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

Toxic Fluorine Compounds. XI.[1] ω-Fluoroaldehydes

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Members of the ω-fluoroaldehyde series were prepared by several methods, of which the Nef and Rosenmund reactions were found to be most convenient. The free ω-fluoroaldehydes proved to be rather unstable, undergoing spontaneous polymerization. The physical constants of their crystalline derivatives provided the most reliable method of characterization. Representative members were shown to undergo the Knoevenagel reaction with malonic acid. The toxicities of the free aldehydes conformed closely to those of the corresponding alcohols and acids, thereby furnishing new evidence for the intimate biological relationship of these three classes of compounds.

The very similar toxicological properties of the ω-fluoroalcohols and ω-fluoroacids have been reported.[2,3] The ω-fluoroaldehydes, being intermediate between these two classes in regard to oxidation, were expected to conform to the same toxicity pattern. It was in order to verify this prediction that representative members of the ω-fluoroaldehyde series were synthesized and examined. Most of the preparations were carried out on a small scale, since the purpose of the investigation was to obtain only sufficient quantities for examination of physical and pharmacological properties; the instability of the members precluded prolonged storage of the aldehydes for other purposes.

Fluoroacetaldehyde, the simplest member of the series, recently has been prepared in a pure state,[4] and earlier studies have been carried out on the hydrate[5,6]; the latter readily formed a 2,4-dinitrophenylhydrazone, gave most of the aldehyde color reactions and on attempted dehydration underwent extensive polymerization. 10-Fluorodecanal also has been mentioned.[7] No other member of the ω-fluoroaldehyde series has been described.

Methods of Preparation.—Direct oxidation of ω-fluoroalcohols was examined briefly but proved unsatisfactory for the lower members. Thus, 3-fluoropropanol, when heated with potassium dichromate in sulfuric acid, formed acrolein, due to loss of hydrogen fluoride.

It seemed therefore that any successful method for the preparation of ω-fluoroaldehydes would require less harsh conditions. In simulation of the suggested metabolism of ω-fluoro-ω′-nitroalkanes to the corresponding aldehydes,[8] the next method of preparation to be examined was the Nef reaction.[9] This proceeds under mild conditions and at room temperature

$$F(CH_2)_nCH_2NO_2 \longrightarrow F(CH_2)_nCH{=}N(\rightarrow O)ONa \longrightarrow F(CH_2)_nCHO$$

By this means, 3-fluoropropanal, 4-fluorobutanal and 5-fluoropentanal were prepared. Yields and physical constants are listed in Table I.

Initially, the Rosenmund reduction[10] of acid chlorides was avoided because of the high temperatures required, but a few trial experiments indicated that it afforded a satisfactory route to the ω-fluoroaldehydes. The reaction was carried out in boiling xylene using a palladium–barium carbonate catalyst and oxygen-free hydrogen. The quality of the catalyst was an important factor in the reaction, and each batch was tested by the reduction of hexadecanoyl chloride to hexadecanal[11] before being used for the reduction of the rare and expensive ω-fluorocarboxylic acid chlorides.[12]

4-Fluorobutanal and 10-fluorodecanal[7] were prepared by conversion of the appropriate ω-fluoroalkene[13] to the glycol, followed by oxidation with periodic acid

$$F(CH_2)_nCH{=}CH_2 \longrightarrow F(CH_2)_nCH(OH)CH_2OH \longrightarrow F(CH_2)_nCHO$$

Methods examined in less detail for preparing ω-fluoroaldehydes included the reduction by lithium aluminum hydride of ω-fluoro-N-methyl-anilides,[14] the reaction of ω-fluoroalkylmagnesium chlorides with triethyl orthoformate,[15] and the reaction of ω-fluoroalkyl bromides[16] with the potassium salt of 2-nitropropane.[17] The products obtained by the last method were contaminated with unchanged fluorobromide but furnished the anticipated 2,4-dinitrophenylhydrazones in a pure state.

Properties.—When freshly prepared, the free ω-fluoroaldehydes were colorless, mobile liquids with the characteristic aldehyde odor. The members listed in Table I were immiscible with water but soluble in ether, benzene and ethanol.

