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The Reverse Vilsmeier Approach to the Synthesis of Quinolines, Quinolinium Salts and Quinolones[1]

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Abstract: *N*-Methylformanilide(MFA) reacts with various electron-rich alkenes in $POCl_3$ solution to give *N*-methylquinolinium salts generally in good yield. The alkenes can be vinyl acetate, an aldehyde or ketone enamine (preferably the morpholine enamine), a methyl aryl ketone (reacting as its enol) or it may be generated from an alkanoamide bearing α-protons (which produces an α-chloroenamine *in situ*). The reaction is effective for a variety of other alkyl-, aryl- and benzyl- formanilides as well as ring substituted anilides though electron-withdrawing groups tend to inhibit cyclisation. The mechanism of the cyclisation has been elucidated and shown to involve an electrocyclic π_6s process . The reactions of MFA with amides in $POCl_3$ gives 4-quinolones on alkaline workup.

Introduction

In past work[2] we have shown that interaction of an acylanilide with a Vilsmeier reagent offers an excellent method for the synthesis of quinolines, pyridines and related systems, exemplified by the synthesis of 2-chloroquinoline-3-aldehyde and 2-chloro-3-substituted quinolines (Scheme 1). This reaction involves the conversion of an acylanilide into an α-chloroenamine by the action of $POCl_3$ which is formylated with a Vilsmeier reagent derived from dimethylformamide and then undergoes an electrocyclic formation of the pyrido-ring. The *acylanilide provides the framework of the quinoline* and the 4-carbon is supplied by the Vilsmeier reagent and we refer to this type of quinoline synthesis as the 'Vilsmeier Approach'.

We now wish to describe the 'Reverse Vilsmeier Approach' (Scheme 2). The role of the two reagents is reversed in that the Vilsmeier reagent **1** forms the framework of the quinoline and the 3,4-carbons derive from a nucleophilic alkene **2**. This important principle is indeed an excellent protocol for quinolinium **3** synthesis. We

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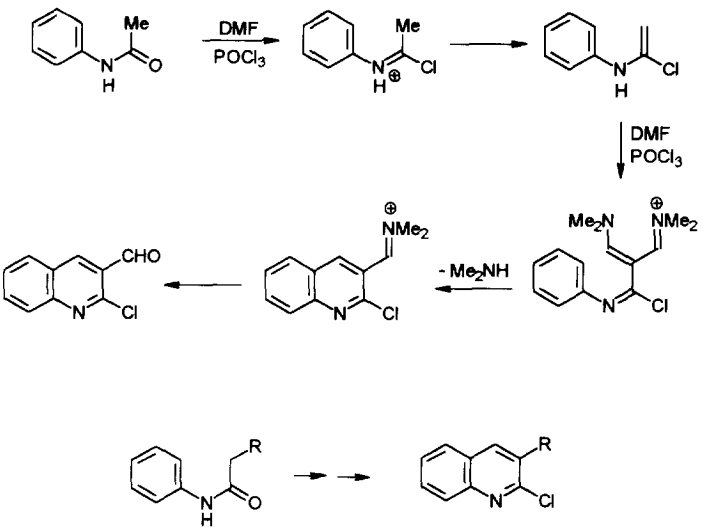
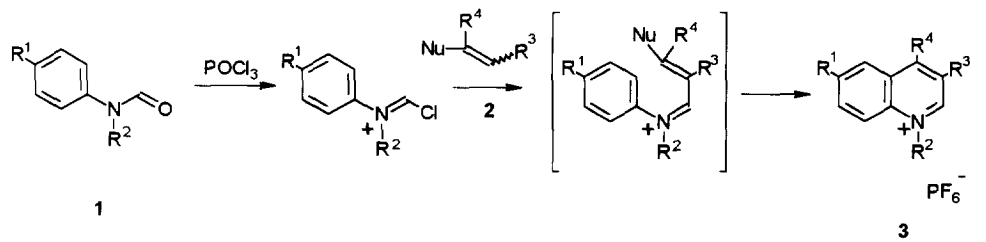
Dedicated to my old mentor, Prof Hans Suschitzky on his 80th birthday.



Scheme 1

have examined a number of electron-rich alkenes as sources of the 3,4-carbon atoms and in most cases have utilised *N*-methylformanilide (MFA) as the Vilsmeier reagent. It is surprising that despite the long use of MFA as a Vilsmeier amide[3], no other reports of quinoline formation have appeared. For example, effective formylations with MFA have been reported for 1,3,3-trimethyl-2-methylenindole[4] and for 1,2-dimethoxyethene[5], both being electron-rich alkenes.

