residue on fractionation yielded 5.0 g. (63.5%) of a colorless, vile-smelling liquid.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO]

Toxic Fluorine Compounds. VIII.[1] ω-Fluoroalkanesulfonyl Chlorides and Fluorides

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Representative members of the series of ω-fluoroalkanesulfonyl chlorides and fluorides were synthesized and their physical and toxicological properties determined. The toxicity figures suggested that the ω-fluoroalkanesulfonyl chlorides were metabolized by a mechanism akin to β-oxidation, whereas no clear-cut characteristics were apparent for the corresponding fluorides.

In earlier papers[2] in this series have been described the toxicological properties of various series of ω-fluoro-compounds. From the results so far presented, it seemed desirable next to examine simple analogs of the ω-fluorocarboxylic acid series, $F(CH_2)_nCOOH$. The ω-fluoroalkanesulfonic acids, $F(CH_2)_nSO_3H$, are the sulfonic acid analogs of the carboxylate series, and the two classes thus bear a superficial resemblance to one another. In order to assess the toxicological effects of these two classes, representative ω-fluoroalkanesulfonyl derivatives were prepared[3,4] for comparison with the previously described ω-fluorocarboxylates.[5] It has been reported that *n*-alkanesulfonic acids are nontoxic[6] and are excreted unchanged by the dog[7]; hence no great activity was anticipated for the ω-fluoro-derivatives.

Two members of the ω-fluoroalkanesulfonyl chloride series, $F(CH_2)_nSO_2Cl$, have been prepared previously, 2-fluoroethanesulfonyl chloride[8] and 3-fluoropropanesulfonyl chloride,[9] but toxicity determinations on these derivatives were indefinite. No member of the ω-fluoroalkanesulfonyl fluoride series, $F(CH_2)_nSO_2F$, has been previously described.

In this work, the ω-fluoroalkanesulfonyl chlorides were generally prepared by treatment of the corresponding thiocyanates[10] with chlorine water.[11] As an alternative route to 2-fluoroethanesulfonyl chloride, 2-fluoroethanol was converted to the *p*-toluenesulfonate,[10] which in turn was treated with thiourea[12] to form 2-fluoroethylisothiouronium *p*-toluenesulfonate; finally, the reaction of this salt with chlorine water[12] formed the sulfonyl chloride; yields are shown in Table I.

$$F(CH_2)_2OH \xrightarrow{TsCl} F(CH_2)_2OTs \xrightarrow{(H_2N)_2CS} [F(CH_2)_2SC(NH_2)=NH_2]^{+-}OTs \xrightarrow{Cl_2\ aq.} F(CH_2)_2SO_2Cl$$

(Ts- = *p*-$CH_3C_6H_4SO_2$-)

TABLE I

PREPARATION AND PHYSICAL CONSTANTS OF ω-FLUOROALKANESULFONYL CHLORIDES

Chloride	Yield, %	B.p., °C.	Mm.	$n^{25}D$
2-Fluoroethanesulfonyl[a]	64[b]	82–83	14	1.4509
	51[c]	82–83	14	
3-Fluoropropanesulfonyl	60	95.5–96	12	1.4481
4-Fluorobutanesulfonyl	77	117–118	13	1.4512
5-Fluoropentanesulfonyl	61	134–135	13	1.4513
6-Fluorohexanesulfonyl	38	150–151	15	1.4518

[a] Saunders, *et al.*,[8] report b.p. 81.5–84.5° (13 mm.). [b] From thiocyanate. [c] From isothiouronium *p*-toluenesulfonate.

The ω-fluoroalkanesulfonyl chlorides were converted to the ω-fluoroalkanesulfonyl fluorides by treatment with aqueous potassium bifluoride. In most instances, the product was steam distilled prior to isolation and purification. Yields are shown in Table II.

TABLE II

PREPARATION AND PHYSICAL CONSTANTS OF ω-FLUOROALKANESULFONYL FLUORIDES

Fluoride	Yield, %	B.p., °C.	Mm.	$n^{25}D$
2-Fluoroethanesulfonyl	45	62–63	14	1.3798
3-Fluoropropanesulfonyl	57	74–75	15	1.3868
4-Fluorobutanesulfonyl	56	89–90	12	1.3970
5-Fluoropentanesulfonyl	45	106–107	12	1.4040
6-Fluorohexanesulfonyl	22[a]	128–129	16	1.4092
n-Butanesulfonyl	57	60–61	17	1.3939

[a] Low yield partly due to very small scale reaction.

The ω-fluorine atom in these compounds is inert

(1) Issued as DRB Report No. SW-24.
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(11) T. B. Johnson and I. B. Douglass, *ibid.*, **61**, 2548 (1939).
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to most reagents, and the properties are therefore very similar to those of the unfluorinated alkanesulfonyl chlorides and fluorides. The physical constants are shown in Tables I and II.

