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Studies on haloquinolines : Part I — Synthesis and characterisation of substituted haloquinolines

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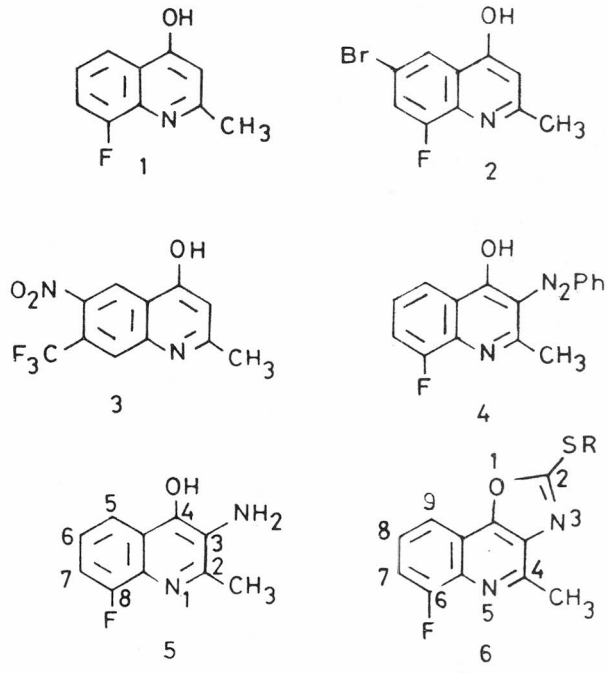
Condensation reaction of halogenated anilines with ethyl acetoacetate affords quinoline **1,2,3**. The compound **1** is coupled with benzenediazonium chloride and then reduced to furnish 3-amino-quinoline **5** which undergoes cyclisation with carbon disulphide to give the mercaptooxazolo[4,5-*c*]-quinoline **6a**. The reaction of **6a** with RX produces the substituted mercapto derivatives **6b-m**. The compounds have been characterised by their analytical and spectral data.

A few quinoline derivatives are well known potential antimalarial drugs[1]. A large number of condensed oxazole systems are claimed to possess antibacterial and antifungal activities[2,3]. Building up of an oxazole ring on quinoline derivatives was carried out and their optical brightening ability and antimicrobial properties[5,6] were reported from our laboratories. Now we report the synthesis of fluoro substituted quinolines which may serve as key intermediates in organic synthesis.

Condensation of 2-fluoroaniline, 2-fluoro-4-bromoaniline or 4-nitro-3-trifluoromethylaniline with ethyl acetoacetate in the presence of polyphosphoric acid afforded the corresponding hydroxy methyl quinolines **1,2** and **3**.

The structures assigned to these compounds were established by their elemental analyses and spectral data. The IR spectra of these compounds showed absorption bands at 3300-3060 (−OH), 1680-1640 (C=O, tautomeric), 1620-1605 and 1570-1540 cm^{-1} (C=C). The ^1H NMR spectra of these compounds also supported their structures. The proton adjacent to fluorine (C7 in **1** and **2**) appeared as a doublet at δ 7.8-8.0. The proton at C-3 atom appeared as singlet at δ 6.0. Other aromatic protons appeared either as a singlets or multiplets. The OH proton appeared as a broad singlet at δ 11.3-12.2. This peak was absent in the deuterium exchanged spectra. The methyl protons at C-2 atom appeared as a singlet around δ 2.2-2.4. The mass spectra of these compounds displayed $M^{+\cdot}$ or MH^+ ion as the base peak. The loss of −CHO unit is common in these compounds.



One of these compounds (**1**) was selected for further investigation. This compound was coupled with benzenediazonium chloride to produce 4-hydroxy-8-fluoro-2-methyl-3-phenylazoquinoline **4** which was later reduced with sodium dithionite to generate 3-amino-4-hydroxy-8-fluoro-2-methyl-

quinoline **5**. Cyclisation of aminohydroxyquinoline **5** with carbon disulphide in methanolic potassium hydroxide produced 2-mercapto-6-fluoro-4-methyloxazolo[4,5-*c*]quinoline **6a**. Structures of all these intermediates were confirmed by their elemental analyses and spectral data. The IR spectrum of **6a** showed the absorption bands at 3254 (N-H), 2500 (w, −SH), 1644 (C=N), 1591.5 cm^{-1} (C=C). The ^1H NMR spectrum of **6a** in DMSO-d_6 displayed a broad singlet at δ 12.15 which disappeared with deuterium exchange was due to −SH proton. The doublet at δ 8.0 was assignable to the proton adjacent to fluorine. The remaining two aromatic protons appeared as a multiplet at δ 7.6-7.8. The methyl protons appeared as singlet at δ 2.65. The mass spectrum of **6a** showed the molecular ion peak as the base peak at m/z 234. Other major peaks appeared at m/z 205, 189, 173, 161.

