*N*-4-methylphenyl-*N*-methylamino)-10*H*-indolo[3,2-*b*]quinolinium hexafluorophosphate 4e (Y = PF_6). Mp 200–202 °C (from methanol) (Found: C, 60.0; H, 5.3; N, 7.6. $C_{27}H_{28}F_6N_3P$ requires C, 60.1; H, 5.2; N, 7.8%); ν_{max}/cm^{-1} 1625, 1585, 1511, 1482 and 838; δ_H([$^2H_6$]DMSO) 6.69–8.81 (10H, m, ArH), 5.14 (3H, s, Me-5), 3.92 (3H, s, Me-10), 3.68 (3H, s, Me), 2.72 (3H, s, Me), 2.64 (3H, s, Me) and 2.32 (3H, s, Me); δ_C([$^2H_6$]DMSO) 189.4, 145.7, 144.7, 139.8, 138.6, 137.5, 135.8, 135.7, 135.3, 134.0, 132.7, 131.1, 129.8, 127.4, 125.7, 125.1, 122.7, 118.5, 114.2, 112.9, 111.0, 40.2, 39.9, 31.0, 20.9, 20.6 and 19.7; *m*/*z* (electrospray) 394 (M^+, 40%) and 379 (100).

5,10-Dimethyl-10*H*-indolo[3,2-*b*]quinolinium hexafluorophosphate 5a (Y = PF_6). Mp 227–228 °C (from acetonitrile and ethyl acetate) (Found: C, 52.1; H, 4.0; N, 7.1. $C_{17}H_{15}F_6N_2P$ requires C, 52.05; H, 3.85; N, 7.1%); ν_{max}/cm^{-1} 1508 and 840; δ_H([$^2H_6$]-DMSO) 9.51 (1H, s, H-11) 8.83 (1H, d, *J* 8.1, H-4), 8.75 (1H, d, *J* 10.8, H-6), 8.48 (1H, d, *J* 8.1, H-1), 8.14 (1H, t, *J* 8.1, H-3), 7.98–8.04 (2H, m, H-2 and 9), 7.51–7.57 (2H, m, H-7 and 8), 5.01 (3H, s, Me-5), 4.14 (3H, s, Me-10); *m*/*z* (electrospray) 247 (M^+).

2,7-Difluoro-5,10-dimethyl-10*H*-indolo[3,2-*b*]quinolinium hexafluorophosphate 5b (Y = PF_6). Mp >300 °C (from acetonitrile and ethyl acetate) (Found: C, 47.9; H, 3.0; N, 6.7. $C_{17}H_{13}F_8N_2P$ requires C, 47.7; H, 3.1; N, 6.5%); ν_{max}/cm^{-1} 1502, 1243 and 838; δ_H([$^2H_6$]DMSO) 9.42 (1H, s, H-11), 8.87 (1H, dd, *J* 7.9, 4.6, H-4), 8.70 (1H, dd, *J* 9.8, 2.6, H-6), 8.28 (1H, dd, *J* 8.6, 2.6, H-1), 7.9–8.2 (3H, m, H-3, 8 and 9), 5.01 (3H, s, Me-5), 4.12 (3H, s, Me-10); *m*/*z* (electrospray) 283 (M^+).

2,7-Dichloro-5,10-dimethyl-10*H*-indolo[3,2-*b*]quinolinium hexafluorophosphate 5c (Y = PF_6). Mp 269–271 °C (from acetonitrile and ethyl acetate) (Found: C, 44.0; H, 2.8; N, 6.1. $C_{17}H_{13}Cl_2F_6N_2P$ requires C, 44.3; H, 2.8; N, 6.1%); ν_{max}/cm^{-1} 1488 and 838; δ_H([$^2H_6$]DMSO) 9.46 (1H, s, H-11), 8.90 (1H, br s, H-6) 8.85 (1H, d, *J* 9.6, H-4), 8.60 (1H, d, *J* 2.0, H-1), 8.19 (1H, dd, *J* 9.6, 2.6, H-3), 8.06 (2H, s, H-8 and 9), 5.03 (3H, s, Me-5), 4.14 (3H, s, Me-10); *m*/*z* (electrospray) 319/317/315 (M^+).

