Syntheses of Flosequinan: a Novel 4-Quinolone shown to be useful in Congestive Heart Failure

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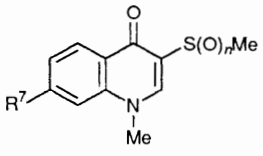
Two synthetic routes to flosequinan **1** and flosequinoxan **2** are described in which either ring closure of the β-keto sulfoxides **12** or **13** with ortho esters or cyclisation of the anilinoacrylates **23**, **28** or **29** are the key steps.

Congestive heart failure affects a significant proportion of the Western world and its prevalence is increasing.[1] Until recently the treatment of heart failure focused on the relief of symptoms and was based primarily on diuretics and digitalis. Despite the introduction of ACE-inhibitors for the treatment of chronic heart failure, patient survival and quality of life remain poor. Thus there is a great deal of scope for improvement.

Flosequinan (7-fluoro-1-methyl-3-methylsulfinyl-4-quinolone **1**) was selected for development from a series of 3-methylsulfinyl-4-quinolones for use in congestive heart failure. It is a new direct acting, arterial-venous vasodilator[2-4] which forms a long-lived active metabolite (flosequinoxan **2**) in a number of animal species, including man,[5] permitting once daily dosing. Flosequinan is an entirely new class of agent, chemically unrelated to the presently available drugs used in heart failure and has a potent inhibitory effect on inositol trisphosphate (IP_3) formation inhibiting the release of intracellular calcium.[6]



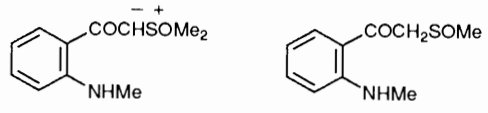
	R^7	n
1	F	1
2	F	2
3	H	1
4	N	1
5	F	0

In this paper we describe two approaches to the synthesis of flosequinan **1** and its metabolite, flosequinoxan **2**.

Results and Discussion

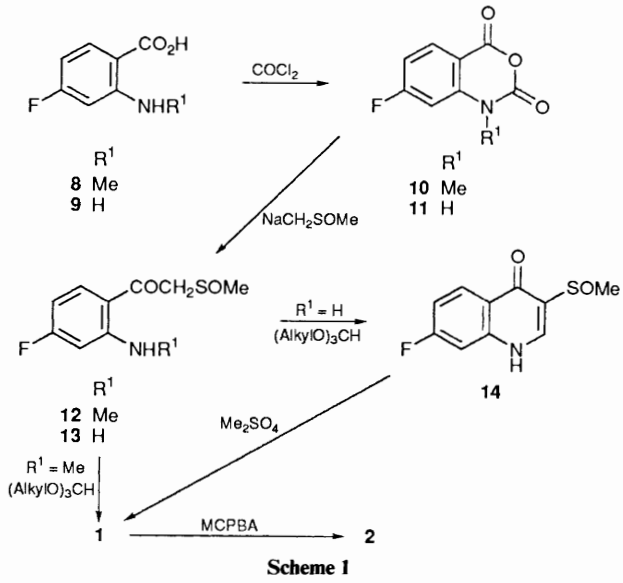
Flosequinan **1** and its major metabolite, flosequinoxan **2**, have been synthesized with either 4-fluoroanthranilic acids or 3-fluoroaniline as starting materials. The syntheses in Schemes 1 (β-keto sulfoxide route) and 3 and 4 (acrylate cyclisation routes) exemplify these two approaches. The β-keto sulfoxides **12** and **13** were readily prepared by reaction of dimsyl sodium with the corresponding dioxobenzoxazines **10** and **11** which, in turn, were prepared by treatment of the corresponding anthranilic acids **8** and **9** with phosgene. The ring closure of **12** (Scheme 1) with triethyl orthoformate gave the best yield of **1** in the presence of a mixture of piperidine and acetic acid, in contrast to the conversion of **13** into **14**, which was achieved in good yield with trimethyl orthoformate in the presence of piperidine alone. Cyclisation of the anilinoacrylates **23** and **28** (Schemes 3 and 4, respectively) was carried out in refluxing diphenyl ether, and heating in polyphosphoric acid was used for the cyclisation of **29** (Scheme 4). Mixtures, of varying proportions, of 5- and 7-fluoro isomers of the respective products were obtained from all acrylate cyclisations.

A literature and patent search revealed relatively few 4-quinolones unsubstituted in the 2-position and bearing a 3-sulfoxide substituent. van Leusen and Taylor[7] have described the synthesis of 1-methyl-3-methylsulfinyl-4-quinolone **3** by ring closure of dimethyloxosulfonium 2-(methylamino)benzoylmethylide **6** with triethyl orthoformate in the presence of acetic acid. Albrecht[8] chose the same route for the synthesis of related 4-quinolones as potential antibacterials. Compound **3** was also prepared by Connor *et al.*[9] by treatment of 1-[2-(methylamino)phenyl]-2-(methylsulfinyl)ethanone **7** with triethyl orthoformate in the presence of piperidine.



6 **7**

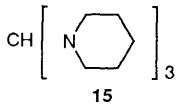
Although we had previously successfully employed ylide intermediates in the synthesis of other 4-quinolones[10] we initially chose to investigate syntheses of flosequinan **1** *via* cyclisation of the β-keto sulfoxides **12** and **13** with trialkyl orthoformates. The most direct route appeared to be cyclisation of **12**.



