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Synthesis of Some Fluoro-hydroxyketones and Related Compounds of Potential Biological Interest

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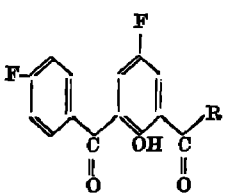
Several fluoro-hydroxy ketones and related compounds, derived from 2-bromo-4-fluoro- and 2-chloro-4-fluoro-phenol, have been prepared with a view to evaluating their biological activity.

Phenolic ketones bearing halogen atoms in the nucleus are known to be of manifold biological interest[1]. The chemistry of fluorine-containing phenolic ketones has recently been studied with a view to preparing substances of clinical importance. Buu-Hoï *et al*[2]. have prepared several fluorine-containing analogues of 4-hydroxypropiophenone as potential inhibitors of the growth of cancer metastasis. Some ketones, derived from *p*-fluoroanisole, have also been reported as possible biologically interesting compounds[3].

The present work is an extension of the same line of investigation. We have now prepared several phenolic ketones containing chlorine or bromine in addition to fluorine atoms. Nineteen esters of 2-bromo-4-fluorophenol and 2-chloro-4-fluorophenol were obtained by the action of the appropriate acid chloride on the phenol.

Thirteen of these esters, on the Fries rearrangement at 130-40° without a solvent, provided the corresponding *o*-hydroxyketones (Pyman test[4]). Six of them (No. 5,6,7, 10,16,19 of Table I) could not be rearranged even in presence of CS_2 as a solvent.

Three substituted 2-hydroxy-4',5-difluorobenzophenones of the following structure:



(R = alkyl)

have also been prepared from the corresponding 2-hydroxy-5-fluoroketones by a second Fries rearrangement. These are likely to possess antiamoebic activity due to presence of chelating -OH and -CO groups in the molecule.

The hydroxyketones and diketones were characterised through their 2,4-DNPs.

In addition to the above ketones, the phenoxyacetic acids, derived from the three phenols, used in this work, viz., 4-fluoro-, 2-chloro-4-fluoro-, and 2-bromo-4-fluoro-phenol,

1. Wilkinson *et al.*, *Biochem. J.*, 1951, **48**, 188; **49**, 710; Buu-Hoi *et al.*, *J. Chem. Soc.*, 1954, 1034.
2. *J. Org. Chem.*, 1953, **18**, 910
3. Buu-Hoi *et al.*, *ibid.*, 1954, **19**, 1617
4. *J. Chem. Soc.*, 1930, 280.
5. Albert *et al.*, *Brit. J. Exptl. Path.*, 1947, **28**, 69.

were converted into their acid hydrazides as some fluoro-acid hydrazides were reported[5,6] to have possessed tuberculostatic activity.

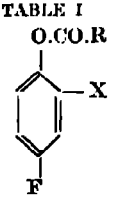
EXPERIMENTAL

2-Bromo-4-fluorophenol was prepared by treatment of *p*-fluorophenol (25 g.) with bromine (36 g.) in CS_2 medium; b.p. 75°/0.4 mm (Finger *et al.*[7], report b.p. 89°/1 mm).

2-Chloro-4-fluorophenol was prepared by bubbling chlorine gas (27g.) into *p*-fluorophenol (84 g.) in presence of iron filings at the room temperature for 7½ hours; b.p. 50°/1 mm (Finger *et al.*[7] report b.p. 88°/40 mm).

Esters.—Nineteen new esters were prepared by heating for 2 hours a mixture of the appropriate acid chloride (0.1*M*), 2-bromo-4-fluorophenol or 2-chloro-4-fluorophenol (0.1*M*), dry benzene (25 ml), and Mg ribbon (1.2 g.). The benzene was then distilled and the residual product was taken in ether. The ethereal layer was washed with 1% NaOH solution and water, dried, and the ether removed. The residual crude ester was either distilled under reduced pressure or recrystallised from aqueous ethanol. The esters obtained are listed in Table I.

TABLE I

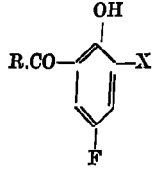


[X=Br or Cl; R=alkyl or substituted aryl group].

