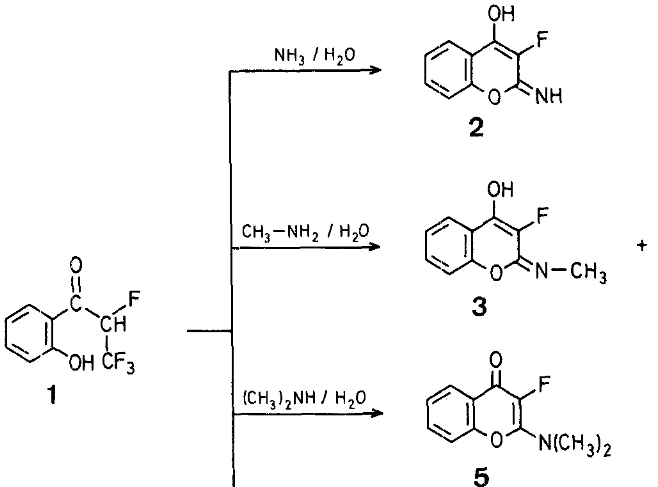
Synthesis of Fluorinated Derivatives of 4-Hydroxycoumarin and Chromone

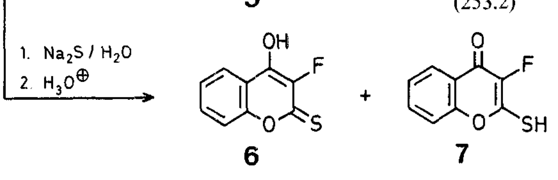
Wojciech DMOWSKI

Institute of Organic Chemistry, Polish Academy of Sciences, 00-961 Warsaw, Poland

The only derivative of coumarin containing a fluorine atom in the heterocyclic ring reported so far is 3-fluorocoumarin[1]. Earlier work in this laboratory has led to the discovery of a simple route to 3-fluoro-4-hydroxycoumarin[2] by treatment of *o*-hydroxy-2,3,3,3-tetrafluoropropiophenone (**1**) with sodium methoxide in methanol or with aqueous potassium hydroxide followed by acidification.

The present communication describes facile preparations of some new ring-fluorinated heterocyclic compounds by treatment of compound **1** with aqueous bases, i.e. ammonia, methylamine, dimethylamine, and sodium sulphide.





o-Hydroxy-2,3,3,3-tetrafluoropropiophenone (**1**) dissolves in an excess of aqueous ammonia to form a yellow solution from which, on standing, yellow crystals of 3-fluoro-4-hydroxy-2-iminocoumarin (**2**) are formed. Similarly, from a solution of compound **1** in aqueous dimethylamine crystallises 2-(*N*,*N*-dimethylamino)-3-fluorochromone (**5**) in the form of white needles.

The reaction with methylamine proceeds in two directions: the expected 3-fluoro-4-hydroxy-2-*N*-methyliminocoumarin (**3**) is obtained as minor product, but most of compound **1** reacts immediately to form a yellow precipitate of its methylammonium salt **4**.

Compound **1** dissolves in aqueous sodium sulphide solution to form a brown-yellow solution from which on acidification an orange precipitate is obtained. The precipitate is a 5 : 1 mixture (integrated ^{19}F-N.M.R. estimate) of 3-fluoro-4-hydroxy-2-thiocoumarin (**6**) and a compound which is supposed to be 3-fluoro-2-mercaptochromone (**7**). Pure **6** in the form of light-yellow crystals is obtained by repeated crystallisations from methanol. Extraction of the crude product with pentane gives very small amount of a purple-red substance enriched in compound **7**, however, product **7** could not be obtained in a pure form.

Melting points were determined on a capillary apparatus and are uncorrected. The I.R. spectra were measured with a Beckman IR 4240 instrument. The mass spectra were recorded at 70 eV with a LKB-2091 spectrometer. N.M.R. spectra were measured in $(CD_3)_2CO$ solutions with a JEOL JMN-4H-100 spectrometer; chemical shifts are in p.p.m. from internal C_6F_6 for the ^{19}F-N.M.R. spectra (positive upfield) and from internal TMS for the ^{1}H-N.M.R. spectra.

3-Fluoro-4-hydroxy-2-iminocoumarin (2):
Compound **1** (2.2 g, 10 mmol) is dissolved in 25% aqueous ammonia (25 ml). After a few minutes the formation of a fine precipitate is observed. After 24 h the precipitate is filtered off and dried over potassium hydroxide pellets; yield: 1.3 g (73%), m.p. 280 °C (dec.).

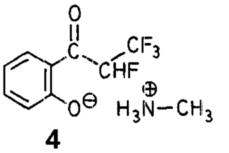
$C_9H_6FNO_2$	calc.	C 60.33	H 3.36	F 10.60	N 7.82
(179.2)	found	60.08	3.26	10.63	7.99

M.S.: $m/e = 179$ (M^+, 100%); 151 (C_8H_6FNO, 34%); 124 (C_7H_5FO, 13%); 121 ($C_7H_5O_2$, 26%); 92 (C_6H_4O, 19%).