Scheme 1

Reaction of **12** with triethyl orthoformate was slow, with only 50% conversion into **1** after 24 h. Under similar conditions to

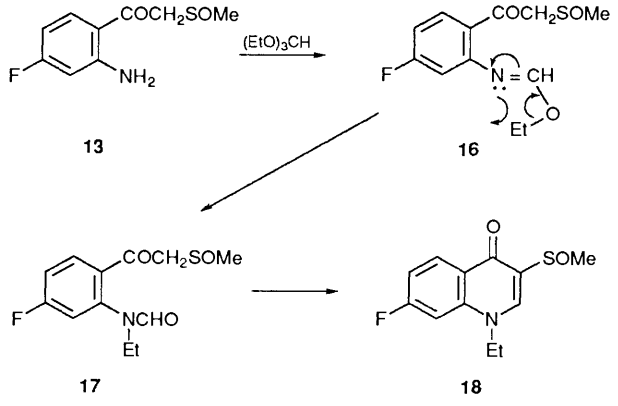
those reported by Connor, cyclisation of **12** with triethyl orthoformate in the presence of piperidine gave **1** in 54% yield compared with Connor's reported yield of 81% for the 7-unsubstituted 4-quinolone **3** obtained from **7**. Preparation of **1** in this way was complicated by the formation of **4** as a side-product. After just 6 h, when the starting material **12** had not been completely consumed, considerable quantities of **4** were detected in the reaction mixture by TLC. It is thought likely that **4** was formed by nucleophilic displacement of the fluorine atom from **1** with piperidine rather than by displacement of the fluorine atom from **12**, followed by cyclisation. Reaction of **1** with piperidine at 100 °C gave complete conversion into **4** in just 18 h whereas little reaction occurred between **12** and piperidine even after 24 h, and after 120 h a complex mixture was obtained. Alternative, more sterically hindered amines, for example 2,2,6,6-tetramethylpiperidine, were much less effective in promoting this cyclisation. Cyclisation of **12** in the presence of concentrated sulfuric acid gave only a 25% yield of **1** and in the presence of acetic acid, conditions similar to those used by van Leusen and Taylor for ylide cyclisations, a complex mixture was obtained and only a 7% isolated yield of **1**. The most successful cyclisation was achieved in the presence of both piperidine and acetic acid when an 80% yield of **1** was obtained after just 2 h. The increased rate of reaction of **12** with triethyl orthoformate and consequent higher yield of **1** is probably due to acetic acid-catalysed formation of the orthoamide **15** under



15

the conditions of the reaction. As a class of compounds aliphatic orthoamides are more reactive than orthoformates[11] and we speculate that cyclisation of **12** is being achieved by reaction with **15**.

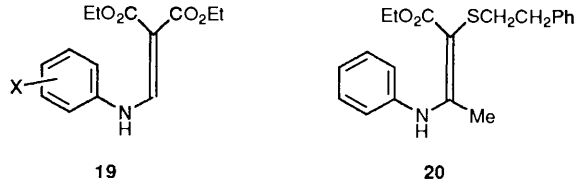
Cyclisation of **13** with triethyl orthoformate in the presence of piperidine gave the 4-quinolone **14** in reasonable yield (58%) compared with the poor yield (36%) reported by Connor for the corresponding 7-unsubstituted 4-quinolone. No 7-piperidino derivatives were isolated. In trial cyclisations of **13** with triethyl orthoformate in the presence of acetic acid, the *N*-ethyl derivative **18** of the product was isolated as a side-product. Since this probably arose from ring closure of **17** obtained from the intermediate ethyl imidate **16** *via* a Chapman type rearrangement as shown in Scheme 2 it was decided to use



Scheme 2

trimethyl orthoformate, when a higher yield (79%) of **14** was obtained than under basic conditions. Methylation of **14** gave flosequinan **1** in 64% yield. Oxidation of **1** with 3-chloroperbenzoic acid readily gave flosequinoxan **2** and deoxygenation of **1** with triphenylphosphine gave a good yield of the corresponding sulfide **5**.

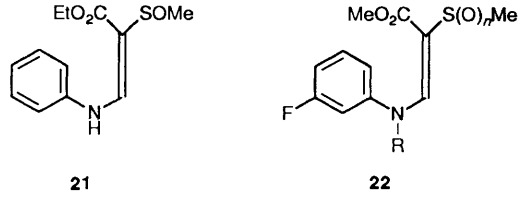
The synthesis of **1** using routes summarised in Scheme 1 suffered from the disadvantage of starting from relatively inaccessible anthranilic acids and an alternative route utilising 3-fluoroaniline as starting material was, therefore, sought. Cyclisation of anilinomethylenemalonates **19** (X = a variety



19 **20**

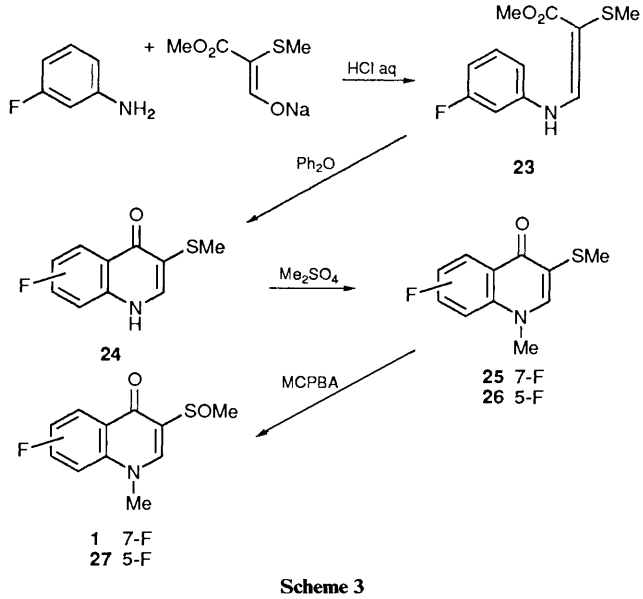
of substituents), formed by Gould–Jacobs condensation of anilines with diethyl ethoxymethylenemalonate, has been extensively utilised in the synthesis of 4-quinolone antibacterials.[12] Although the cyclisation of 1-(2-phenylethylmercapto)crotonate **20** has been reported by Bohme and Braun[13] to yield the corresponding 4-quinolone in poor yield (30%), we could find no literature examples of cyclisation of the anilinoacrylate **21**, or substituted derivatives thereof, to give the corresponding 3-methylsulfinyl-4-quinolones.