2,7-Dimethoxy-5,10-dimethyl-10*H*-indolo[3,2-*b*]quinolinium hexafluorophosphate 5f (Y = PF_6). Mp 301–303 °C (from acetonitrile and ethyl acetate) (Found: C, 49.9; H, 4.0; N, 6.1. $C_{19}H_{19}F_6N_2O_2P$ requires C, 50.45; H, 4.2; N, 6.2%); ν_{max}/cm^{-1} 1641, 1627, 1502, 1488 and 840; δ_H([$^2H_6$]DMSO) 9.21 (1H, s, H-11), 8.64 (1H, d, *J* 9.6, H-4), 8.05 (1H, d, *J* 2.7, H-1), 7.86 (1H, d, *J* 9.2, H-9), 7.64–7.68 (2H, m, H-3 and 6), 7.63 (1H, dd, *J* 9.2, 2.3, H-8), 4.98 (3H, s, Me-5), 4.03 (3H, s, Me-10) 3.92 (3H, s, OMe), 3.90 (3H, s, OMe); δ_C([$^2H_6$]DMSO) 157.2, 154.2, 140.8, 134.8, 134.7, 130.8, 127.4, 124.6, 123.5, 121.2, 119.2, 113.3, 111.9, 107.0, 106.6, 56.1, 55.8, 40.0 and 29.6; *m*/*z* (electrospray) 307 (M^+).

Conversion of indoloquinolinium hexafluorophosphate salts 4 and 5 (Y = PF_6) to iodides (Y = I)

To the indoloquinolinium salt **4** or **5** (1 mmol) in acetone (10 cm^3) was added sodium iodide (0.22 g, 1.5 mmol) and the solution stirred overnight. The precipitated iodide salt was filtered and washed with cold acetone and recrystallised from acetonitrile and ethyl acetate to give the following red coloured salts as needles.

2,7-Difluoro-5,10-dimethyl-11-(*N*-4-fluorophenyl-*N*-methylamino)-10*H*-indolo[3,2-*b*]quinolinium iodide 4b (Y = I). Mp 232–235 °C (Found: C, 53.75; H, 3.5; N, 7.7. $C_{24}H_{19}F_3IN_3$ requires C, 54.0; H, 3.6; N, 7.9%); ν_{max}/cm^{-1} 1506; δ_H([$^2H_6$]-

‡ Major peak first then minor.

DMSO) 8.95 (1H, dd, *J* 9.9 and 4.6, H-4), 8.73 (1H, dd, *J* 8.1 and 2.7, H-6), 7.8–8.15 (3H, m, ArH), 7.75 (1H, dd, *J* 9.2 and 2.6, H-1), 7.08 (2H, t, *J* 8.6, H-3′ and 5′), 6.76 (2H, m, H-2′ and 6′), 5.06 (3H, s, Me-5), 3.89 (3H, s, Me-10) and 3.61 (3H, s, Me).

2,7-Dichloro-5,10-dimethyl-11-(*N*-4-dichlorophenyl-*N*-methylamino)-10*H*-indolo[3,2-*b*]quinolinium iodide 4c (Y = I). Mp 214–215 °C (Found: C, 49.6; H, 3.0; N, 7.4. $C_{24}H_{19}Cl_3IN_3$ requires C, 49.5; H, 3.3; N, 7.2%); ν_{max}/cm^{-1} 1492 and 1227; δ_H([$^2H_6$]DMSO) 8.95 (1H, d, *J* 2.0, H-6), 8.91 (1H, d, *J* 9.9, H-4), 8.19 (1H, dd, *J* 9.9, 2.6, H-3), 8.0–8.15 (3H, m, H-1, 8 and 9), 7.27 (2H, d, *J* 8.1, H-3′ and 5′), 6.7 (2H, br, H-2′ and 6′), 5.06 (3H, s, Me-5), 3.85 (3H, s, Me-10) and 3.61 (3 H, s, Me).