No.	Esters.	%Yield.	B.P. or M.P.	Formula.	%Carbon. Found.	%Carbon. Reqd.	%Hydrogen. Found.	%Hydrogen. Reqd.
			I. Esters of 2-bromo-4-fluorophenol.					
1	α-Crotonate	76.90	115-20°/2-2.5 mm	$C_{10}H_8O_2BrF$	46.18	46.33	2.99	3.68
2	Butyrate[n]	94.70	115-20°/1.5	$C_{10}H_{10}O_2BrF$	45.68	45.97	3.52	3.83
3	Valerate[n]	90.00	115-20°/2	$C_{11}H_{12}O_2BrF$	47.82	48.00	4.01	4.36
4	Caproate[n]	86.60	115°/2.5	$C_{12}H_{14}O_2BrF$	49.58	49.82	4.65	4.84
5	*p*-Fluorobenzoate	68.00	83°	$C_{13}H_7O_2BrF_2$	49.65	49.34	2.02	2.23
6	*o*-Chlororobenzoate	81.30	72°	$C_{13}H_7O_2BrClF$	47.15	47.34	2.00	2.12
7	Benzoate	74.00	54-55°	$C_{13}H_8O_2BrF$	52.59	52.88	2.53	2.71
8	Heptoate[n]	82.30	143°/1.5	$C_{13}H_{16}O_2BrF$	51.21	51.48	5.14	5.28
9	Caprylate[n]	97.00	140°/0.2	$C_{14}H_{18}O_2BrF$	52.87	52.99	5.49	5.67
10	Cinnamate	99.00	76°	$C_{15}H_{10}O_2BrF$	55.89	56.07	3.01	3.11
			II. Esters of 2-chloro-4-fluorophenol.					
11	Monochloroacetate	73.50	123-25°/2	$C_8H_5O_2Cl_2F$	42.90	43.04	2.09	2.24
12	α-Crotonate	69.00	117°/0.7-1	$C_{10}H_8O_2ClF$	55.00	55.17	3.61	3.67
13	Butyrate[n]	61.50	110°/0.5-1mm	$C_{10}H_{10}O_2ClF$	55.38	55.51	4.51	4.61
14	Valerate[n]	78.00	110°/1.5	$C_{11}H_{12}O_2ClF$	57.12	57.26	5.18	5.20
15	Caproate[n]	66.60	136°/2.5-3	$C_{12}H_{14}O_2ClF$	58.54	58.89	5.58	5.72
16	*o*-Chlorobenzoate	57.10	148°/50	$C_{13}H_7O_2Cl_2F$	54.56	54.73	2.31	2.45
17	Heptoate[n]	82.20	152°/1-1.5	$C_{13}H_{16}O_2ClF$	60.12	60.34	6.15	6.18
18	Caprylate[n]	77.80	140°/0.4	$C_{14}H_{18}O_2ClF$	61.49	61.65	6.51	6.60
19	Cinnamate	88.20	75°	$C_{15}H_{10}O_2ClF$	64.85	65.09	3.41	3.61

6. Buu-Hoi *et al.*, *Compt. rend.*, 1952, **235**, 329.
7. *J. Amer. Chem. Soc.*, 1959, **81**, 94.

TABLE II



[X=Br or Cl; R=alkyl or substituted aryl group].