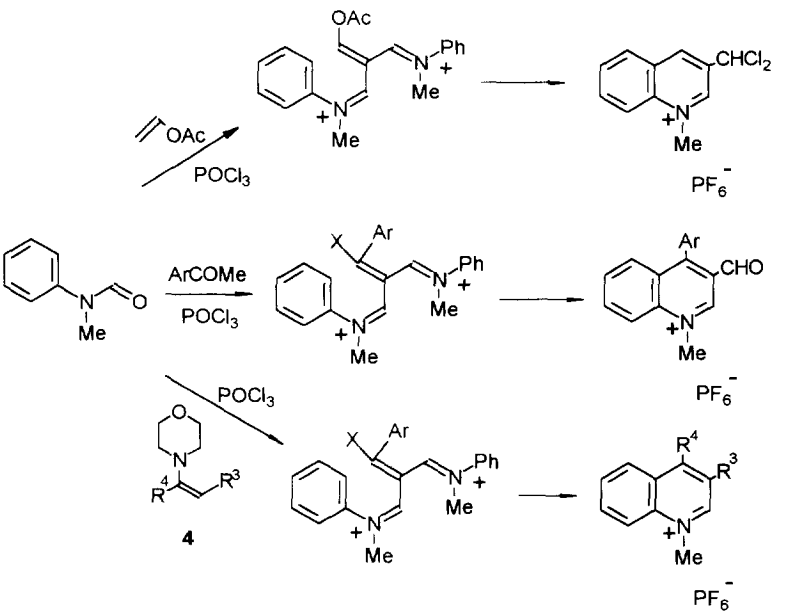


Scheme 2

In all the reactions below, $POCl_3$ has been used as solvent and the reaction was monitored and optimised by following its NMR spectrum, the quinolinium 2-proton (~9-10ppm) and *N*-methyl group (4.5-5ppm) being readily observed as well separated singlets.

Vinyl ethers and esters as the electron-rich alkene

Lee and coworkers[6] have reported that butyl vinyl ether can be formylated with MFA and $POCl_3$ and that the reaction can be conducted on a kilo scale in high yield to give on work-up *3-(N*-methyl-*N*-phenylamino)acrolein. We concur with their observations and were unable to force cyclisation of the precursor to this product. Similar results were observed with ethyl vinyl ether and ethyl prop-1-enyl ether. However, when vinyl acetate was similarly formylated, 3-dichloromethyl-1-methylquinolinium hexafluorophosphate was isolated in 79% yield on addition of ammonium hexafluorophosphate to the quenched reaction mixture (Scheme 3). This product can be seen to arise from diformylation of vinyl acetate followed by cyclisation. The reason why vinyl esters cyclise but ethers do not is unclear as is the isolation of the dichloromethyl rather than the formyl derivative. It would seem that the cisoid geometry of the intermediate to cyclisation requires

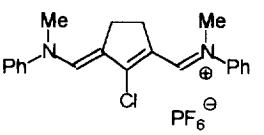


Scheme 3

considerable energy to form and that bis-formylation ensures the correct cyclisation geometry. The dichloromethyl derivative reacts as a masked aldehyde to give, for example, a hydrazone with phenylhydrazine.

Ketones as the source of electron-rich alkenes

Ketones are well known to be formylated by way of their enol tautomers on treatment with Vilsmeier reagents[7]. However we have found that for cyclisation to quinolinium salts, effective ketones are limited to methyl aryl ketones, which undergo diformylation on the methyl group and cyclise to give 4-aryl-3-formylquinolinium salts in good yield (Scheme 3). However, methyl 4-pyridyl ketone, acetone and 1,1,1-trifluoroacetone, α-tetralone, phenacyl chloride and propiophenone did not yield quinolines. Cyclohexanone monoformylates while cyclopentanone yielded solely a 2,5-'diformylated' derivative **5** .



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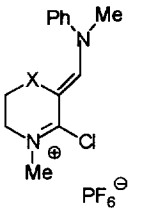


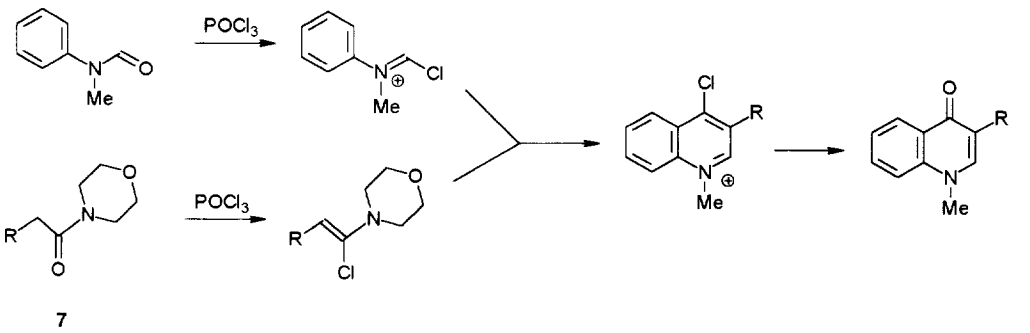
6

a X = —
b X = CH_2

Enamines as electron-rich alkenes

By contrast with ketones and enol esters and ethers we find that enamines of aldehydes or ketones react vigorously and effectively with MFA and $POCl_3$ to give quinolinium salts (Scheme 3). Several bases were examined for enamine formation, the more handlable and easily formed morpholine derivatives being preferred. To obviate formation of mixtures we have tended to utilise symmetrical ketone enamines. The reaction is effective for acyclic enamines and enamines of cyclic ketones (such as those of cyclo-hexanone, -heptanone, -octanone and -decanone) the yields and reaction rates diminishing with increase in ring size. Furthermore the morpholine enamine of n-butyraldehyde reacts effectively to give the 3-ethyl-1-methylquinolinium salt.