5,10-Dimethyl-10*H*-indolo[3,2-*b*]quinolinium iodide 5a (Y = I). Mp >300 °C (Found: C, 54.75; H, 4.1; N, 7.7. $C_{17}H_{15}IN_2$ requires C, 54.6; H, 4.0; N, 7.5%); ν_{max}/cm^{-1} 1504; δ_H([$^2H_6$]-DMSO) 9.55 (1H, s, H-11) 8.86 (1H, d, *J* 8.1, H-4), 8.78 (1H, d, *J* 10.8, H-6), 8.52 (1H, d, *J* 8.1, H-1), 8.19 (1H, t, *J* 8.1, H-3), 8.01–8.08 (2H, m, H-2 and 9), 7.54–7.61 (2H, m, H-7 and 8), 5.06 (3H, s, Me-5), 4.17 (3H, s, Me-10); *m*/*z* (electrospray) 247 (M^+).

2,7-Difluoro-5,10-dimethyl-10*H*-indolo[3,2-*b*]quinolinium iodide 5b (Y = I). Mp 276 °C (Found: C, 49.65; H, 3.3; N, 6.8. $C_{17}H_{13}F_2IN_2$ requires C, 49.8; H, 3.2; N, 6.8%); ν_{max}/cm^{-1} 1503 and 1243; δ_H([$^2H_6$]DMSO) 9.49 (1H, s, H-11) 8.91 (1H, dd, *J* 8.1, 4.6, H-4), 8.73 (1H, dd, *J* 9.8, 2.6, H-6), 8.32 (1H, dd, *J* 8.6, 2.6, H-1), 8.13 (1H, dt, *J* 8.1, 2.6, H-3), 8.08 (1H, dd, *J* 10.4, 5.4, H-9), 7.97 (1H, dt, *J* 8.1, 2.6, H-8), 5.04 (3H, s, Me-5), 4.15 (3H, s, Me-10); *m*/*z* (electrospray) 283 (M^+).

2,7-Dichloro-5,10-dimethyl-10*H*-indolo[3,2-*b*]quinolinium iodide 5c (Y = I). Mp 262 °C (Found: C, 46.2; H, 3.0; N, 6.3. $C_{17}H_{13}Cl_2IN_2$ requires C, 46.2; H, 3.0; N, 6.3%); ν_{max}/cm^{-1} 1488 and 1226; δ_H([$^2H_6$]DMSO) 9.50 (1H, s, H-11), 8.92 (1H, br s, H-6), 8.87 (1H, d, *J* 9.6, H-4), 8.63 (1H, d, *J* 2.0, H-1), 8.20 (1H, dd, *J* 9.6, 2.6, H-3), 8.09 (2H, s, H-8 and 9), 5.05 (3H, s, Me-5), 4.16 (3H, s, Me-10); *m*/*z* (electrospray) 319/317/315 (M^+).

2,7-Dimethoxy-5,10-dimethyl-10*H*-indolo[3,2-*b*]quinolinium iodide 5f (Y = I). Mp 241–242 °C (Found: C, 52.3; H, 4.3; N, 6.3. $C_{19}H_{19}IN_2O_2$ requires C, 52.55; H, 4.4; N, 6.45%; ν_{max}/cm^{-1} 1502 and 1255; δ_H([$^2H_6$]DMSO) 9.19 (1H, s, H-11), 8.62 (1H, d, *J* 9.6, H-4), 8.03 (1H, d, *J* 2.7, H-1), 7.85 (1 H, d, *J* 9.2, H-9), 7.64–7.67 (2H, m, H-3 and 6), 7.61 (1H, dd, *J* 9.2, 2.3, H-8), 4.94 (3H, s, Me-5), 4.02 (3H, s, Me-10), 3.96 (3H, s, OMe), 3.93 (3H, s, OMe); δ_C([$^2H_6$]DMSO) 157.2, 154.2, 140.8, 134.8, 134.7, 130.8, 127.4, 124.6, 123.5, 121.2, 119.2, 113.3, 111.9, 107.0, 106.6, 56.1, 55.8, 40.0 and 29.6; *m*/*z* (electrospray) 307 (M^+).