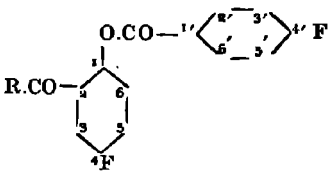
Sl. No.	Sl. No. of ester used.	R.	% Yield.	B.P.	% Carbon. Found.	% Carbon. Reqd.	% Hydrogen. Found.	% Hydrogen. Reqd.	2,4-Dinitrophenylhydrazones. M.P.	Formula.	%Nitrogen. Found.	%Nitrogen. Reqd.
I. *o*-Hydroxyketones derived from 2-bromo-4-fluorophenyl esters.												
1	1	Propenyl-	37.50	130°/1.5-2mm	46.15	46.33	2.91	3.08	above 250°	$C_{15}H_{12}O_5N_4BrF$	12.54	12.75
2	2	Propyl-	63.30	125-30°/2	45.72	45.97	3.61	3.83	187-89°	$C_{15}H_{14}O_5N_4BrF$	12.56	12.67
3	3	Butyl^n-	70.50	145-50°/4.5	47.52	48.00	4.10	4.36	183-84°	$C_{17}H_{16}O_5N_4BrF$	12.11	12.30
4	4	Amyl^n-	40.10	135°/0.2	49.64	49.82	4.70	4.84	147°	$C_{18}H_{18}O_5N_4BrF$	11.78	11.94
5	8	Hexyl^n-	90.00	148°/0.2-0.5	51.30	51.48	4.85	5.28	140-41°	$C_{19}H_{20}O_5N_4BrF$	11.41	11.59
6	9	Heptyl^n-	84.60	150°/0.2-0.3	52.70	52.99	5.51	5.67	150°	$C_{20}H_{22}O_5N_4BrF$	11.20	11.26
II. *o*-Hydroxyketones derived from 2-chloro-4-fluorophenyl esters.												
7	11	Chloromethyl-	63.30	116°/2mm	42.87	43.04	2.10	2.24	125°	$C_{14}H_9O_5N_4Cl_2F$	13.62	13.89
8	12	Propenyl-	85.50	138°/1.5	55.00	55.17	3.51	3.67	170°	$C_{15}H_{12}O_5N_4ClF$	13.87	14.19
9	13	Propyl-	93.70	122°/0.5	55.31	55.51	4.50	4.61	187-89°	$C_{15}H_{14}O_5N_4ClF$	14.00	14.12
10	14	Butyl^n-	77.70	140-41°/1	57.08	57.26	5.09	5.20	159°	$C_{17}H_{16}O_5N_4ClF$	13.49	13.64
11	15	Amyl^n-	62.50	130°/4	58.61	58.89	5.61	5.72	150°	$C_{18}H_{18}O_5N_4ClF$	13.01	13.19
12	17	Hexyl^n-	90.00	140°/0.5	60.10	60.34	6.09	6.18	132°	$C_{19}H_{20}O_5N_4ClF$	12.51	12.77
13	18	Heptyl^n-	70.00	160°/2.5-3	61.53	61.65	6.49	6.60	120°	$C_{20}H_{22}O_5N_4ClF$	12.01	12.37

Fries Rearrangement of the Esters.—The rearrangement was carried out by heating the ester (0.1*M*) and anhydrous aluminium chloride (0.1*M*) at 130-40° for 3 hours[8]. The *o*-hydroxyketones were isolated and purified in the usual manner and all responded to Pyman's test[4]. These were characterised through their 2,4-DNPs. The *o*-hydroxyketones obtained are listed in Table II. Esters (No. 5,6,7,10,16,19 of Table I) could not be rearranged even when CS_2 was used and later the reaction product was heated at 140° for 6 hours.

2-*Acetophenyl*-4,4′-*difluorobenzoate.*—2-Hydroxy-5-fluoroacetophenone (0.1*M*) was treated with *p*-fluorobenzoyl chloride (0.1*M*) in presence of Mg ribbon[9] (1.2 g.) in dry benzene (50 ml) at 90-100° for 4 to 5 hours under calcium chloride guard tubes. The esters were isolated as usual.

2-*Propiophenyl*- and 2-*butyrophenyl*-4,4′-*difluorobenzoates* were also prepared by a similar method. The ketonic esters were characterised through their 2,4-DNPs. These are listed in Table III.