We therefore decided to investigate routes to flosequinan and flosequinoxan involving cyclisation of anilinoacrylates **22**



21 **22**

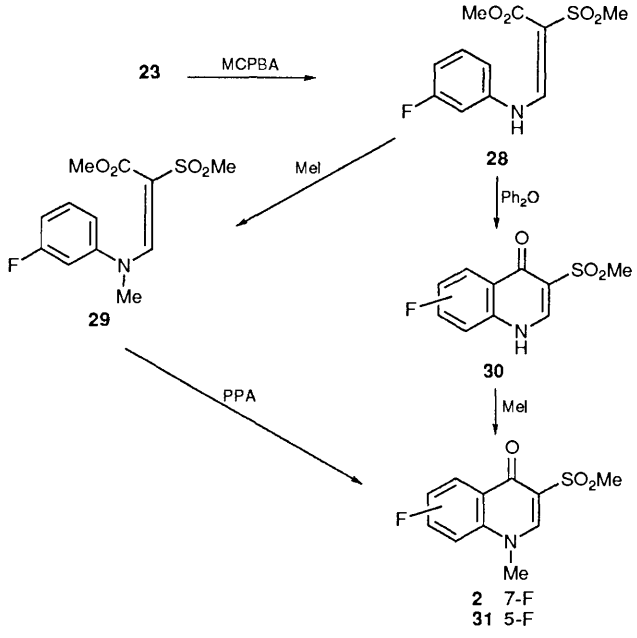
(R = H or Me and *n* = 0, 1 or 2) which could be synthesised from 3-fluoroaniline. We concluded from our work on the synthesis of other benzo-substituted 4-quinolones that cyclisation of **22** (*n* = 1 and R = H or Me) to the corresponding 3-methylsulfinyl-4-quinolones was not feasible and that cyclisation of **22** (*n* = 0 and R = Me) would be likely to give only poor yields of cyclised material. We concentrated therefore on the routes outlined in Schemes 3 and 4.



Scheme 3

The anilinoacrylate **23** is readily prepared by condensation of

3-fluoroaniline with the sodium salt of methyl 3-hydroxy-2-methylthioacrylate in hydrochloric acid. Cyclisation of **23** (Scheme 3) in refluxing diphenyl ether gave a 64% yield of a mixture of regioisomers **24** indicated by high performance liquid chromatography to be a 75:25 mixture of the 7-:5-fluoro regioisomers. Methylation of this mixture followed by oxidation gave a mixture of the corresponding sulfoxide regioisomers **1** and **27**, only marginally richer in the required 7-fluoro isomer **1**. This 5-step process, including chromatographic purification of the final isomer mixture, gave flosequinan **1** in overall 20% yield. No advantage was gained by separating the regioisomer mixtures **24** or **25**/**26**.



Scheme 4

Oxidation of **23** with MCPBA gave **28** which when refluxed in diphenyl ether (Scheme 4) gave a marginally improved cyclisation yield of 70% of regioisomers **30**. However, after just one crystallisation, ^{1}H NMR indicated the ratio of 7-fluoro-:5-fluoro regioisomers to be 95:5. Methylation of this material gave a good yield of flosequinoxan **2** identical with that obtained by oxidation of flosequinan **1** obtained from the route outlined in Scheme 1. These results are consistent with regioselectivity in cyclised products being influenced by the bulk of the substituent in the 2-position of the anilinoacrylates **22**. More hindered acrylates favour the formation of 7-fluoro cyclised products. Cyclisation of **29** (Scheme 4) in polyphosphoric acid gave an even higher yield (80%) of a mixture of 7-fluoro and 5-fluoro regioisomers, **2** and **31**, but containing a similar proportion of 5-fluoro isomer to that described for mixture **24**. Purification by flash chromatography gave pure **2**.

In summary, we have successfully synthesised flosequinan **1** and derivatives based on a route involving ring closure of β-keto sulfoxides (Scheme 1) and have demonstrated the feasibility of routes to flosequinan and derivatives *via* certain anilinoacrylates (Scheme 3). Problems with the formation of unwanted regioisomers render the latter route less attractive for the preparation of flosequinan **1** than the route outlined in Scheme 1. However, cyclisation of **28** (Scheme 4), followed by methylation, gives flosequinoxan **2** in a 4-step route from 3-fluoroaniline, of comparable quality and yield (~23%) to that obtained in 4 steps from the anthranilic acid **8** (Scheme 1).

Experimental

M.p.s were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded using either a Perkin-Elmer 157, a Perkin-Elmer 298, a Perkin-Elmer 841 or a Unicam 3020 FT-IR spectrometer. ^{1}H NMR spectra were determined using a JEOL C60HL, a JEOL FX90Q, a JEOL PFT100 or a Bruker AC250 spectrometer with tetramethylsilane as the internal standard. All *J* values are in Hz. Elemental analyses were conducted with a Carlo Erba model CE1106 CHN analyser; halogen was determined by argentometric titrimetry and sulfur was determined by colorimetric titrimetry. Concentration and evaporation refer to the removal of volatile materials under reduced pressure at 25–95 °C on a Büchi Rotovapor. IMS refers to industrial methylated spirit, HPLC to high-performance liquid chromatography and TLC to thin-layer chromatography.

4-Fluoro-N-methylanthranilic Acid **8**.*—Methylamine (30% w/w aqueous solution; 50 cm^3) was added to a stirred mixture of 2-chloro-4-fluorobenzoic acid (7.97 g, 45.7 mmol), copper powder (0.2 g), copper(II) chloride dihydrate (0.05 g) and water (50 cm^3). The mixture was stirred at 75–80 °C for 30 min and then under reflux for 5 h. A solution of sodium sulfide (2 g) in water (5 cm^3) was then added to the mixture which after being heated under reflux for 10 min was cooled to room temperature and filtered through a Clarcel® filter aid. Acetic acid (13.5 cm^3) was added to the filtrate. The pale brown solid was filtered off and recrystallised from IMS to give the *title compound* as pale brown crystals (5.0 g, 65%), m.p. 187–189 °C (Found: C, 56.5; H, 4.8; F, 11.2; N, 8.2. Calc. for $C_8H_8FNO_2$: C, 56.8; H, 4.7; F, 11.2; N, 8.3%); ν_{max}(KBr)/cm^{-1} 3389 (NH), 2500–3200 (OH and CHs) and 1656 (C=O); δ_H(250 MHz; CD_3SOCD_3) 2.82 (3 H, s, NMe), 6.35 (1 H, ddd, *J* 8.6, 8.6, 2.5, 5-H), 6.45 (1 H, dd, *J* 12.7, 2.5, 3-H) and 7.83 (1 H, dd, *J* 8.9, 7.1, 6-H).