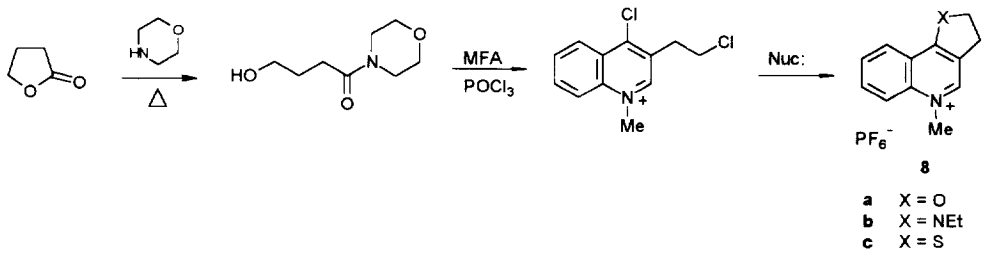
Amides as the source of electron-rich alkenes



Scheme 4

Tertiary amides bearing α-protons should behave as an effective source of an α-chloroenamine suitable for the formation of 4-chloro-3-substituted quinoliniums or -quinolones depending upon work-up (Scheme 4). This approach proves to be the most versatile and effective synthesis in this series and is very revealing in terms of mechanism. We found in preliminary work that morpholides gave better yields than dimethylamides or pyrrolidides and thus all the work subsequently utilised morpholine amides. Good yields of quinolinium salts were obtained bearing 3-alkyl, 3-aryl, 3-halo, and 3-haloalkyl substituents. *N*-methyl-2-pyrrolidone and -2-piperidinone both formylated as expected but gave solely the corresponding iminium salt **6**.

The 3-chloroethyl-4-chloroquinolinium salt is a versatile intermediate (the precursor amide of which is readily available from γ-butyrolactone and morpholine). Treatment of the salt with cold NaOH solution gave the dihydrofuranoquinolinium salt **8a** while heating with base gave the 3-hydroxyethyl-4-quinolone. Similar

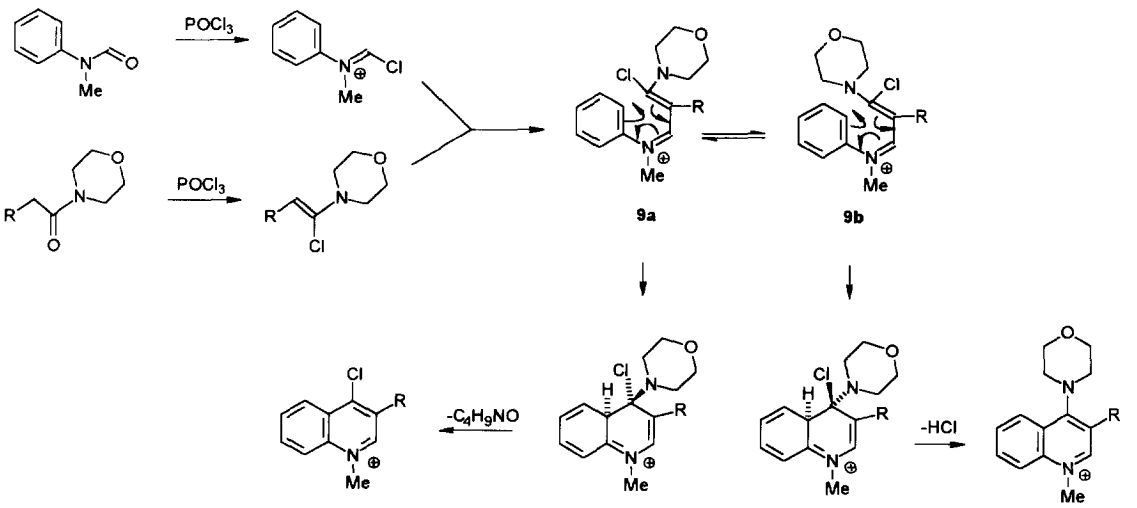


Scheme 5

treatment with Na_2S or an amine gave the dihydrothieno- or -pyrrolo-analogues (**8c** and **8b** respectively; Scheme 5).

The mechanism of the cyclisations

We envisage the reaction to proceed by way of an electrocyclic ring closure of an azatrienium intermediate 9. This compound must be forced into the cyclising geometry, aided by the steric interaction of substituents on