TABLE III



[R=alkyl group]

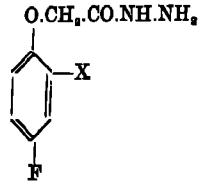
Sl. No.	Esters.	B.P.	Formula.	2,4-Dinitrophenylhydrazones. M.P.	Formula.	%Nitrogen. Found.	Reqd.
1	2-Acetophenyl-4,4′-	131°/0.5-1mm	$C_{15}H_{10}O_3F_2$	151°	$C_{21}H_{16}O_6N_4F_2$	7.41	7.65
2	2-Propiophenyl-4,4′-	110°/0.5	$C_{16}H_{12}O_3F_2$	140°	$C_{22}H_{18}O_6N_4F_2$	7.02	7.36
3	2-Butyrophenyl-4,4′-	131°/1.5-2	$C_{17}H_{14}O_3F_2$	182°	$C_{23}H_{20}O_6N_4F_2$	6.89	7.10

Migration of the Ketonic Esters.—The ester (1*M*) was intimately mixed with anhydrous aluminium chloride (4 to 5 *M*) and the reaction mixture was heated in an oil bath at 140-60° for 5 to 6 hours. The diketones were isolated in the usual manner. These were characterised through their 2,4-DNPs (Table V).

Fluoroaryloxyacetic Acid Hydrazides.—4-Fluoro-, 2-chloro-4-fluoro-, and 2-bromo-4-fluoro-phenols were convrted into the corresponding aryloxyacetic acids by the usual method of condensing fluorophenols with chloroacetic acid in presence of 33% NaOH solution. Their m.p.'s corresponded to those previously reported[7].

8. Sen and Tiwari, this *Journal*, 1952, **29**, 421.
9. Sen and Gupta, *ibid.*, 1961, **38**, 825.
10. Mel'nikov and Kukalenko. *Zhur. Obsh. Khim.*, 1959, **29**, 3708.

TABLE IV

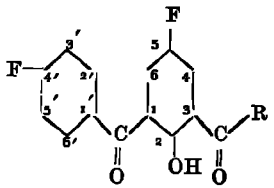


[X = H, Cl or Br].

Sl. No.	Ester.	B.P.	Formula.	Acid hydrazide.	M.P.	Formula.	%Nitrogen. Found.	%Nitrogen. Reqd.
1.	4-Fluorophenoxy-ethyl acetate	125°/1 mm 147-48°/22 mm (reported[10])	$C_{10}H_{11}O_3F$	4-Fluorophenoxy-acetyl hydrazide	103°	$C_8H_9O_2N_2F$	14.98	15.21
2.	2-Bromo-4-fluoro-phenoxyethyl acetate	120-25°/0.5	$C_{10}H_{10}O_3BrF$	2-Bromo-4-fluorophe-noxyacetyl hydrazide	112-15°	$C_8H_8O_2N_2BrF$	10.28	10.64
3.	2-Chloro-4-fluoro-phenoxyethyl acetate	117°/0.2	$C_{10}H_{10}O_3ClF$	2-Chloro-4-fluorophe-noxyacetyl hydrazide	94°	$C_8H_8O_2N_2ClF$	12.56	12.91

The aryloxyacetic acids were converted into their ethyl esters and the latter (1 *M*) refluxed with hydrazine hydrate (2*M*, 24%) for 3 hours in absolute ethanol medium. After removal of the solvent, the acid hydrazides were obtained as crystalline solids. These are recorded in Table IV.

TABLE V



R=alkyl group

Sl No.	Diketone.	M.P.	Formula.	Temp.	2,4-Dinitrophenylhydrazones. M.P.	Formula.	%Nitrogen. Found.	Reqd.
1.	2-Hydroxy-3-aceto-D	124-25°	$C_{15}H_{10}O_3F_2$	140°	190°	$C_{27}H_{22}ON_4Fz$	12.00	12.28
2.	2-Hydroxy-3-propio-D	160-61°	$C_{16}H_{12}O_3F_2$	150°	144-45°	$C_{28}H_{24}ON_4F_2$	11.73	11.91
3.	2-Hydroxy-3-butyro-D	150°	$C_{17}H_{14}O_3F_2$	160°	147°	$C_{29}H_{26}ON_4F_2$	11.33	11.57

N. B. D denotes 4′,5-difluorobenzophenone.

Attempts are being made to evaluate the possible biological activity of some of these compounds. The authors are thankful to the Council of Scientific and Industrial Research, New Delhi, for the award of a junior research fellowship to one of them (J.S.G.)

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