The reaction of **6a** with various alkyl/aralkyl/acyl halides in the presence of methanolic potassium hydroxide gave the corresponding thioethers and thioesters. They were characterised by their analytical and spectral data.

Most of the IR absorption of alkyl/aralkyl/acyl derivatives were similar to those of mercaptooxazoloquinolines except for the bands around 2860 and 1475 ($-S-CH_2$) and 1360 cm^{-1} ($-S-CH_3$). The chemical shifts in the ^1H NMR spectra of these compounds indicated the presence of aromatic protons. The splitting pattern was similar to that of **6a**. The singlet at δ 2.65 is attributable to the methyl group. The characteristic peaks for other protons in the side chain were also present. The mass spectra of these derivatives also indicated similar type of fragmentation of quinoline ring. The loss of substituent attached to sulphur was common in many of these compounds.

Experimental Section

All melting points are uncorrected. Purity of the compounds was checked by TLC on silica gel-G with benzene-ethyl acetate (1 : 1) as solvent system. Elemental analyses were carried out on a Carlo-Erba Model EA 1108, CHNS-O elemental analyser. IR spectra (KBr) were taken on a Shimadzu FT IR-8101M spectrophotometer. ^1H NMR spectra were recorded at 200 MHz on a Varian Gemini FT NMR instrument using TMS as internal reference (chemical shifts in δ, ppm). Mass spectra were obtained on a Hewlett-Packard MS, EM-5989 A spectrometer at 70 eV. The physical and analytical data of compounds **6** are given in Table I.

8-Fluoro- 4-hydroxy- 2-methylquinoline 1. 2-Fluoroaniline (5.55 g, 0.05 mole) was added to polyphosphoric acid, prepared by stirring a mixture of phosphorous pentoxide (20 g) in phosphoric acid (12 mL), then ethyl acetoacetate (6.65 g, 0.05 mole) was added to it, and again stirred for 10 min. The reaction mass was slowly heated and maintained at 140°C for 2 hr. It was cooled to ambient temperature and 1 *N* hydrochloric acid (50 mL) added to it. After stirring for 10 min, the reaction mixture was neutralised with conc. aq. sodium hydroxide solution. The crude product separated was collected by filtration after washing with cold water. The solid was recrystallised from water, yield 6.5 g (73.5%), m.p. 232-36° (Found : C, 67.75; H, 4.50; N, 7.88; F, 10.71. $C_{10}H_8NOF$ requires C, 67.79; H, 4.52; N, 7.90; F, 10.73%); IR : 3260-3165 (OH), 1664 (C=O, tautomeric), 1600 (C=N), 1558 cm^{-1} (C=C); ^1H NMR (DMSO-d_6) : δ 11.6 (s, 1H, OH), 7.95 (d, 1H, C-7), 7.6 (m, 1H, C-6), 7.3 (m, 1H, C-5), 6.0 (s, 1H, C-3), 2.4 (s, 3H, CH_3); MS : m/z 178 (MH^+, 100), 177 ($M^{+\cdot}$, 74), 158 (M − F, 5), 148 (M − CHO, 44).

6-Bromo-8-fluoro- 4 -hydroxy- 2-methylquinoline (2). The above procedure was used with 4-bromo-2-fluoroaniline, yield 70%, m.p. 278-81° (Found : C, 46.86; H, 2.71; N, 5.45; F, 7.40. $C_{10}H_7NOFBr$ requires C, 46.89; H, 2.73; N, 5.47; F, 7.42%); ^1H NMR (DMSO-d_6 : δ 11.75 (s, br, 1H, OH), 7.95 (m, 2H, C-7, C-5), 6.0 (s, 1H, C-3), 2.4 (s, 3H, CH_3); MS : m/z 257 (M+2, 100), 255 (M^+, 98), 226 (M − CHO, 25), 176 (M − Br, 14), 148 (176 − CO, 12).