Hydrolysis of trimer 4e to give 5,11-dihydro-2,5,7,10-tetramethyl-10*H*-indolo[3,2-*b*]quinol-11-one 6

To trimer **5e** (1.00 g, 1.85 mmol) in ethanol (50 cm^3) was added sodium hydroxide (100 cm^3, 10% w/v) and the mixture refluxed for 2 h. The cooled mixture was extracted with chloroform (3 × 50 cm^3), the solution dried ($MgSO_4$) and evaporated, and the residue chromatographed on silica gel, eluting with light petroleum and ethyl acetate (1:1) to give the *title product* as a yellow solid (0.41 g, 75%), mp 238–240 °C (Found: C, 78.0; H, 6.4; N, 9.45. $C_{19}H_{18}N_2O$ requires C, 78.6; H, 6.25; N, 9.65%); ν_{max}/cm^{-1} 1673, 1596, 1558 and 1502; δ_H($CDCl_3$) 8.40 (1H, d, *J* 0.8, H-1), 7.90 (1H, s, H-6), 7.43 (2H, m, H-3 and 4), 7.32 (2H, s, H-8 and 9), 4.32 (3H, s, Me-5), 4.22 (3H, s, Me-10), 2.52 (3H, s, Me-2), 2.46 (3H, s, Me-7); δ_C($CDCl_3$) 168.7, 138.6, 137.9, 132.4, 130.4, 130.1, 128.8, 128.0, 125.4, 124.3, 122.7, 121.8, 115.5, 113.9, 109.5, 35.7, 31.2, 21.5 and 20.6; *m*/*z* (EI) 290 (M^+, 100%), 289 (M − 1, 52) and 275 (32).

Demethylation of indoloquinolinium salts

Method 1: sodium iodide and triphenylphosphine. The trimer (1 mmol), triphenylphosphine (1.05 g, 4 mmol) and sodium iodide (0.15 g, 1 mmol) in dry DMF (10 cm^3) were heated at reflux for 5 h, when the solvent was removed *in vacuo* to leave a yellow solid. Flash chromatography with light petroleum and ethyl acetate (70:30) gave firstly triphenylphosphine followed by the pure demethylated product **7** and **8**. In this way the following products were made.

2,7-*Difluoro*-10-*methyl*-11-(N-4-*fluorophenyl*-N-*methylamino*)-10H-*indolo*[3,2-b]*quinoline* **7b**.—Yield, 42%, mp 261–262 °C (from ethyl acetate and light petroleum) (Found: C, 70.35; H, 4.0; N, 10.6. $C_{23}H_{16}F_3N_3$ requires C, 70.6; H, 4.1; N, 10.7%); ν_{max}/cm^{-1} 1509, 1484, 1220 and 819; δ_H($CDCl_3$) 8.33 (1H, dd, *J* 9.2, 5.3, H-4), 8.19 (1H, dd, *J* 8.6, 2.7, H-4), 7.27–7.46 (4H, m, ArH), 6.91 (2H, t, *J* 8.6, H-3′ and 5′), 6.49 (2H, br, H-2′ and 6′), 3.75 (3H, s, Me-5) and 3.48 (3H, s, 11-NMe); *m*/*z* (EI) 391 (M^+).

2,7-*Dichloro*-10-*methyl*-11-(N-4-*chlorophenyl*-N-*methylamino*)-10H-*indolo*[3,2-b]*quinoline* **7c**.—Yield, 79%, mp 295–298 °C (from ethyl acetate and light petroleum) (Found: C, 62.7; H, 3.9; N, 9.5. $C_{23}H_{16}Cl_3N_3$ requires C, 62.7; H, 3.7; N, 9.5%); ν_{max}/cm^{-1} 1494, 1276 and 809; δ_H($CDCl_3$) 8.48 (1H, d, *J* 2.0, H-6), 8.26 (1H, d, *J* 9.3, H-4), 7.72 (1H, d, *J* 2.3, H-1), 7.56–7.65 (2H, m, H-3 and 8), 7.31 (2H, d, *J* 8.6, H-3′ and 5′), 7.18 (2H, m, H-2′ and 6′), 3.72 (3H, s, Me-5) and 3.50 (3H, s, 11-NMe); *m*/*z* (EI) 445/443/441/439 (M^+).

2,7-*Difluoro*-10-*methyl*-10H-*indolo*[3,2-b]*quinoline* **8b**.—Yield, 71%, mp 170–172 °C (from ethyl acetate and light petroleum) (Found: C, 71.3; H, 3.6; N, 10.35. $C_{16}H_{10}F_2N_2$ requires C, 71.6; H, 3.8; N, 10.4%); ν_{max}/cm^{-1} 1486, 1274 and 819; δ_H($CDCl_3$) 8.18 (1H, dd, *J* 8.1, 5.4, H-4), 8.07 (1H, dd, *J* 8.1, 2.7, H-6), 7.67 (1H, br s, H-11), 7.17–7.47 (4H, m, ArH) and 3.72 (3H, s, Me); *m*/*z* (EI) 268 (M^+).