It must be emphasized that the ω-fluoroaldehydes are all unstable to varying degrees, undergoing ready polymerization; for example, in some of the preparations of 11-fluoroundecanal, the trimer was formed almost instantaneously and crystallized in the condenser during the distillation. This gen-

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eral instability readily explains the many low yields listed in Table I. For the same reason, the physical constants and toxicities are unreliable for any but a freshly prepared sample; in illustration of this, the refractive index of 4-fluorobutanal rose from 1.3837 to 1.4108 in about nine months, although stored in the dark in a sealed glass ampoule. It is therefore recommended that solid derivatives of the ω-fluoroaldehydes be used as the most reliable means of characterization.

The chemical properties of the free ω-fluoroaldehydes appear to be very similar to those of the non-fluorinated analogs. Thus, they readily form 2,4-dinitrophenylhydrazone and methone derivatives and undergo condensation reactions of the Knoevenagel type.[3]

Fluoroacetaldehyde hydrate had previously been reported[5] to have a toxicity equal to that of methyl fluoroacetate. The toxicities of the higher, free ω-fluoroaldehydes, listed in Table I, follow the usual dichotomous pattern previously described[7,18] for other series of ω-fluoro compounds and in particular for the ω-fluoroalcohols[2] and ω-fluorocarboxylic acids.[3] Thus new evidence for the intimate biological relationship of alcohols, aldehydes and acids is furnished, together with a further example of the ω-fluorine atom acting as a biological "tracer."

Experimental[19]

The experimental details are subdivided according to the methods listed in Table I. Representative examples are given below.

Method 1. The Nef Reaction.[9] **4-Fluorobutanal.**—4-Fluoro-1-nitrobutane[8] (0.52 g.) was dissolved in aqueous sodium hydroxide (50 ml., containing 2.67 g. of sodium hydroxide), and the solution was added dropwise to an ice-cold stirred solution of sulfuric acid (6 g.) in water (35 ml.). Nitrous fumes were evolved and an aldehyde odor was apparent. When the addition was complete, the reaction mixture was added slowly to a solution of 2,4-dinitrophenylhydrazine (0.85 g.) in ethanol (30 ml.) and concd. sulfuric acid (5 ml.). The resultant precipitate (0.85 g., 73%) was filtered, washed, dried and recrystallized from methanol. The derivative was proved (mixed m.p.) to be identical with that obtained by the oxidation of 5-fluoro-1-pentene.

In order to obtain the free 4-fluorobutanal, 4-fluoro-1-nitrobutane (23.32 g.) was dissolved in cold aqueous sodium hydroxide (325 ml. containing 24 g. of sodium hydroxide); this solution was added dropwise over a period of 90 minutes to a stirred ice-cold solution of sulfuric acid (35 g.) in water (200 ml.). The mixture was extracted with ether. The extracts were washed once with aqueous sodium bicarbonate, three times with water and dried over anhydrous sodium sulfate. Removal of the solvent followed by fractional distillation of the residue afforded 4-fluorobutanal (3.9 g., 22%).

5-Fluoropentanal.—5-Fluoro-1-nitropentane[8] (18.84 g.) was added to a suspension of calcium hydroxide (10 g.) in water (250 ml.), and the mixture was stirred for 1 hr. to dissolve the nitrocompound. The resultant suspension was added dropwise over a period of 45 minutes to an ice-cold stirred solution of sulfuric acid (15 g.) in water (150 ml.). After stirring for 15 minutes longer, the mixture was filtered and the precipitate washed with ether. The filtrate was extracted with additional ether and the combined extracts were washed once with saturated sodium bicarbonate solution and twice with water. After drying over anhydrous sodium sulfate and removal of the solvent, the residue on fractionation yielded 5-fluoropentanal (4.7 g., 32%).

Method 2. Olefin Oxidation.[20,21] **10-Fluorodecanal.**—To a well-stirred mixture of 11-fluoro-1-undecene[13] (10 g., 0.058 mole) and 100% formic acid (30 ml.) at room temp. was added 29% hydrogen peroxide (7 g., 0.06 mole). The mixture was stirred and heated at 40° for 21 hr. The excess formic acid was removed under reduced pressure at 40°, and the residue was refluxed for 1 hr. with 3 *N* aqueous sodium hydroxide (50 ml.). A large excess of hot water was added, and the crude glycol layer was separated. This was washed with hot water, extracted with ether and the extract washed with cold water. Removal of the ether gave crude 11-fluoro-1,2-dihydroxyundecane (9 g., 75%), which, after drying for two days in a vacuum desiccator, had a m.p. of 42–43°.