4-Hydroxy- 2 -methyl- 6 -nitro- 7 -trifluoromethylquinoline 3. The method adopted was similar to that for **1** except that 4-nitro-3-trifluoromethylaniline was used, yield 53%, m.p. 310-12° (Found : C, 48.49; H, 2.55; N, 10.28; F, 20.93. $C_{11}H_7N_2O_3F_3$ requires C, 48.52; H, 2.57; N, 10.29; F, 20.95%); ^1H NMR (DMSO-d_6) : 12.25 (br, 1H, OH), 8.65 (s, 1H, C-5), 8.05 (s, 1H, C-8), 6.2 (s, 1H, C-3), 2.4 (s, 3H, CH_3), MS : m/z 272 ($M^{+\cdot}$, 71), 242 (M − NO, 100), 226 (M − NO_2, 30), 222 (242 − HF, 38), 198 (226 − CO, 39).

8-Fluoro-4-hydroxy-2-methyl- 3 -phenylazoquinoline 4. A mixture of **1** (8.85 g, 0.05 mole), 5 *N* sodium hydroxide solution (100 mL) and water (20 mL) was cooled to 5°C and treated with ice-cold benzenediazonium chloride (from 0.06 mole aniline). The reaction mass was neutralised with ice-cold solution of 5 *N* hydrochloric acid. The red phenylazo derivative was collected and washed with water. The solid was dried and recrystallised from alcohol, yield 10.3 g (73%), m.p.

Table I — Characterisation data of 2-substituted mercapto-6-fluoro-4-methyloxazolo[4,5-*c*]quinolines **6**

Compd.	R	m.p. °C	Yield (%)	Mol. formula	Calcd. (Found) (%)			
					C	H	N	S
6a	H	260-65	43	$C_{11}H_7N_2OSF$	56.41 (56.39	2.99 2.97	11.96 11.95	13.67 13.65)
6b	CH_3	279-82	47	$C_{12}H_9N_2OSF$	58.06 (58.01	3.62 3.61	11.29 11.27	12.90 12.88)
6c	C_2H_5	282-84	41	$C_{13}H_{11}N_2OSF$	59.54 (59.53	4.19 4.19	10.68 10.68	12.20 12.19)
6d	$CH_2-CH=CH_2$	290-91	37	$C_{14}H_{11}N_2OSF$	61.31 (61.30	4.01 4.00	10.21 10.20	11.67 11.67)
6e	C_3H_7	287-88	42	$C_{14}H_{13}N_2OSF$	60.86 (60.85	4.71 4.70	10.14 10.11	11.59 11.57)
6f	$CH_2CH_2-CH_2Cl$	190-91	32	$C_{14}H_{12}N_2OSFCl$	54.10 (54.08	3.86 3.85	9.01 9.00	10.30 10.28)
6g	$CH_2-CO-ph$	165-67	31	$C_{19}H_{13}N_2O_2SF$	64.77 (64.75	3.69 3.68	7.95 7.92	9.09 9.07)
6h	$CH_2-CO-C_6H_4Cl(p)$	172-74	48	$C_{19}H_{12}N_2O_2SFCl$	58.99 (58.96	3.10 3.09	7.24 7.23	8.27 8.26)
6i	$CH_2-CO-C_6H_4Br(p)$	188-90	45	$C_{19}H_{12}N_2O_2SFBr$	52.91 (52.89	2.78 2.77	6.49 6.48	7.42 7.40)
6j	$CH_2-CO-C_6H_4NO_2(p)$	169-71	51	$C_{19}H_{12}N_3O_4SF$	57.43 (57.41	3.02 3.01	10.58 10.56	8.06 8.05)
6k	$CH_2-CO-C_6H_3F_2(2,4)$	163-64	53	$C_{19}H_{11}N_2O_2SF_3$	58.76 (58.74	2.83 2.81	7.21 7.19	8.24 8.23)
6l	$COCH_3$	250-52	39	$C_{13}H_9N_2O_3SF$	53.42 (53.40	3.76 3.76	9.58 9.56	10.95 10.93)
6m	COPh	270-71	40	$C_{18}H_{11}N_2O_2SF$	63.90 (63.87	3.25 3.24	8.28 8.26	9.46 9.45)

Compounds **6a-f, 6l-m** were crystallised from aq. methanol and **6g-k** from aq. dioxan. Satisfactory analyses were obtained for halogens.