7-Fluoro-1-methyl-3,1-benzoxazine-2,4-dione **10**.—A solution of phosgene (17.6 g, 177 mmol) in toluene (58 cm^3) was added dropwise over 50 min to a stirred mixture of 4-fluoro-*N*-methylanthranilic acid (9.2 g, 54.4 mmol), sodium carbonate (6.28 g, 59.2 mmol) and water (180 cm^3) at room temperature. The mixture was stirred for 19 h at this temperature after which the product was filtered off, washed with water (25 cm^3) and dried to give the *title compound* as a white solid, m.p. 159–162 °C (Found: C, 54.8; H, 3.1; N, 6.8. Calc. for $C_9H_6FNO_3 \cdot 0.17H_2O$: C, 54.5; H, 3.2; N, 7.1%); ν_{max}(KBr)/cm^{-1} 3300–3600br (H_2O), 3000–3200 (CHs), 1788, 1781, 1752 and 1727 (C=O); δ_H(250 MHz; CD_3SOCD_3) 3.44 (3 H, s, 1-Me), 7.19 (1 H, ddd, *J* 8.6, 8.6, 2.3, 6-H), 7.39 (1 H, dd, *J* 11.0, 2.3, 8-H) and 8.07 (1 H, dd, *J* 8.8, 6.2, 5-H).

1-(4-Fluoro-2-methylaminophenyl)-2-methylsulfinylethanone **12**.—Dimethyl sulfoxide (25 cm^3) was added dropwise over 35 min to a stirred mixture of sodium hydride (80% dispersion in oil; 2.78 g, 93 mmol) and toluene (40 cm^3) at 70–75 °C under a nitrogen atmosphere. After the mixture had been stirred for 1 h at 70–75 °C, it was cooled to 30 °C and a suspension of the dione **10** (8.5 g, 43.6 mmol) in dimethyl sulfoxide (30 cm^3) was added to it over 15 min. The mixture was stirred for a further 1 h after which methanol (5 cm^3) was added to it and the whole added to diethyl ether (200 cm^3). The solvent was decanted from the resultant brown oil which was triturated with water (50 cm^3) to give a thick yellow suspension. Water (50 cm^3) was added to the mixture which was then basified to pH 12 with an excess of aqueous sodium hydroxide. Undissolved solids were

* The preparation of **8** was described in an Australian Patent AU-A-40095/89 some years after we had prepared it in our laboratories.

filtered off and the solution acidified to pH 3–4, and then extracted with chloroform (300 cm^3). The extract was dried ($MgSO_4$) and evaporated to give the title compound (7.0 g, 70%) as a yellow solid, m.p. 139–140 °C (Found: C, 52.8; H, 5.4; N, 6.2; S, 13.9. Calc. for $C_{10}H_{12}FNO_2S$: C, 52.4; H, 5.2; N, 6.1; S, 14.0%); ν_{max}(KBr)/cm^{-1} 3303 (NH), 2700–3000 (CHs), 1639 (C=O) and 1015 (S=O); δ_H(250 MHz; CD_3SOCD_3) 2.67 (3 H, s, SOMe), 2.86 (3 H, d, *J* 5.0, collapsing to s with D_2O, NHMe), 4.47 and 4.55 (2 H, AB coupled, *J* 14.3, CH_2), 6.43 (1 H, ddd, *J* 8.6, 8.6, 2.5, 5-H), 6.53 (1 H, dd, *J* 12.8, 2.5, 3-H), 7.98 (1 H, dd, *J* 9.0, 6.8, 6-H) and 8.88 (1 H, br s, exch; NH).

7-Fluoro-1-methyl-3-methylsulfinyl-4-quinolone **1**.—*Method A: from cyclisation of* **12** *in the presence of base.* Piperidine (8.5 g, 0.1 mol) was added to a solution of the ketone **12** (22.9 g, 0.1 mol) in triethyl orthoformate (200 cm^3) heated under reflux under nitrogen. After 6 h the mixture was allowed to cool to room temperature overnight. It was poured into diethyl ether (800 cm^3) and the resultant precipitated solid (19.24 g) was collected, washed with diethyl ether and dried *in vacuo* at 70 °C.

A portion of the precipitated solid (2 g) was dissolved in dichloromethane (100 cm^3) and extracted with 2.5 mol dm^{-3} hydrochloric acid (2 × 50 cm^3). The organic phase was washed with water, dried ($MgSO_4$) and evaporated to give the title compound **1** as a white crystalline solid, recrystallisation of which from IMS gave the final product (1.35 g, equivalent to 54%), m.p. 227–228 °C (Found: C, 55.2; H, 4.2; N, 5.8; S, 13.6. Calc. for $C_{11}H_{10}FNO_2S$: C, 55.2; H, 4.2; N, 5.9; S, 13.4%); ν_{max}(KBr)/cm^{-1} 2850–3150 (CHs), 1630 (C=O), 1605, 1590 (C=C) and 1050 (S=O); δ_H(250 MHz; CD_3SOCD_3) 2.82 (3 H, s, SOMe), 3.97 (3 H, s, 1-Me), 7.40 (1 H, ddd, *J* 8.7, 8.7, 2.3, 6-H), 7.70 (1 H, dd, *J* 11.3, 2.3, 8-H), 8.17 (1 H, s, 2-H) and 8.23 (1 H, dd, *J* 8.9, 6.52, 5-H).