A solution of potassium periodate (6.9 g., 0.03 mole) in 1 *N* sulfuric acid (300 ml.) at 20° was added to a solution of the crude glycol (6 g., 0.03 mole) in ethanol (350 ml.) at 40°. After 10 minutes, the clear solution was cooled to 15° and diluted with sufficient water to dissolve the precipitate. The product was extracted with ether and then steam distilled. The crude aldehyde was isolated from the distillate by extraction with ether and purified by distillation. Two grams of 10-fluorodecanal were thus obtained; this represents a yield of 30% based on 11-fluoro-1-undecene, or 39.5% on the crude glycol.

In the preparation of **4-fluorobutanal**, the very soluble intermediate glycol was not isolated. Instead, the solution obtained after boiling with 3 *N* sodium hydroxide was acidified with dilute sulfuric acid and then added dropwise to the solution of periodic acid. The aldehyde was isolated by extraction with ether and purified in the usual way.

Method 3. Reduction of N-Methylanilide.[14] **6-Fluorohexanal.**—6-Fluorohexanoyl chloride[12] (10.48 g., 0.069 mole) was dissolved in anhydrous benzene (20 ml.) and added dropwise to a solution of N-methylaniline (15 g., 0.14 mole) in anhydrous benzene (20 ml.). After standing for one hour at room temperature, the mixture was poured into water and extracted with ether. The ether extracts were washed twice with dilute hydrochloric acid, once with water, once with saturated sodium bicarbonate solution and finally with water. After drying over anhydrous sodium sulfate and removal of the solvent, the pale yellow oil was further dried by azeotropic distillation of three successive portions of anhydrous benzene.

Lithium aluminum hydride (0.76 g., 0.02 mole) in anhydrous tetrahydrofuran (60 ml.) was added dropwise to a solution of the above crude N-methylanilide in anhydrous tetrahydrofuran (50 ml.). The reaction was carried out in an atmosphere of nitrogen, and moisture was rigorously excluded. The temperature of the stirred mixture was maintained at −10° for 2 hr., and then allowed to warm slowly to room temperature overnight. The careful addition of water (50 ml.) destroyed the excess hydride, and the gelatinous precipitate so formed was dissolved by 6 *N* hydrochloric acid. The solution was extracted with ether, and the extract was washed successively with saturated sodium chloride, saturated sodium bicarbonate and water. After drying over anhydrous sodium sulfate and removing the ether, the residual liquid was fractionated, yielding 6-fluorohexanal (1.90 g., 23%). By the direct addition of the N-methylanilide to lithium aluminum hydride, even lower yields were obtained. Depending on the conditions of the reaction, varying amounts (20–30%) of 6-fluorohexanol[2] were always isolated.

Method 4. Rosenmund Reduction.[10] **Reagents.**—The palladium–barium carbonate catalyst was prepared as described by Vogel.[22] Xylene and toluene were purified by treatment with concentrated sulfuric acid.[23] Oxygen-free hydrogen was prepared as follows: commercial hydrogen was passed through a guard tube, two oxygen scrubbers containing an alkaline solution of sodium anthraquinone-β-sulfonate over zinc amalgam,[24] a soda-lime tower and a final guard tube, before being passed into the hydrogenation apparatus. The sulfur–quinoline poison was prepared as described by Mosettig and Mozingo.[10]