2,7-*Dichloro*-10-*methyl*-10H-*indolo*[3,2-b]*quinoline* **8c**.—Yield 61%, mp 227–229 °C (from ethyl acetate and light petroleum) (Found: C, 64.3; H, 3.1; N, 9.55. $C_{16}H_{10}Cl_2N_2$ requires C, 63.8; H, 3.4; N, 9.3%); ν_{max}/cm^{-1} 1454, 1270 and 813; δ_H($CDCl_3$) 8.46 (1H, d, *J* 2.7, H-6), 8.22 (1H, d, *J* 10.8, H-4), 7.90 (1H, d, *J* 2.7, H-1), 7.79 (1H, s, H-11), 7.56–7.61 (2H, m, H-3 and 8), 7.33 (1H, d, *J* 8.1, H-9), 3.85 (3H, s, Me-5); *m*/*z* (EI) 304/302/300 (M^+).

2,7-*Dimethoxy*-10-*methyl*-10H-*indolo*[3,2-b]*quinoline* **8f**.—Yield, 88%, mp 123–123.5 °C (from ethyl acetate and light petroleum) (Found: C, 74.8; H, 5.4; N, 9.4. $C_{18}H_{16}N_2O_2$ requires C, 73.9; H, 5.5; N, 9.6%); ν_{max}/cm^{-1} 2923, 1623, 1490, 1203 and 819; δ_H($CDCl_3$) 8.11 (1H, br d, *J* 9.5, H-4), 7.93 (1H, br s, H-6), 7.49 (1H, s, H-11), 6.9–7.3 (4H, m, ArH) 3.85 (3H, s, Me-5) and 3.97 and 3.98 (2 × 3H, s, OMe); *m*/*z* (EI) 304/302/300 (M^+).

Method 2: pyridinium hydrochloride. Pyridine hydrochloride (10 cm^3) in an open stirred flask was heated at 220 °C for 20 min to remove water and then the trimer **4c** (0.80 g, 1.42 mmol) was added followed by further heating for 15 min at the same temperature. The cooled (~100 °C) reaction mixture was poured into dilute aqueous ammonium hydroxide (~50 cm^3) and ice and extracted with chloroform (3 × 50 cm^3), the solvent was dried ($MgSO_4$) and evaporated, and the residue chromatographed on silica gel, eluting with light petroleum and ethyl acetate (4:1) to give the demethylated product **7c** as a yellow solid (0.51 g, 80%).

Preparation of isatins 9 and 10

The dimer **3** (10 mmol) was prepared as described above, using oxalyl chloride and Hünig's base. The solution was cooled in an ice-bath and bromine (0.26 cm^3, 5 mmol) was added. After 2 min, water (25 cm^3) and dichloromethane were added and the mixture washed with aqueous hydrochloric acid (3 × 25 cm^3) and then water. The solution was dried ($MgSO_4$) and evaporated and the residue purified by recrystallisation or flash chromatography on silica gel, eluting with light petroleum and ethyl acetate (1:1) to give the products in Table 3. Other

reagents or conditions used than those indicated above are shown in Table 3.

Tetramers 11 isolated by treatment of 4-halo-*N*-methylformanilides 1 in $POCl_3$ with base utilising the general method above

2,2′-Bi[5-chloro-3-(*N*-4-chlorophenyl-*N*-methylamino)-1-methylindolyl] 11b. (Using triethylamine, yield 5%; *N*-methylmorpholine, yield 17%; 1,4-diaza[2.2.2]bicyclooctane, yield 27%) Mp 199–201 °C (ethyl acetate) (Found: C, 63.2; H, 4.3; N, 9.2. $C_{32}H_{26}N_4Cl_4$ requires C, 63.2; H, 4.3; N, 9.2%); ν_{max}/cm^{-1} 1594, 1492 and 1473; $\delta_H(CDCl_3)$ 6.45–7.31 (14H, m, ArH), 3.54 (6H, s, indole NMe) and 2.95 (6H, s, NMe); $\delta_C(CDCl_3)$ 147.5, 135.4, 128.7, 126.2, 126.1, 125.4, 124.8, 123.9, 122.6, 119.1, 114.4, 111.2, 40.0 and 31.2; *m*/*z* (EI) 614/612/610/608/606 (M^+).