Scheme 6

what will become the quinoline 1- and 3-positions. Thus MFA and *N*-acetylmorpholine give only the acyclic 'formylated' intermediate (reminiscent of vinyl ethers) despite the fact that with DMF a rapid bis-formylation is reported[8]. Even when one mole of MFA followed by one of DMF is utilised we still observed solely monoformylation. All the other higher homologous amides investigated cyclised effectively. It is also evident that two geometries of the terminal azatriene carbon bearing the chloro- and morpholino-units are possible. That with the Z-geometry **9a** reveals steric crowding of the 3- and 4-substituents (relative to the product quinoline) but allows minimal steric inhibition to cyclisation, which should thus occur rapidly. It will result in an intermediate in which the *trans* elimination of HX to rearomatise the intermediate should result in elimination of morpholine. We observe morpholine elimination in most of our reactions. However when a bulky 3-substituent is present (e.g. phenyl or t-butyl) this geometry becomes untenable and the slower cyclising E-intermediate **9b** dominates the process with the remarkable result in the latter case that the more crowded 3-(t-butyl)-1-methyl-4-morpholinoquinolinium salt is formed initially. It is of interest that this product is slowly

converted into the 4-chloroquinolinium salt on prolonged heating in $POCl_3$, probably by way of $POCl_3$ attack at the morpholine *N*-atom followed by nucleophilic substitution by Cl^-. Albeit the action of LiCl in MeOH solution is of no effect on the 4-morpholino-derivative while heating with $POCl_3$ results in 60% exchange after one hour. The 3-phenyl derivative yields a 50:50 mixture of the 4-chloro- and 4-morpholino salt. These were both formed simultaneously rather than sequentially as evidenced by following the reaction by NMR, indicating that both cyclisation geometries are involved due to the steric factors already described.

In order to illuminate further the mechanistic aspects of this reaction we have endeavoured to conduct kinetic measurements on this process using a series of *p*-substituted *N*-methylformanilides. The kinetic data was obtained by observation of the formation of the quinolinium salt by ^{1}H-NMR spectroscopy, following the appearance of the low-field 2-proton singlet at 9.0-9.5ppm for the *para*-Me, -OMe, -Cl, -F and -H. Although the complications of the various reactions and their rates did not allow straight line kinetic plots to be drawn, we noted that at 35% completion the relative rates were in the order Me>H>Cl~OMe>F, an order consistent with the substituent exerting purely an *inductive* effect at the site of ring closure. Substituents that increased the nucleophilicity of this position enhanced the reaction. Indeed strongly electron withdrawing *para*-substituents such as F, COOEt, CN and NO_2 resulted in no formation of quinolinium salt. In effect the electrocyclic process is an intramolecular Friedel-Crafts reaction.

Variation of the 1-substituent on the quinolinium ring

We have made a limited examination of the range of *N*-substituents compatible with the above cyclisations. Alkyl, allyl, aryl and benzyl substituents proved effective. Synthetic routes to *N*-aryl quinoliniums is limited[9] and this method is particularly simple and effective and the results are collected in the Table. Since there are a number of important quinolone antibiotics derived from *N*-aryl-4-quinolone-3-carboxylic acids, this route has some virtue as a simple method. When the 1-substituent was proton the reaction failed even in the presence of added acid or Lewis acid.

Other attempted cyclisations

We considered that phenols and anilines could behave as enols and enamines respectively in the above reactions but examination of several phenols such as β-naphthol, its methyl ether and 1,3,5-trimethoxybenzene and anilines including *NN*-dimethyl-p-toluidine yielded no quinolinium salt and generally resulted solely in the known formylation[7].

In order to clarify this lack of reactivity semi-empirical AM1 calculations were undertaken. When the enamine azatrienium intermediate ions (Scheme 3) were examined a matching of the LUMO of the iminium group with the HOMO of the aromatic *ortho*-position was observed. However, for the aromatic 'enamines' and enol ethers, molecular orbital calculations revealed that while the LUMOs were positioned over the iminium carbon, the HOMO was not at the aromatic *ortho*-position. A uniform electron distribution over the aromatic ring was observed with very little difference between donor and acceptor moieties.

In conclusion, the ready formation of quinolinium salts and 4-quinolones has been demonstrated by interaction of *N*-substituted formanilides and sources of nucleophilic alkenes in $POCl_3$. These alkene precursors include vinyl acetate, methyl aryl ketones, aldehyde and ketone enamines, and, most effectively, *N*-acylmorpholides. It is noteworthy that the reaction which lead to the discovery of the Vilsmeier formylation reaction was indeed the formation of a quinolinium salt by the dimerisation of *N*-methylacetanilide, a reaction that we can now interpret as the first example of 'the Reverse Vilsmeier' cyclisation[10].

Experimental

Melting points were conducted on a Reichert Kofler hot stage apparatus. Infrared spectra were obtained on a Unicam Research Series 1 FTIR instrument as liquid films or KBr discs. NMR spectra were recorded in $CDCl_3$ or for the salts in d_6-acetone solution with tetramethylsilane as internal standard on a Jeol 270 (^1H, 270MHz; ^{13}C, 67.5MHz), while reaction monitoring by NMR was conducted on a Perkin Elmer R 24B. *J* values are in Hz. Mass spectra were obtained with a Kratos MS8ORF mass spectrometer and microanalyses were carried out at Newcastle University on a Carlo Erba 1106 Elemental Analyser. TLC were performed with Merck silica 60 F254 plates and for flash chromatography Janssen silica (35-70 mm) was used. Light petroleum refers to that of b.p. 60-80°C and ether implies diethyl ether.