165-68° (Found: C, 68.30; H, 4.25; N, 14.92; F, 6.73. $C_{10}H_{12}N_3OF$ requires C, 68.32; H, 4.27; N, 14.95; F, 6.76%); ^{1}H NMR (DMSO-d_6): δ 7.2-7.8 (m, 8H, Ar), 2.55 (s, 3H, CH_3); MS: m/z 281 ($M^{+\cdot}$, 26), 266 (M − CH_3, 10), 252 (M − CHO, 40), 204 (M − 77,10), 176 (M − $C_6H_5N_2$, 30), 120 (C_7H_3NF, 100).

3-Amino-8-fluoro-4-hydroxy- 2 -methylquinoline 5. A mixture of **4** (2.81 g, 0.01 mole), sodium dithionite (9 g), ethanol (15 mL), water (30 mL) and liquor ammonia (30 mL) was refluxed for 30 min until the colour of the solution was changed to yellow. The reaction mixture was filtered. The filtrate on cooling produced the hydroxyamino derivative. It was recrystallised from ethanol, yield 1.6 g (83%), m.p. 262-63° (Found: C, 62.48; H, 4.66; N, 14.55; F, 9.87. $C_{10}H_9N_2OF$ requires C, 62.50; H, 4.68; N, 14.58; F, 9.89%); ^{1}H NMR (DMSO-d_6): δ 11.3 (br, singlet, 1H, OH), 7.95 (d, 1H, C-7), 7.35-7.55 (m, 1H, C-6), 7.05-7.15 (m, 1H, C-5), 4.4 (br singlet, 2H, NH_2), 2.4 (s, 3H, CH_3); MS: m/z 192 (M^+, 100), 164 (M − CO, 23), 163 (M − CHO, 22), 148 (164 − NH_2, 10), 136 (164 − H_2CN, 15).

2-Mercapto-6-fluoro-4-methyloxazolo[4, 5-*c*]-quinoline 6a. A mixture of **5** (9.6 g, 0.05 mole), carbon disulphide (30 mL), potassium hydroxide (0.05 mole), methanol (40 mL) and water (10 mL) was refluxed for 36 hr. The reaction mixture was cooled and acidified with dil. acetic acid. The precipitated solid was collected by filtration and dried. The compound was recrystallised from ethanol, yield 8.0 g (68%), m.p. 260-65°; ^{1}H NMR (DMSO-d_6): δ 12.15 (br s, 1H, SH), 8.0 (d, 1H, C-7), 7.6-7.8 (m, 2H, C-8, C-9), 2.65 (s, 3H, CH_3); MS: m/z 234 ($M^{+\cdot}$, 100), 205 (M − CHO, 17), 201 (M − SH, 9), 189 (M − HCS, 5), 173 (201 − CO, 8), 161 (205 − CS, 7).

6-Fluoro-2-substituted mercapto-4-methyloxazolo[4,5-*c*]quinolines (6b-m). Compound **6a** (0.01 mole) was dissolved in methanol (20 mL) containing potassium hydroxide (0.015 mole) and

then an appropriate halide (0.01 mole added to it. The reaction mixture was refluxed for 4 hr and cooled. The solid that separated out was collected by filtration, washed with water, dried and recrystallised from a suitable solvent (Table I).

6b: ^{1}H NMR (DMSO-d_6): δ 7.8-7.9 (d, 1H, C-7), 7.3-7.5 (m, 2H, C-8, C-9), 2.6 (s, 3H, 4-CH_3), 1.9 (s, 3H, S-CH_3); MS: m/z 248 ($M^{+\cdot}$, 100), 233 ($M-CH_3$, 13), 215 ($M-CH_2F$, 56), 205 (233 − CO, 51).

6i: ^{1}H NMR (DMSO-d_6): δ 8.1 (d, 1H, C-7), 7.6-7.9 (m, 6H, Ar), 5.3 (s, 2H, CH_2), 2.8 (s, 3H, CH_3); MS: m/z 432 (M+2, 17), 430 (M^+, 14), 398 (M − S, 4), 234 ($M-C_8H_5OBr$, 38), 185 (98), 183 ($BrC_6H_4CO^+$, 100).

6j: ^{1}H NMR (DMSO-d_6): δ 8.45 (m, 4H, Ar), 7.95 (d, 1H, C-7), 7.65 (m, 2H, C-8, C-9), 5.35 (s, 2H, $-CH_2$), 2.8 (s, 3H, CH_3); MS: m/z 397 (M^+, 17), 367 (M − NO, 5), 335 (M − NOS, 5), 234 ($M-C_8H_5NO_3$, 39), 202 (234 − S, 15), 150 ($O_2NC_6H_4CO^+$, 100).

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