2,2′-Bi[5-fluoro-3-(*N*-4-fluorophenyl-*N*-methylamino)-1-methylindolyl] 11c. (Using *N*-methylmorpholine, yield 28%) Mp 212–214 °C (Found: C, 70.5; H, 4.7; N, 10.3. $C_{32}H_{26}N_4F_4$ requires C, 70.8; H, 4.8; N, 10.3%); ν_{max}/cm^{-1} 1589, 1504 and 1488; $\delta_H(CDCl_3)$ 6.51–7.31 (14H, m, ArH), 3.55 (6H, s, indole NMe) and 2.97 (6H, s, NMe); $\delta_C(CDCl_3)$ 159.3, 157.4, 155.8, 154.0, 145.2, 145.1, 133.4, 126.4, 126.0, 125.9, 123.9, 123.7, 115.1, 114.8, 114.0, 113.9, 111.7, 111.4, 110.8, 110.7, 104.6, 40.0 and 31.1; *m*/*z* (EI) 542 (M^+).

2,2′-Bi[5-bromo-3-(*N*-4-bromophenyl-*N*-methylamino)-1-methylindolyl] 11d. (Using *N*-methylmorpholine, yield 18%) Mp 157–159 °C (Found: C, 48.7; H, 3.4; N, 7.1. $C_{32}H_{26}Br_4N_4$ requires C, 48.9; H, 3.3; N, 7.1%); ν_{max}/cm^{-1} 1590, 1509, 1488 and 1469; $\delta_H(CDCl_3)$ 6.41–7.40 (14H, m, ArH), 3.53 (6H, s, indole NMe) and 2.93 (6H, s, NMe); $\delta_C(CDCl_3)$ 147.6, 135.4, 131.4, 126.3, 125.6, 125.1, 124.8, 122.0, 114.6, 113.5, 111.6, 109.5, 39.9 and 31.2; *m*/*z* (EI) 788/786/784 (M^+).

Other products from the action of base on Vilsmeier salts in $POCl_3$ solution

***N*-Methyl-*N*-(4-nitrophenyl)carbamoyl chloride 12.** Mp 104–105 °C (Found: C, 44.9; H, 3.2; N, 13.2. $C_8H_7N_2O_3Cl$ requires C, 44.8; H, 3.3; N, 13.05%); ν_{max}/cm^{-1} 1735, 1592 and 1521; $\delta_H(CDCl_3)$ 8.30 (2H, d, *J* 9.0, H-3 and 5), 7.48 (2H, d, *J* 9.0, H-2 and 6) and 3.48 (3H, s, Me); *m*/*z* (EI) 216/214 (M^+, 50%), 179 (M − Cl, 100%) and 105 (80).

Acknowledgements

We thank SmithKline Beecham for a grant to Ying Cheng and the EPSRC and Synthetic Chemicals Ltd for a CASE Award to Simon Goon. We also thank Dr Brian Warrington of SB for his interest and help.