General Methods for the Preparation of N-Substituted Formanilides And Other Amides

Four methods were employed for the preparation of *N*-substituted formanilides:

Method 1.- Formanilide (6.05g, 50 mmol) in dry DMF (20 mL), was added to a stirred solution of sodium hydride (80% dispersion in oil) (2.00g, 67 mmol) in dry DMF (10 mL) at room temperature. The resulting buff solution was heated at 60 °C for 60 minutes, and allowed to cool, after which time a solution of alkyl halide (50 mmol) in dry DMF was added dropwise. This solution was then heated at 60 °C, and the reaction was

monitored by TLC (solvent; 30% ethyl acetate, 70% ligroin) to determine the disappearance of formanilide, and hence the completion of the reaction. After the appropiate time the reaction mixture was poured onto water (200 mL), extracted with diethyl ether (3 x 40 mL) and the combined organic extracts were washed with water (4 x 40 mL), dried ($MgSO_4$) and evaporated. The residue was distilled *in vacuo* to yield the *N*-substituted formanilides shown below. In this way was prepared *N*-isobutylformanilide (b.p. 95-104°C/0.05mmHg, lit.[11] b.p. 120/4.5mmHg) and *N*-allylformanilide (b.p. 90-98°C/0.06mmHg, lit.[11] b.p. 136/10mmHg).

Method 2.- Diphenylamine (8.45g, 50 mmol), formic acid (9.4 mL, 0.25 mol) and acetic anhydride (23.6 mL, 0.25 mol) were heated together with stirring, the reaction being monitored by TLC (solvent; 20% ethyl acetate, 80% ligroin). The amine was consumed within 30 minutes. The reaction mixture was poured onto water (50 mL) giving a pale yellow oil, which solidified on cooling. The solid was recrystallised from aqueous ethanol to give white platelets of diphenylformamide (8.36g, 85%), m.p. 73°C (lit.[12] m.p. 73-4°C).

Method 3.- *N*-benzylideneaniline (3.62g, 20 mmol) and trimethylammonium formate[13] (TMAF) (27.8g, 0.1 mol) were heated at 120 °C (reflux) for 2.5 hours. The apparatus was rearranged for distillation, and the excess TMAF was removed (40-48 °C, 0.1 mmHg). *N*-benzylformanilide was obtained (146 °C, 0.1 mmHg) as a colourless oil (3.48g, 82%) which solidified on standing, m.p. 46-48 °C (lit.[14] 45-48 °C).

Method 4[15].- A *para*-substituted aniline (0.125 mol), trimethyl orthoformate (19.9g, 0.1875 mol) and conc. sulphuric acid (0.25g) were heated together in a round bottomed flask set up for distillation according to the literature method. In this way was prepared *N*-methyl-4-chloroformanilide (97%) (b.p. 74°C/0.2mmHg, lit.[16] b.p. 160°C/20mmHg), N-methyl-4-fluoroformanilide (46%) (m.p.. 42-44°C, lit.[17] m.p.45-48°C), *N*,4-dimethylformanilide (26%) (b.p.108°C/0.5mmHg, lit.[16] b.p. 116-118°C/2mmHg) and *N*-methyl-4-methoxyformanilide (42%) (b.p. 86°C/0.2mmHg, lit.[18] b.p. 122-4°C/2mmHg)

Preparation of Other Amides.- The following morpholides were prepared by literature methods : *N*-acetyl and -propionyl[19], -n-butanoyl, -isobutanoyl and -phenylacetyl[20], -chloroacetyl[21] and -3,3-dimethylbutanoyl[22] Using the same literature method was obtained *N-(3-chloropropionyl)morpholide*, b.p. 140°C/5mmHg (m/z 177.0561. $C_6H_{12}ClNO_2$ requires m/z 177.0557) and *N-(3-phenylpropionyl)morpholide* b.p. 185°C/5mmHg (m/z 1219.1257. $C_{13}H_{17}NO_2$ requires m/z 219.1259).

4-(4-Hydroxybutanoyl)morpholine.- γ-Butyrolactone (4.3g, 50mmol) and morpholine (4.35g, 50mmol) were heated together at 110°C for 2.5h and the mixture then distilled (Kugel-rohr) at 75°C/2mmHg to remove unchanged material and at 100-105°C to give *the title product*, (8.2g, 94%) as a pale yellow oil which solidified on standing, m.p.33-36°C (Lit[23] m.p. 39-40°C).

The Synthesis of Quinolinium Salts

General method.- MFA (1.35g, 10 mmol) and $POCl_3$ (5 mL, 54 mmol) were heated together for 5 minutes at 80 °C. This solution was cooled in an ice bath, and a nucleophilic alkene or its precursor (11 mmol) was added with stirring. A small sample of the homogeneous reaction mixture was withdrawn and placed in a capped nmr tube. The reaction mixtures were heated at 80 °C in an oil bath, the reaction being monitored by 60 MHz nmr spectroscopy. When it was determined that the reaction had reached completion, the contents of both the flask and the nmr tube were poured onto ice (100 mL) and ethyl acetate (25 mL). Ammonium hexafluorophosphate was added to the resulting solution to precipitate the product, which if formed was filtered, washed with ethyl acetate and water and dried. Recrystallisation from acetonitrile and ethyl acetate gave the salts recorded in the Table .