Method B: from cyclisation of **12** *in the presence of acid and base.* A mixture of the ketone **12** (17.3 g, 77.5 mmol), acetic acid (7.5 cm^3), piperidine (7.9 cm^3) and triethyl orthoformate (200 cm^3) was stirred under reflux for 2 h under a nitrogen atmosphere. The mixture was cooled to room temperature, poured into diethyl ether (1 dm^3) and the whole stirred for 20 min to afford a pale grey powder (14.35 g, 79.5%). This was filtered off and identified by TLC (silica, eluting with dichloromethane–methanol, 9:1) and IR spectroscopy as the title compound **1**, m.p. 224–228 °C.

Method C: from methylation of **14**. 7-Fluoro-3-methylsulfinyl-4-quinolone **14** (277.8 g, 1.23 mol) was dissolved in a solution of potassium hydroxide (137.8 g, 2.46 mol) in water (4 dm^3) at 50 °C. Decolourising charcoal (30 g) was added to the mixture which was then stirred for 20 min at 50 °C before filtration through Clarcel®. The filtrate was stirred and cooled to room temperature and dimethyl sulfate (240 cm^3, 319 g, 2.53 mol) was added to it over 10 min. The mixture was stirred at room temperature for 3 h when further potassium hydroxide (138 g, 2.46 mol) and dimethyl sulfate (120 cm^3, 159.5 g, 1.27 mol) were added to it. After the mixture had been stirred overnight at room temperature the resulting solid was filtered off and recrystallised from IMS. This gave the title compound **1** (261 g, 89%) as a white solid, m.p. 226–228 °C identical by TLC (silica, eluting with dichloromethane–methanol, 9:1) and IR and ^1H NMR spectroscopy to that obtained in A.

1-(2-Amino-4-fluorophenyl)-2-methylsulfinylethanone **13**.—Sodium hydride (50% dispersion in oil; 70.9 g, 1.48 mol) was added portionwise over 5 min to a stirred mixture of anhydrous dimethyl sulfoxide (728 cm^3) and anhydrous toluene (940 cm^3) at room temperature under a nitrogen atmosphere. The mixture was stirred and heated at 70–75 °C for *ca.* 1 h and then cooled to 30 °C when the dione **11** (88 g, 0.49 mol) was added to it over 20 min. The temperature of the mixture rose to 46 °C and a dark green solution formed. After this had been stirred for 5 min, ethanol (83 cm^3) was added to it, dropwise initially, then rapidly to give a brown solution. This was stirred at room temperature for 2 h and then poured into diethyl ether (3.15 dm^3) with rapid stirring. The supernatant was decanted from the resultant resin and the resin triturated with diethyl ether (500 cm^3). The pale grey solid was collected and immediately dissolved in water (630 cm^3) and the aqueous phase separated from an oily upper layer containing undissolved solids. The aqueous solution was acidified to pH 5–6 with 5 mol dm^{-3} hydrochloric acid (290 cm^3) when the product separated as a dark oil; this was extracted into dichloromethane (5 × 200 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to give an oil which solidified on trituration with diethyl ether (200 cm^3) followed by a mixture of diethyl ether (100 cm^3) and methanol (10 cm^3). This gave the title compound as a pale yellow powder (68.1 g, 65%), m.p. 112–114 °C (Found: C, 49.4; H, 4.3; N, 5.8; S, 15.0. Calc. for $C_9H_{10}FNO_2S$·0.1 CH_3SOCH_3: C, 49.6; H, 4.8; N, 6.3; S, 15.8%); ν_{max}(KBr)/cm^{-1} 3370 (NH), 2800–3000 (CHs), 1635 (C=O) and 1015 (S=O); δ_H(60 MHz; CD_3SOCD_3) 2.64 (3 H, s, SOMe), 4.48 (2 H, s, CH_2), 6.20–6.70 (2 H, m, 3-H and 5-H), 7.60 (2 H, br, exch., NH_2) and 7.92 (1 H, dd, 6-H).

7-Fluoro-3-methylsulfinyl-4-quinolone **14**.—*Method A: from cyclisation of* **13** *in the presence of acid.* A mixture of the ketone **13** (127.2 g, 0.592 mol), trimethyl orthoformate (1016 cm^3), ethanol (1016 cm^3) and glacial acetic acid (63.5 cm^3) was stirred under reflux for 24 h under a nitrogen atmosphere. The precipitated solid was filtered off and recrystallised from IMS to give two crops (83.2 g + 12.2 g, 79%) of the title compound as a white solid, m.p. 265–266 °C (Found: C, 53.8; H, 3.5; N, 6.3; S, 14.3. Calc. for $C_{10}H_8FNO_2S$: C, 53.3; H, 3.6; N, 6.2; S, 14.2%); ν_{max}(KBr)/cm^{-1} 2800–3300 (complex, CHs), 1635 (C=O) and 1030 (S=O); δ_H(100 MHz; CD_3SOCD_3) 2.82 (3 H, s, SOMe), 7.70–7.46 (2 H, m, 6-H and 8-H), 8.07 (1 H, d, *J* 0.6, 2-H) and 8.20 (1 H, dd, *J* 9.0, 6.4, 5-H).

Method B: from cyclisation of **13** *in the presence of base.* Piperidine (34 cm^3, 29.3 g, 0.35 mol) was added dropwise to a stirred solution of the ketone **13** (75.1 g, 0.35 mol) in triethyl orthoformate (800 cm^3) at 100 °C under an atmosphere of nitrogen. After a colourless distillate had been collected over 30 min the residue was cooled to room temperature and the resulting solid filtered off to provide the title compound **14** (40.8 g, 52%) identical (TLC and NMR and IR) with that obtained in (A). Further product (4.35 g, 58% total), was obtained by trituration with diethyl ether and ethanol of the residue obtained from evaporation of the filtrate.