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TABLE I

ω-FLUOROALDEHYDES AND DERIVATIVES

Compound	Formula	Method of prepn.[a]	Yield, %	B.p. °C.	B.p. Mm.	$n^{25}D$	Melting point, °C.	L.D.50 to mice (intraperitoneal), mg./kg.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
3-Fluoropropanal	$F(CH_2)_2CHO$	1	42[b]											
2,4-DPH[c,k]							127–127.5						21.88	21.78
4-Fluorobutanal	$F(CH_2)_3CHO$	1	73[b]											
		1	22[d]	49	50	1.3837		2.05	53.33	53.44	7.78	7.66		
		2	18[d]											
2,4-DPH[e]							127–128						20.74	20.99
Methone deriv.[f]							119.5–120.5		68.18	68.44	8.29	8.29		
5-Fluoropentanal	$F(CH_2)_4CHO$	1	56[b]											
		1	18[d]	55–56	20	1.3948		81	57.69	57.45	8.65	8.44		
		1[g]	32[d]											
2,4-DPH[c]							116–117						19.72	19.78
6-Fluorohexanal	$F(CH_2)_5CHO$	3	23[d,h]	65–68	12	1.4078		0.58	60.96	60.64	9.32	9.19		
2,4-DPH[e]							105.5–106						18.79	18.77
7-Fluoroheptanal	$F(CH_2)_6CHO$	4	24[d]	74–75	10	1.4120		>100	63.63	63.56	9.85	9.73		
2,4-DPH[e]							103–104						17.95	18.01
8-Fluoroöctanal	$F(CH_2)_7CHO$	4	48[d]	85–86	9	1.4158		2.0	65.75	65.74	10.34	10.56		
2,4-DPH[e]							97–98						17.18	17.46
9-Fluorononanal	$F(CH_2)_8CHO$	5	37[d,i]	99–100	9	1.4220		53	67.50	67.54	10.70	10.82		
2,4-DPH[e]							101.5–102						16.46	16.36
10-Fluorodecanal	$F(CH_2)_9CHO$	2	30[d]	119–120	15	1.4258		1.95	68.98	68.80	10.92	10.77		
		4	40[d]											
2,4-DPH[e]							94–95						15.82	15.98
11-Fluoroundecanal[j]	$F(CH_2)_{10}CHO$	4	44[d]	130–131	11	1.4270		>40	70.18	70.34	11.25	11.16		
2,4-DPH[e]							103–104						15.22	15.48

[a] Methods of preparation: 1, Nef reaction; 2, from the ω-fluoroalkene[13] by conversion to the diol and then oxidation with periodic acid (% yield based on ω-fluoroalkene); 3, reduction by lithium aluminum hydride of ω-fluoro-N-methyl-anilides; 4, Rosenmund reduction of ω-fluorocarboxylic acid chlorides[12]; 5, the reaction of ω-fluoroalkylmagnesium chlorides with triethyl orthoformate. [b] Yield estimated as the 2,4-dinitrophenylhydrazone. [c] Recrystallized from ethanol. [d] Isolated as the free aldehyde. [e] Recrystallized from methanol. [f] Recrystallized from aqueous methanol. [g] Using the calcium salt as the intermediate. [h] 6-Fluorohexanol[2] was also isolated (20–30% yield). [i] Total yield of free aldehyde and corresponding diethyl acetal[15]; yield of pure, free aldehyde was 25%. [j] A solid was often obtained in this preparation, which, from molecular weight determinations, proved to be the trimer. It formed a 2,4-dinitrophenylhydrazone, identical with that derived from the monomer. The toxicity determination was carried out using the trimer, the relative insolubility of which in propylene glycol precluded high dose levels. [k] 2,4-DPH = 2,4-dinitrophenylhydrazone.

The reaction was carried out in an all-glass micro-hydrogenator.[25] The equipment and each batch of catalyst were tested by the reduction of hexadecanoyl chloride to hexadecanal.[11]

8-Fluoroöctanal.—Xylene (50 ml.), palladium–barium carbonate catalyst (2.0 g.) and sulfur–quinoline poison (0.2 ml.) were heated to boiling. A slow stream of oxygen-free hydrogen was bubbled through the boiling solution to remove any residual traces of moisture. Freshly prepared 8-fluorooctanoyl chloride[12] (12.9 g., 0.071 mole) was then added and the passage of hydrogen was continued, but more rapidly. The effluent gases were passed through a gas disperser into water. This aqueous solution was titrated with 1 *N* sodium hydroxide (using phenolphthalein as indicator), and the hydrogenation was continued until no further liberation of hydrogen chloride could be detected (total quantity evolved usually amounted to 75–85% of the theoretical). After cooling, the mixture was filtered and the catalyst washed thoroughly with ether. The ethereal washings were added to the xylene solution, and the combined solutions were washed once with water, once with saturated sodium bicarbonate solution and finally with water. After drying over sodium sulfate and removing the solvents, the residue was fractionated under reduced pressure, yielding 8-fluorooctanal (5.07 g., 48%).

Method 5. Grignard Reaction with Triethyl Orthoformate.—To be described later.[15]

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