Reactions of 4-Chloro-3-(2-chloroethyl)-1-methylquinolinium hexafluorophosphate 3 (R^1 = H, R^2 = Me, R^3 = CH_2CH_2Cl, R^4 = Cl)

4-Chloro-3-(2-chloroethyl)-1-methylquinolinium hexafluorophosphate (2.05g, 5mmol) was suspended in methanol (30 mL). To this solution a nucleophile (6mmol) was added and the reaction mixture was refluxed for 120 min. The reaction mixture was allowed to cool to ambient, water (50 mL) was added, and the reaction mixture further cooled in an ice bath. The precipitate was collected by filtration.

(i)-Using sodium hydroxide.- (i) The base in 10 mL of water was heated under reflux with the salt. Water (50 mL) was added and the reaction mixture was extracted with dichloromethane (4 x 25 mL). The organic portions were combined and washed with water (2 x 25 mL), dried ($MgSO_4$) and concentrated to afford *3-(2-hydroxyethyl)-1-methyl-4-quinolone* as a pale yellow solid, (0.79g, 78%) which recrystallised from ethyl acetate and methanol to give fine white needles, m.p. 169-170°C. (Found C 70.89; H 6.51; N 6.82. $C_{12}H_{13}NO_2$ requires C 70.92; H 6.45; N 6.89%.) δ_H 2.80 (2H, t, J5.3); 3.82 (5H, m); 4.48 (1H, broad); 7.38 (2H, m); 7.50 (1H, s); 7.67 (1H, dt, J8.6, J7.3, J1.6); 8.46 (1H, dd, J8.6, J1.6). ν_{max} 3301 cm^{-1} (OH), 1567 cm^{-1} (C=O).

(ii)-Using ethylamine.- 1-Ethyl-5-methyl-2,3-dihydropyrrolo[3,2-c]quinolinium hexafluorophosphate ***7b*** was collected as a fine yellow precipitate (1.41g, 74%) which recrystallised from acetonitrile and ethyl acetate to yield yellow needles, m.p. 188-189 °C. (Found C 46.64; H 5.09; N 7.73. $C_{14}H_{17}F_6N_2P$ requires C 46.94; H 4.78; N 7.82%.) δ_H 1.52 (3H, t, J7.3); 3.36 (2H, t, J8.9); 4.15 (2H, q, J7.3); 4.19 (3H, s); 4.33 (2H, t, J8.9); 7.73 (1H, m); 8.07 (2H, m); 8.28 (1H, s); 8.49 (1H, d, J8.8). ν_{max} 840 cm^{-1} (PF_6^-).