In a similar way to that described above the ketone **13** (57.8 g, 0.27 mol) was treated with triethyl orthoformate (616 cm^3) to give the title compound **14**. The residue obtained from evaporation of the filtrate from the first crop was triturated with diethyl ether (500 cm^3) to give an oily solid, the liquors from which were decanted and stored at room temperature for 5 d. The solid which separated during this time was collected by filtration and recrystallised from dichloromethane–light petroleum to give *1-ethyl-7-fluoro-3-methylsulfinyl-4-quinolone* **18** as a white crystalline solid, m.p. 169–171 °C (Found: C, 56.9; H, 4.4; N, 5.3; S, 12.8. Calc. for $C_{12}H_{12}FNO_2S$: C, 56.9; H, 4.7; N, 5.5; S, 12.6%); ν_{max}(KBr)/cm^{-1} 2800–3100 (CHs), 1630 (C=O), 1610 (C=C) and 1045 (S=O); δ_H(90 MHz; CD_3SOCD_3) 1.40 (3 H, t, *J* 7.0, Me), 2.86 (3 H, s, SOMe), 4.49 (2 H, q, *J* 7.0, CH_2), 7.37 (1 H, ddd, *J* 8.5, 8.5, 2.0, 6-H), 7.79 (1 H, dd, *J* 11.6, 2.4, 8-H) and 8.19–8.27 (2 H, m, 2-H and 5-H); *m/z* 253 (M^+, 19%).

Methyl 3-(3-Fluoroanilino)-2-methylthioacrylate **23**.—Sodium metal (9.835 g, 0.428 mol) was dissolved in methanol

(250 cm^3) and excess of solvent removed by distillation. Diethyl ether (400 cm^3) was added to the residue and the mixture stirred at 0–5 °C while methyl methylthioacetate (51.25 g, 0.427 mol) was added over 15 min. The mixture was stirred at this temperature for 1 h and then methyl formate (30.85 g, 0.517 mol) was added dropwise to it, the temperature being kept < 5 °C. The mixture was stirred overnight at room temperature and then extracted with water (2 × 150 cm^3).

3-Fluoroaniline (46.25 g, 0.417 mol) was dissolved in a solution of concentrated hydrochloric acid (34 cm^3) in water (580 cm^3) at 3 °C and the aqueous sodium methyl 3-hydroxy-2-methylthioacrylate, prepared as described above, was added to it over 10 min. The initially formed oil solidified when stirred for 15 min and after being filtered off was washed with water. Recrystallisation from isopropyl alcohol gave the title compound (78.4 g, 78%), m.p. 83–86 °C; ν_{max}(KBr)/cm^{-1} 3280 (NH), 2800–3100 (CHs) and 1680 (C=O); δ_H(60 MHz; $CDCl_3$) 2.23 (3 H, s, SMe), 3.87 (3 H, s, OMe), 6.50–8.00 (5 H, m, collapsing to 4 H, m, with D_2O, NH and 4 ArH) and 8.33 (1 H, d, collapsing to s with D_2O, 3-H).

7-Fluoro-3-methylthio-4-quinolone and as a Mixture with the 5-Fluoro Isomer **24**.—Methyl 3-(3-fluoroanilino)-2-methylthioacrylate (60.0 g, 0.248 mol) was added portionwise to stirred diphenyl ether (300 cm^3) at 250 °C under nitrogen. The mixture was stirred at this temperature for 50 min, and then cooled to room temperature and poured into light petroleum (b.p. 60–80 °C; 1500 cm^3). Filtration gave a grey powder (16.4 g) indicated by TLC (silica gel, developing with ethyl acetate) to be a mixture of two components. Purification of an aliquot of the mixture by HPLC (silica gel, eluting with ethyl acetate–isopropyl alcohol, 9:1) followed by recrystallisation from IMS gave *7-fluoro-3-methylthio-4-quinolone*, m.p. 235–236 °C (Found: C, 57.1; H, 3.7; N, 6.2; S, 15.8. Calc. for $C_{10}H_8FNOS$: C, 57.4; H, 3.8; N, 6.7; S, 15.3%); ν_{max}(KBr)/cm^{-1} 2500–3200br (NH and CHs) and 1630 (C=O).

The diphenyl ether–light petroleum filtrate was evaporated on a steam-bath to remove the light petroleum and the diphenyl ether residue was then heated at 250–260 °C under nitrogen in a distillation apparatus until *ca.* 50 cm^3 of diphenyl ether had been collected. The residue was cooled, filtered and washed with diethyl ether (1 dm^3) to give a solid (22.5 g, corresponding to 64% yield) identical by TLC with that described above and indicated by HPLC (silica gel eluting with acetonitrile–triethylammonium formate buffer, 20:80) to be a 3:1 mixture of 7-fluoro-3-methylthio-4-quinolone (R_T 6.77 min) and 5-fluoro-3-methylthio-4-quinolone (R_T 4.23 min).

7-Fluoro-1-methyl-3-methylthio-4-quinolone **25**.—*Method A: by deoxygenation of corresponding sulfoxide* **1**. A mixture of 7-fluoro-1-methyl-3-methylsulfinyl-4-quinolone (23 g, 96 mmol), triphenylphosphine (44.66 g, 170 mmol) and carbon tetrachloride (962 cm^3) was stirred and heated under reflux for 1 h. The mixture was cooled to room temperature and filtered to give a colourless solid; the filtrate was further cooled in ice to give a second crop of solid. The combined solids were recrystallised from IMS to give the *title compound* (18.85 g, 88%) as colourless needles, m.p. 173–175 °C (Found: C, 58.9; H, 4.5; N, 6.2; S, 14.5. Calc. for $C_{11}H_{10}FNOS$: C, 59.2; H, 4.5; N, 6.3; S, 14.4%); ν_{max}(KBr)/cm^{-1} 2800–3100 (CHs) and 1635 (C=O); δ_H(90 MHz; CD_3SOCD_3) 2.33 (3 H, s, SMe), 3.84 (3 H, s, 1-Me), 7.24 (1 H, ddd, *J* 8.6, 8.6, 2.3, 6-H), 7.48 (1 H, dd, *J* 11.4, 2.2, 8-H), 8.05 (1 H, s, 2-H) and 8.22 (1 H, dd, *J* 8.8, 6.6, 5-H).