From an examination of the toxicity values presented in Table III, it can be seen that the sulfonyl chlorides exhibit a definite alternation in toxicity. This suggests[3] that they are being metabolized by a biological mechanism similar or identical to β-oxidation and thus that they may be giving rise to ω-fluorocarboxylates of one less carbon atom, which in turn are responsible for the alternation in toxicity. On the other hand, the correlation between structure and toxicity is less apparent in the case of the sulfonyl fluorides; such activity as they possess may be connected with cholinesterase inhibition.[13]

TABLE III

TOXICITY RESULTS

Value of n in $F(CH_2)_nSO_2X$	L.D. 50 for mice, mg./kg. (intraperitoneal) X = Cl	X = F
2	19.5	8.8
3	64	84
4	18	10
5	>100	88
6	9	45
$CH_3(CH_2)_3SO_2X$	>100	70

Experimental[14]

Preparation of ω-Fluoroalkanesulfonyl Chlorides.—These were prepared from ω-fluoroalkyl thiocyanates or from ω-fluoroalkyl *p*-toluenesulfonates. The two procedures are represented by the following examples.

5-Fluoropentanesulfonyl Chloride.—5-Fluoroamyl thiocyanate[10] (16.5 g., 0.11 mole) was suspended in water (150 ml.) in a flask fitted with a stirrer and immersed in an ice–HCl bath at −5°. A rapid stream of chlorine gas was passed into the mixture, with constant stirring, until a permanent green color appeared in the aqueous phase (*ca.* 5 hr.). The stirring was continued for a further 4 hr. at 0–5°. The reaction mixture was extracted with ether and the extracts washed successively with aqueous sodium bisulfite, water, aqueous sodium carbonate and finally water again. After drying over anhydrous sodium sulfate and removing the ether, fractionation yielded 12.7 g. (61%) of 5-fluoropentanesulfonyl chloride, a colorless, pungent-smelling liquid.

2-Fluoroethanesulfonyl Chloride.—A mixture of 2-fluoroethanol (29 g., 0.45 mole) and *p*-toluenesulfonyl chloride (38 g., 0.2 mole) was stirred at 5–10°, and aqueous sodium hydroxide (32 ml. of 25% solution) was added. Stirring was continued at 12–14° for 2 hr. The solution was treated with thiourea (13 g., 0.175 mole) and warmed on a water-bath at 80° for 2 hr. After evaporation to dryness, the product was recrystallized from absolute ethanol and dried in a vacuum desiccator. 2-Fluoroethylisothiouronium *p*-toluenesulfonate (38.4 g., 73%) was thus obtained as a colorless solid, m.p. 127–128°.

2-Fluoroethylisothiouronium *p*-toluenesulfonate (25 g., 0.085 mole) was chlorinated and the acid chloride isolated and purified by the procedure described above for the preparation of 5-fluoropentanesulfonyl chloride. 2-Fluoroethanesulfonyl chloride (6.3 g., 51%) was thus obtained as a colorless, pungent-smelling liquid.

Preparation of ω-Fluoroalkanesulfonyl Fluorides.—The procedure used to prepare the members listed in Table II is represented by the following examples.

2-Fluoroethanesulfonyl Fluoride.—A mixture of 2-fluoroethanesulfonyl chloride (10 g., 0.07 mole), potassium bifluoride (11 g., 0.14 mole) and water (11 ml.) was stirred at room temperature for 20 hr. and then heated on a water-bath (70°) for 1 hr. The mixture was diluted with water and extracted with ether. The extract was dried over anhydrous sodium sulfate. After removal of the ether, the residue on fractionation through a modified Podbielniak column gave 4.0 g. (45%) of 2-fluoroethanesulfonyl fluoride, a colorless, pungent-smelling liquid.

4-Fluorobutanesulfonyl Fluoride.—A mixture of 4-fluorobutanesulfonyl chloride (8 g., 0.046 mole), potassium bifluoride (7.8 g., 0.10 mole) and water (15 ml.) was heated under reflux with constant stirring for 10 hr. The reaction mixture was steam distilled and the distillate extracted with ether. The extract was dried over anhydrous calcium chloride. After removal of the ether, the residue on fractionation yielded 4.0 g. (56%) of 4-fluorobutanesulfonyl fluoride, a colorless, pungent-smelling liquid.

TABLE IV

ANALYTICAL DATA FOR NEW COMPOUNDS

Compound	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Sulfur, % Calcd.	Found	Chlorine, % Calcd.	Found
$F(CH_2)_2SO_2Cl$	16.38	16.38	2.73	2.80			24.23	23.99
$F(CH_2)_3SO_2Cl$							22.12	22.16
$F(CH_2)_4SO_2Cl$	27.51	27.86	4.58	4.76	18.34	18.25	20.34	20.47
$F(CH_2)_5SO_2Cl$	31.83	31.76	5.30	5.41			18.82	18.72
$F(CH_2)_6SO_2Cl$	35.55	35.56	5.93	5.82			17.53	17.71
$F(CH_2)_2SO_2F$	18.46	18.72	3.08	3.26	24.62	24.25		
$F(CH_2)_3SO_2F$	25.00	24.95	4.17	4.31				
$F(CH_2)_4SO_2F$	30.38	30.88	5.06	5.18	20.25	20.09		
$F(CH_2)_5SO_2F$	34.89	34.96	5.82	5.90	18.61	18.79		
$F(CH_2)_6SO_2F$	38.71	38.84	6.45	6.58				
$CH_3(CH_2)_3SO_2F$	34.29	34.31	6.43	6.30	22.86	22.72		

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(14) (a) The majority of the microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J. Some of the chlorine determinations were carried out in the authors' laboratory by boiling with alkali followed by the standard Volhard method. Results are shown in Table IV. (b) The boiling points are uncorrected.