Table Quinolinium Salt Formation

Formanilide **1**		Other	Time	Product **3**					M.p.	Found			Formula	Required		
R^1	R^2	reagent	(min)	R^1	R^2	R^3	R^4	%	(°C)	C	H	N		C	H	N
H	Me	$AcOCH=CH_2$	20	H	Me	$CHCl_2$	H	79	203-4	36.3	2.7	3.8	$C_{11}H_{10}Cl_2F_6NP$	35.5	2.7	3.8
H	Me	PhCOMe	180	H	Me	CHO	Ph	54	224	51.9	3.4	3.6	$C_{17}H_{14}F_6NOP$	51.9	3.6	3.6
H	Me	p-MeC_6H_4-Ac	180	H	Me	CHO	p-tol	32	215-6	53.1	4.1	3.5	$C_{18}H_{16}F_6NOP$	53.1	4.1	3.4
H	Me	2-Thienyl-Ac	150	H	Me	CHO	2-Th	63	263	45.2	2.9	3.6	$C_{15}H_{12}F_6NOPS$	45.1	3.0	3.5
H	Me	**4**, R-R' = c-C_6H_8	180	H	Me	-$(CH_2)_4$-		64	200-1	48.8	4.8	4.1	$C_{14}H_{16}F_6NP$	49.0	4.7	4.1
H	allyl	**4**, R-R' = c-C_6H_8	180	H	allyl	-$(CH_2)_4$-		34	140-2	52.0	5.1	3.75	$C_{16}H_{18}F_6NP$	52.0	4.9	3.8
H	i-Bu	**4**, R-R' = c-C_6H_8	180	H	i-Bu	-$(CH_2)_4$-		68	184-5	52.9	5.9	3.6	$C_{17}H_{22}F_6NP$	53.0	5.75	3.6
H	CH_2Ph	**4**, R-R' = c-C_6H_8	180	H	CH_2Ph	-$(CH_2)_4$-		58	247-8	57.2	4.9	3.35	$C_{20}H_{20}F_6NP$	57.3	4.8	3.3
H	Ph	**4**, R-R' = c-C_6H_8	180	H	Ph	-$(CH_2)_4$-		15	218	57.5	4.7	3.2	$C_{20}H_{20}F_6NP$	57.3	4.8	3.3
H	Me	**4**, R-R' = c-C_7H_{11}	180	H	Me	-$(CH_2)_5$-		38	184	50.6	5.1	3.9	$C_{15}H_{18}F_6NP$	50.4	5.1	3.9
H	Me	**4**, R-R' = c-C_8H_{13}	180	H	Me	-$(CH_2)_6$-		43	207-8	56.5	4.4	3.3	$C_{20}H_{16}F_6NP$	56.3	4.5	3.5
H	Me	**4**, R-R' = c-$C_{10}H_{17}$	180	H	Me	-$(CH_2)_8$-		38	172-3	56.3	6.65	3.3	$C_{20}H_{28}F_6NP$	56.2	6.6	3.3
H	Me	**4**, =Et R'=Me	180	H	Me	Me	Et	60	166-7	46.5	4.7	4.7	$C_{20}H_{16}F_6NP$	47.1	4.9	4.2
H	Me	**4**, R =H R' =Et	180	H	Me	Et	H	35	156-8	45.5	4.45	4.4	$C_{12}H_{14}F_6NP$	45.4	4.45	4.4
H	Me	**7**, R = Me	150	H	Me	Me	Cl	79	222-3	39.1	3.3	4.1	$C_{11}H_{11}ClF_6NP$	39.1	3.3	4.15
H	Me	**7**, R = Et	90	H	Me	Et	Cl	73	171	41.0	3.7	3.9	$C_{11}H_{13}ClF_6NP$	41.0	3.7	4.0
H	Me	**7**, R = Cl	270	H	Me	Cl	Cl	76	249-50	33.5	2.3	3.85	$C_{10}H_8Cl_2F_6NP$	33.55	2.25	3.9
H	Me	**7**, R = i-Pr	135	H	Me	i-Pr	Cl	78	190-1	42.8	4.1	4.1	$C_{13}H_{15}ClF_6NP$	42.7	4.1	3.8
H	Me	**7**, R = CH_2Ph	120	H	Me	CH_2Ph	Cl	93	211-2	49.3	3.6	3.3	$C_{19}H_{15}ClF_6NP$	49.35	3.65	3.4
H	Me	**7**, R = CH_2Cl	90	H	Me	CH_2Cl	Cl	61	184-6	35.6	2.7	3.8	$C_{11}H_{10}Cl_2F_6NP$	35.5	2.7	3.8
H	Me	**7**, R = $(CH_2)_2Cl$	90	H	Me	$(CH_2)_2Cl$	Cl	63	232	37.3	3.1	3.6	$C_{12}H_{12}Cl_2F_6NP$	37.3	3.1	3.6
H	CH_2Ph	**7**, R = Me	150	H	CH_2Ph	Me	Cl	93	211-2	49.3	3.6	3.3	$C_{19}H_{15}ClF_6NP$	49.35	3.65	3.4
H	Ph	**7**, R = Me	150	H	Ph	Me	Cl	87	248-9	48.2	3.1	3.4	$C_{16}H_{13}ClF_6NP$	48.1	3.3	3.5
Cl	Me	**7**, R = Me	150	Cl	Me	Me	Cl	37	227-9	35.4	2.7	3.6	$C_{11}H_{10}Cl_2F_6NP$	35.5	2.7	3.8
MeO	Me	**7**, R = Me	150	MeO	Me	Me	Cl	56	217	39.4	3.4	3.7	$C_{12}H_{13}ClF_6NOP$	39.2	3.6	3.8
Me	Me	**7**, R = Me	150	Me	Me	Me	Cl	55	204-6	40.9	3.8	4.0	$C_{12}H_{13}ClF_6NP$	41.0	3.7	4.0
H	Me	**7**, R = Me	150	H	Me	Ph	X*	70								
H	Me	**7**, R = t-Bu	150	H	Me	t-Bu	X#	37								

Footnotes to Table :

**A mixture of 4-morpholino- and 4-chloroquinolinium salt is formed; on heating the crude salt withan excess of morpholine in methanol for 1h at reflux, the 4-morpholino-salt is formed on addition of water (70%), m.p. 214-5°C. (Found: C 53.3, H 4.7, N 6.15. $C_{20}H_{21}F_6N_2OP$ requires C 53.3, H 4.7, N 6.2%).*

#A mixture of 4-morpholino- and 4-chloroquinolinium salt is formed(4.5:1); on heating the crude salt withan excess of morpholine in methanol for 1h at reflux, the 4-morpholino-salt is formed on addition of water (37%), m.p. ~260d°C. (Found: C 50.3, H 5.8, N 6.5. $C_{18}H_{25}F_6N_2OP$ requires C 50.2, H 5.85, N 6.5%). When the reaction of MFA and the morpholide in $POCl_3$ was continued for 10h the ratio of products increased to 77:23 while after 24h pure 4-chloroquinolinium salt was isolated (39%), m.p. 269°C. (Found: C 44.9, H 4.4, N 3.6. $C_{24}H_{27}F_6NP$ requires C 53.3, H 4.7, N 6.2%).

N.B. Full spectroscopic details of the quinolinium salts (IR,1-H NMR and some 13-C NMR and MS) are available on request.