Method B: by methylation of a mixture of 7-fluoro- and 5-fluoro-3-methylthio-4-quinolones **24**. The mixture described above (18.4 g, 88 mmol) was dissolved in a mixture of potassium hydroxide (9.9 g, 176 mmol), water (100 cm^3) and THF (50 cm^3) and dimethyl sulfate (22 g, 16.5 cm^3, 176 mmol) was added dropwise with vigorous stirring to it to give a thick solid precipitate after *ca.* 5 min. This was filtered off and washed with water to give a solid (11.0 g, 56%) indicated by TLC to be a two-component mixture which was separated by HPLC on silica gel eluting with ethyl acetate. This gave the *title compound* (7.6 g, 39%), m.p. 161–162 °C; TLC (silica gel, eluting with ethyl acetate) R_F 0.39 (Found: C, 58.9; H, 4.5; N, 6.2; S, 14.6. Calc. for $C_{11}H_{10}FNOS$: C, 59.2; H, 4.5; N, 6.3; S, 14.3%); ν_{max}(KBr)/cm^{-1} 2800–3100 (CHs) and 1630 (C=O); δ_H(60 MHz; $CDCl_3$) 2.31 (3 H, s, SMe), 3.67 (3 H, s, 1-Me), 6.70–7.20 (2 H, m, 6-H and 8-H), 7.58 (1 H, s, 2-H) and 8.27 (1 H, dd, 5-H) and *5-fluoro-1-methyl-3-methylthio-4-quinolone* (1.8 g, 9%), m.p. 136 °C (shrinking from 120 °C) TLC (silica gel, eluting with ethyl acetate) R_F 0.23; ν_{max}(KBr)/cm^{-1} 2800–3100 (CHs) and 1625 (C=O); δ_H(60 MHz; $CDCl_3$) 2.32 (3 H, s, SMe), 3.70 (3 H, s, 1-Me), 6.60–7.70 (3 H, m, 6-H, 7-H and 8-H) and 7.50 (1 H, s, 2-H).

Methyl 3-(3-Fluoroanilino)-2-methylsulfonylacrylate **28**.—A solution of 3-chloroperbenzoic acid (85%; 32.93 g, 174 mmol), in dichloromethane (600 cm^3) was added over 30 min to a stirred solution of methyl 3-(3-fluoroanilino)-2-methylthioacrylate (20.0 g, 83 mmol) in dichloromethane (400 cm^3). The mixture was kept at room temperature overnight, after which 3-chlorobenzoic acid was filtered off, and the filtrate was washed with saturated aqueous sodium carbonate (3 × 200 cm^3), dried ($MgSO_4$) and evaporated to give a solid which was recrystallised from diethyl ether. This gave the *title compound* (20.91 g, 92%), m.p. 130–132 °C (Found: C, 48.2; H, 4.3; N, 5.1; S, 11.4. Calc. for $C_{11}H_{12}FNO_4S$: C, 48.4; H, 4.4; N, 5.1; S, 11.7%); ν_{max}(KBr)/cm^{-1} 2900–3300 (CHs), 1670 (C=O), 1640 (C=C), 1290 and 1130 (SO_2); δ_H(90 MHz; CD_3SOCD_3) 3.18 (3 H, s, SO_2Me), 3.85 (3 H, s, OMe), 6.95–7.61 (4 H, m, ArH), 8.21 (1 H, br collapsing to s with D_2O, 3-H) and 10.36 (1 H, br, NH).

7-Fluoro-3-methylsulfonyl-4-quinolone containing the 5-Fluoro Isomer **30**.—A suspension of the ester **28** (4.0 g, 14.65 mmol) in diphenyl ether (30 cm^3) was added over 5 min to stirred diphenyl ether (60 cm^3) at 260–270 °C under nitrogen. The mixture was stirred at this temperature for 45 min and then allowed to cool to room temperature overnight. Diethyl ether (100 cm^3) was then added to the mixture which after being stirred for 5 min was filtered and the solid so collected was recrystallised from IMS. This gave *7-fluoro-3-methylsulfonyl-4-quinolone* (2.58 g, 73%), m.p. > 320 °C (Found: C, 49.9; H, 3.45; N, 5.75; S, 13.7. Calc. for $C_{10}H_8FNO_3S$: C, 49.8; H, 3.3; N, 5.8; S, 13.3%); ν_{max}(KBr)/cm^{-1} 2700–3300br (OH and CHs), 1620 (C=O) and 1300 and 1145 (SO_2); δ_H(90 MHz; CD_3SOCD_3) 3.25 (3 H, s, SO_2Me) 7.19–7.50 (2 H, m, 6-H and 8-H), 8.25 (1 H, dd, 5-H) and 8.50 (1 H, s, 2-H) containing *ca.* 5% of 5-fluoro-3-methylsulfonyl-4-quinolone as indicated by signal at δ 8.40 (0.05 H, s, 2-H in 5-isomer).

Methyl 3-(3-Fluoro-N-methylanilino)-2-methylsulfonylacrylate **29**.—Methyl iodide (1.8 cm^3, 29 mmol) was added to a stirred mixture of the ester **28** (5.0 g, 18 mmol), anhydrous potassium carbonate (2.65 g, 19 mmol) and dimethylformamide (70 cm^3). After the mixture had been stirred overnight at room temperature the solvent was removed by evaporation under reduced pressure and water (100 cm^3) was added to the residue. The mixture was extracted with dichloromethane (3 × 100 cm^3) and the combined extracts dried ($MgSO_4$) and evaporated to give a dark residue which was purified by flash chromatography (silica gel eluting with dichloromethane–IMS, 97.5:2.5). This gave the *title compound* (2.3 g, 44%) as a pale brown wax (Found: C, 49.7; H, 4.85; N, 4.6; S, 10.8. Calc. for $C_{12}H_{14}FNO_4S$: C,

50.2; H, 4.9; N, 4.9; S, 11.1%); ν_{max}(KBr)/ cm^{-1} 2900–3100 (CHs), 1700 (C=O) and 1295 and 1130 (SO_2); δ_H(90 MHz; CD_3SOCD_3) 3.19 (3 H, s, SO_2Me), 3.40 (3 H, s, NMe), 3.46 (3 H, s, OMe), 7.02–7.62 (4 H, m, ArH) and 7.72 (1 H, s, 3-H).