I.R. (Nujol): $\nu = 3280$ (br., NH); 3080 (br., OH); 1652, 1600, 1540 cm^{-1} (C=N, C=C).

^{19}F-N.M.R. (DMF): $\delta = 23.4$ ppm.

Methylammonium *o*-(2,3,3,3-tetrafluoropropanoyl)-phenolate (4) and 3-Fluoro-4-hydroxy-2-(*N*-methylimino)-coumarin (3):
To 25% aqueous methylamine (15 ml), compound **1** (2.2 g, 10 mmol) is added in one portion. A yellow precipitate of the salt **4** is immediately filtered off, washed with small amount of the methylamine solution, and dried in the air at 20 °C for 48 h; yield: 1.8 g (71%); m.p. 78–80 °C.



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$C_{10}H_{11}F_4NO_2$	calc.	C 47.43	H 4.38	F 30.02	N 5.53
(253.2)	found	47.34	4.42	29.80	5.41

The methylammonium salt **4** dissolves readily in water and on acidification gives compound **1**.

From the filtrate, after removal of methylamine under vacuum, crystallises compound **3**. The product is filtered off, washed with water, and dried over potassium hydroxide. Compound **3** is purified by crystallisation from chloroform (white needles); yield: 0.5 g (20%); m.p. 167–169 °C.

$C_{10}H_8FNO_2$	calc.	C 62.17	H 4.17	F 9.84	N 7.25
(193.2)	found	61.86	4.03	9.94	7.11

M.S.: $m/e = 193$ (M^+, 100%); 165 (C_9H_8FNO, 22%); 150 (C_8H_5FNO, 30%); 121 ($C_7H_5O_2$, 20%); 96 (C_6H_4O, 16%).

I.R. (CCl_4): $\nu = 3450$ (sh, OH); 1660, 1623, 1562 cm^{-1} (C=N, C=C).

^{1}H-N.M.R.: $\delta = 3.22$ ppm (N—CH_3).

^{19}F-N.M.R.: $\delta = 24.9$ ppm.

2-(*N*,*N*-Dimethylamino)-3-fluorochromone (5):
Compound **1** (2.2 g, 10 mmol) is dissolved in 50% aqueous dimethylamine (20 ml) and left for 48 h. The crystalline product is filtered off and dried over potassium hydroxide pellets; yield: 1.5 g (73%); m.p. 133–134 °C.

$C_{11}H_{10}FNO_2$	calc.	C 63.76	H 4.86	F 9.17	N 6.76
(207.2)	found	63.53	4.72	9.09	6.59

M.S.: $m/e = 207$ (M^+, 100%); 179 ($C_{10}H_{10}FNO$, 13%); 165 (C_9H_8FNO, 18%); 164 ($C_9H_5FO_2$, 75%); 108 (C_7H_5F, 12%); 86 (C_4H_5FN, 33%).

I.R. (CCl_4): $\nu = 1640$, 1615, 1525 cm^{-1} (C=O, C=C).

^{1}H-N.M.R.: $\delta = 3.25$ ppm [$N(CH_3)_2$].

^{19}F-N.M.R.: $\delta = 19.0$ ppm.

3-Fluoro-4-hydroxy-2-thiocoumarin (6):

Compound **1** (5.0 g, 23 mmol) is dissolved in a solution of crystalline sodium sulphide (24 g, 100 mmol; ($Na_2S \cdot 9H_2O$)) in water (70 ml), the mixture is then left overnight, and then acidified with hydrochloric acid. The precipitate is filtered off and washed with water. The product is purified by dissolving the solid in 5% aqueous sodium hydroxide, filtration (removal of elemental sulphur and sodium fluoride) and acidification to leave a mixture of **6** and **7**; yield: 3.8 g (85%). Microanalysis of the mixture gives satisfactory results for the formula $C_9H_5FSO_2$.

$C_9H_5FSO_2$	calc.	C 55.09	H 2.57	F 9.68	S 16.31
(196.2)	found	54.89	2.60	9.62	16.15

M.S.: $m/e = 196$ (M^+, 68%); 180 (C_9H_5FSO, 29%); 121 ($C_7H_5O_2$, 100%); 120 ($C_7H_4O_2$, 29%); 93 (17%); 92 (19%).

Fractional crystallisation of the mixture from methanol gives pure **6**; yield: 0.8 g (18%); m.p. 198–201 °C.

$C_9H_5FSO_2$	calc.	C 55.09	H 2.57	F 9.68	S 16.31
(196.2)	found	55.17	2.37	9.63	16.09

I.R. (Nujol): $\nu = 3200$ (br., OH); 1610, 1560 (C=C); 1040 cm^{-1} (C=S).

^{19}F-N.M.R.: $\delta = -19.4$ ppm.

Compound **7** could not be obtained in pure form.

I.R. (Nujol): $\nu = 2550$ (br., SH); 1700; 1670 cm^{-1}.

^{19}F-N.M.R.: $\delta = 3.8$ ppm.

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[1] E. D. Bergmann, I. Shahak, *J. Chem. Soc.* **1961**, 4033.

[2] W. Dmowski, *J. Fluorine Chem.* **20**, 589 (1982).