(iii) 4-Chloro-3-(2-chloroethyl)-1-methylquinolinium hexafluorophosphate (2.05g, 5 mmol) was suspended in methanol (40 mL) and water (5 mL) in a water bath. 5M NaOH solution (3 mL, 15 mmol) was added to this suspension causing immediate dissolution of the salt, followed by the appearance of a fine white precipitate, which redissolved with the addition of a small amount of water (~3 mL). The solution was allowed to stir at ambient for 10 minutes followed by the addition of water (50 mL) and the reaction mixture being cooled in an ice bath. This caused *5-methyl-2,3-dihydrofurano[3,2-c]quinolinium hexafluorophosphate 7a* to precipitate as a fine white powder (0.77g, 43%). This was recrystallised from acetonitrile and ethyl acetate to yield white needles, m.p. 209 °C. (Found C 43.47; H 3.61; N 4.19. $C_{12}H_{12}F_6NOP$ requires C 43.52; H 3.65; N 4.23%.) δ_H 3.76 (2H, t, J9.0); 4.62 (3H, s); 5.37 (2H, t, J9.0); 8.01 (1H, dt, J1.0, 7.0, 8.1); 8.28 (1H, dt, J1.4, 7.0, 8.9); 8.35 (1H, dd, J8.1, 1.4); 8.44 (1H, d, J8.9); 9.22 (1H, s). ν_{max} 840 cm^{-1} (PF_6^-).

(iv)-Using sodium sulfide.- 5-Methyl-2,3-dihydrothieno[3,2-c]quinolinium hexafluorophosphate 7c precipitated as a yellow powder (0.80g, 43%) which recrystallised from acetonitrile and ethyl acetate to furnish yellow needles, m.p. 223-225 °C. (Found C 41.80; H 3.50; N 3.96. $C_{12}H_{12}F_6NPS$ requires C 41.51; H 3.48; N 4.03%.) δ_H 3.88 (2H, m); 4.02 (2H, m); 4.68 (3H, s); 8.04 (1H, dt, J0.8, 6.8, 8.1); 8.20 (1H, dd, J8.1, 1.4); 8.29 (1H, dt, J1.4, 6.8, 9.1); 8.50 (1H, d, J9.1); 9.12 (1H, s). ν_{max} 842 cm^{-1} (PF_6^-).

The Conversion of Quinolinium Salts into Quinolones

Conversion of the 4-chloroquinolinium salts 3into the corresponding 4-quinolone .- General procedure.- A 4-chloroquinolinium salt (5 mmol) was partially dissolved in methanol (40 mL) and water (10 mL). The solution was warmed slightly to aid dissolution of the salt. To this solution, was added NaOH (2mL, 5M, 10 mmol), causing immediate dissolution of the salt. After a short while (~60 seconds) a fine white precipitate began to appear, which redissolved when further water was added (~10 mL). The solution was left stirring at ambient for 10 minutes after which time water (50 mL) was added. This solution was extracted with dichloromethane (4 x 25 mL), and the combined organic portions were washed with water (3 x 25 mL), dried ($MgSO_4$) and concentrated to obtain the desired 4-quinolone.

1, 3-Dimethyl-4-quinolone .- From 4-chloro-1, 3-dimethylquinolinium hexafluorophosphate (1.69g) the title quinolone was obtained as a buff solid (0.82g, 95%) which recrystallised from ethyl acetate and ligroin as colourless plates, m.p. 159 °C. δ_H ($CDCl_3$) 2.08 (3H, s); 3.72 (3H, s); 7.32 (2H, t, J7.4); 7.40 (1H, s); 7.60 (1H, dt, J8.6, 1.6, 7.3); 8.45 (1H, dt, J1.6, 8.5). ν_{max} 1573 cm^{-1} (C=O).

3-Chloro-1-methyl-4-quinolone .- From 3, 4-dichloro-1-methylquinolinium hexafluoro- phosphate (1.79g) the title product was obtained as a red viscous oil (0.94g, 97%), which solidified and was recrystallised from ethyl acetate and ligroin to give pale red needles (0.72g, 74%), m.p. 236-237 °C. (Found C 62.16; H 4.16; N 7.23. $C_{10}H_8ClNO$ requires C 62.06; H 4.16; N 7.23%.) δ_H ($CDCl_3$) 3.84 (3H, s); 7.42 (2H, m); 7.70 (1H, dt, J1.4, 7.0, 8.6); 7.82 (1H, s); 8.50 (1H, dd, J1.4, 8.2). ν_{max} 1586 cm^{-1} (C=O).

3-Benzyl-1-methyl-4-quinolone .- From 3-benzyl-4-chloro-1-methylquinolinium hexafluoro- phosphate (2.07g) was isolated a viscous green oil which solidified and was recrystallised from ethyl acetate and ligroin to yield a pale green powder (1.13g, 91%). Further recrystallisation with ethyl acetate and ligroin furnished very pale green needles, m.p. 123 °C. (Found C 82.00; H 6.06; N 5.59. $C_{17}H_{15}NO$ requires C 81.90; H 6.06; N 5.62%.0 δ_H ($CDCl_3$) 3.69 (3H, s); 3.92 (2H, s); 7.29 (8H, m); 7.63 (1H, dt, J1.6, 7.0, 8.6); 8.50 (1H, dd, J1.6, 8.2). ν_{max} 1577 cm^{-1} (C=O).

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