7-Fluoro-1-methyl-3-methylsulfonyl-4-quinolone **2**.—*Method A: by oxidation of the corresponding 3-sulfoxide* **1**. To a stirred solution of the 3-sulfoxide **1** (25.0 g, 0.105 mol) in dichloromethane (500 cm^3) was added a solution of 3-chloroperbenzoic acid (85%; 18.1 g, 0.105 mol) in dichloromethane (500 cm^3) over 30 min at room temperature. More 3-chloroperbenzoic acid was added portionwise to the mixture until TLC showed that the reaction was complete. The mixture was kept at room temperature for 72 h and the resulting solid then filtered off and recrystallised from IMS to give the *title compound* (17.0 g, 64%), m.p. 231–236 °C (Found: C, 51.7; H, 4.1; N, 5.4; S, 12.8. Calc. for $C_{11}H_{10}FNO_3S$: C, 51.8; H, 3.9; N, 5.5; S, 12.55%); ν_{max}(KBr)/cm^{-1} 2800–3200 (CHs), 1645 (C=O) and 1300 and 1120 (SO_2); δ_H(90 MHz; CD_3SOCD_3) 3.25 (3 H, s, SO_2Me), 3.94 (3 H, s, 1-Me), 7.38 (1 H, ddd, *J* 2.2, 8.5, 6-H), 7.63 (1 H, dd, *J* 2.4, 11.2, 8-H), 8.31 (1 H, dd, *J* 6.6, 8.8, 5-H) and 8.60 (1 H, s, 2-H).

Method B: by methylation of 7-fluoro-3-methylsulfonyl-4-quinolone **30**. Methyl iodide (0.4 cm^3, 4.3 mmol) was added to a stirred mixture of the alcohol **30** (containing *ca.* 5% of the 5-fluoro isomer; 1.0 g, 4 mmol), anhydrous potassium carbonate (0.6 g, 4.3 mmol) and dimethylformamide (10 cm^3). After being stirred overnight at room temperature the mixture was poured into water (50 cm^3) and the resulting solid was filtered off. This gave the *title compound* (0.76 g, 72%), m.p. 222–224 °C, as a 0.2 hydrate (Found: C, 51.0; H, 4.1; N, 5.4; S, 12.6; H_2O 1.1. Calc. for $C_{11}H_{10}FNO_3S{\cdot}0.2H_2O$: C, 51.0; H, 4.0; N, 5.4; S, 12.4; H_2O 1.4%) identical (TLC, IR and NMR) with that described in A.

Method C: by cyclisation of methyl 3-(3-fluoro-N-methylanilino)-2-methylsulfonylacrylate **29**. A solution of the ester **29** (2.2 g, 7.7 mmol) in diethyl ether (40 cm^3) was added to stirred polyphosphoric acid (30 cm^3) at room temperature. The mixture was heated to 95 °C for 4.5 h, and the diethyl ether was allowed to distil off. The mixture was then cooled and poured into water (180 cm^3) and the resultant mixture neutralised with aqueous 5 mol dm^{-3} sodium hydroxide. The resulting brown solid (1.51 g, 80%) was filtered off; TLC (silica gel, developing with dichloromethane–IMS, 98:2) indicated this to be a mixture of *7-fluoro-1-methyl-3-methylsulfonyl-4-quinolone* and a second component likely to be the corresponding 5-isomer (Found: C, 50.9; H, 4.1; N, 5.2; S, 12.5; H_2O 0.8. Calc. for $C_{11}H_{10}FNO_3S{\cdot}0.15H_2O$: C, 51.2; H, 4.0; N, 5.4; S, 12.4; H_2O 1.0%). Analytical HPLC (silica gel eluting with acetonitrile–triethylammonium formate buffer, 20:80) indicated an approximate 70:30 ratio for 7-:5-isomers. Flash chromatographic purification of a sample of the mixture (silica gel, eluting with dichloromethane–IMS, 97.5:2.5) gave pure 7-fluoro isomer identical (TLC and NMR) to that obtained in A.

1-Methyl-3-methylsulfinyl-7-piperidino-4-quinolone **4**.—A mixture of the ketone **1** (21.0 g, 87.9 mmol) and piperidine (210 cm^3) was stirred at 95–100 °C for 18 h to give a dark solution which was diluted with diethyl ether (1 dm^3) and cooled to 0 °C. The resulting solid was filtered off and recrystallised from isopropyl alcohol to give the *title compound* (21.7 g, 81%), m.p. 235–238 °C (Found: C, 62.85; H, 6.6; N, 9.0; S, 10.35. Calc. for $C_{16}H_{20}N_2O_2S$: C, 63.2; H, 6.6; N, 9.2; S, 10.5%); ν_{max}(KBr)/ cm^{-1} 2700–3050 (CHs), 1620 (C=O) and 1040 (S=O); δ_H(100 MHz; CD_3SOCD_3) 1.64 (6 H, br, 3 × CH_2), 2.80 (3 H, s, SOMe), 3.41 (4 H, br m, 2 × CH_2), 3.86 (3 H, s, 1-Me), 6.73 (1 H, d, 8-H), 7.05 (1 H, dd, 6-H), 7.89 (1 H, s, 2-H) and 7.99 (1 H, dd, 5-H).

Acknowledgements

We thank Dr. J. R. Housley and Dr. K. J. Nichol for discussions and encouragement when carrying out this work and Prof. A. McKillop (University of East Anglia) for help in the preparation of this manuscript. We also thank A. Beeby, A. Brewin, P. Daniels, V. Henstock and I. Millichip for technical support.

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Paper 3/05780A
Received 24*th September* 1993
Accepted 20*th October* 1993