References

1 Part of this work appeared as preliminary communications: Y. Cheng, S. Goon and O. Meth-Cohn, *Chem. Commun.*, 1996, 1395; S. Goon and O. Meth-Cohn, *Tetrahedron Lett.*, 1996, **37**, 9381.
2 For reviews see, for example: C. Jutz, *Adv. Org. Chem.*, 1976, **9**, pt. 1, 225; O. Meth-Cohn and S. Stanforth, in *Comprehensive Organic Synthesis*, ed. B. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 4, p. 777; C. M. Marson and P. R. Giles, in *Synthesis Using Vilsmeier Reagents*, CRC Press, Boca Raton, 1994.
3 For reviews see, O. Meth-Cohn and B. Tarnowski, *Adv. Heterocycl. Chem.*, 1981, **31**, 207; O. Meth-Cohn, *Heterocycles*, 1993, **35**, 539.
4 O. Meth-Cohn and D. L. Taylor, *Tetrahedron*, 1995, **51**, 12 869.
5 O. Meth-Cohn and D. L. Taylor, *Chem. Commun.*, 1995, 1463; O. Meth-Cohn and Y. Cheng, *Tetrahedron Lett.*, 1996, **37**, 2679.
6 Y. Cheng, O. Meth-Cohn and D. L. Taylor, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 1257.
7 H. Böhme and P. Sutoyo, *Tetrahedron Lett.*, 1981, **22**, 1671.
8 J. M. Dalziel, 'The Useful Plants of West Tropical Africa', Crown Agents for Overseas Governments and Administrations, London, 1955, 387; M. H. M. Sharaf, P. L. Schiff, A. N. Tackie, C. H. Phoebe and R. L. Johnson, *J. Heterocycl. Chem.*, 1996, **33**, 789 and refs. therein.
9 L. G. Dubenko, R. E. Gerber, J. Litvak, J. Pererli-Roth, B. Sloan, N. Waldeck, J. Luo, M. J. Reed and D. E. Bierer, Abstracts of Papers of the American Chemical Society, 1997, **213**, Pt. 2, 131- and 132-Medi.
10 D. Aumann and L. W. Deady, *J. Chem. Soc.*, *Chem. Commun.*, 1973, 32; J. Kutney and R. Greenhouse, *Synth. Commun.*, 1975, **5**, 119; U. Berg, R. Gallo and J. Metzger, *J. Org. Chem.*, 1976, **41**, 2621; L. W. Deady and L. Korytsky, *Tetrahedron Lett.*, 1979, **20**, 451.
11 A. Ruiz, P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron Lett.*, 1997, **38**, 6205.
12 *As anti-inflammatory agents:* W. J. Welstead, *J. Med. Chem.*, 1979, **22**, 1074; *as antibacterial and antifungal agents:* J. Breinholt, H. Demuth, M. Heide, G. W. Jensen, I. L. Moller, R. I. Nielsen, C. E. Olsen and C. N. Rosendahl, *Acta Chem. Scand.*, 1996, **50**, 443; K. Cimanga, T. de Bruyn, A. Lasure, B. van Poel and L. Pieters, *Planta Med.*, 1996, **62**, 22; *as anxiogenic agents:* T. R. Norman, *Med. Sci. Res.*, 1996, **3**, 153 and refs. therein; also F. Y. Pang, F. H. Hucklebridge, G. Forster, K. Tan and A. Clow, *Stress Med.*, 1996, **12**, 35 and refs. therein; *as agents involved in bulimia nervosa:* T. D. Brewerton, J. J. Zealberg, R. B. Lydiard, V. Glover, M. Sandler and J. C. Ballenger, *Biol. Psychiatry*, 1995, **37**, 481.
13 W. Pfitzinger, *J. Prakt. Chem.*, 1886, **33**, 100.
14 E.g. see C. S. Marvel and G. S. Hiers, *Org. Synth.*, **Coll. Vol. 1**, 327; W. C. Sumpter, *Chem. Rev.*, 1944, **34**, 407; F. D. Popp, *Adv. Heterocycl. Chem.*, 1975, **18**, 2.
15 R. C. Elderfield and H. H. Rembgers, *J. Org. Chem.*, 1967, **32**, 3809.
16 P. W. Sadler, *J. Chem. Soc.*, 1961, 243.
17 S. Inaba, M. Akatsu, T. Hirohashi and H. Yamamoto, *Chem. Pharm. Bull.*, 1976, **24**, 1076.
18 A. P. Stankyavichvus, L. I. Mazhilis, V. N. Garbene, S. P. Risyalis, M. S. Saparagorene and L. M. Dzhyakcheryus, *Pharm. Chem. J.* (*Engl. transl.*), 1981, **12**, 858.
19 W. E. Noland and R. R. Kent, *J. Org. Chem.*, 1965, **30**, 3457.
20 A. Mangini and R. Passerini, *Gazz. Chim. Ital.*, 1955, **85**, 840.
21 W. J. Welstead, *J. Med. Chem.*, 1979, **22**, 1074.
22 A. R. Peacocke and J. N. H. Skerret, *Trans. Faraday Soc.*, 1956, **52**, 261; M. J. Waring, *J. Mol. Biol.*, 1965, **13**, 269; A. Blake and A. R. Peacocke, *Biopolymers*, 1968, **6**, 1225.

Paper 8/00800K
Received 29*th January* 1998
Accepted 20*th March* 1998