mercury-filled gas storage buret and two manometers, for measuring pressure in both the buret and the equilibration flask. The free volume in the flask and line were known. Increments of carbon dioxide were admitted to the flask and the solution was stirred magnetically until equilibrium was reached. Measurement of total pressure over the solution allowed calculation of the quantity of carbon dioxide absorbed by the solution after each addition. Figure 2 is a plot of the data.

Repetition of the experiment with pure methanol (measured vapor pressure at 30°, 162 mm.; literature,[33] 163 mm.) yielded the following solubility data, in mmoles of carbon dioxide per 50 ml. of methanol at the indicated pressure: 1.6 at 566 mm., 2.7 at 621; 3.2 at 688, 3.5 at 723.

(33) N. A. Lange, "Handbook of Chemistry," 9th Ed., Handbook Publishers, Inc., Sandusky, Ohio, 1956, p. 1432.

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

Toxic Fluorine Compounds. XVIII.[1] The Synthesis of the Toxic Principle of *Dichapetalum toxicarium* (18-Fluoro-*cis*-9-octadecenoic Acid) and Related ω-Fluoro Unsaturated Acids[2,3]

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18-Fluoro-*cis*-9-octadecenoic acid (ω-fluoro-oleic acid), synthesized in 36.5% over-all yield utilizing acetylenic intermediates, has been shown to be identical with the toxic principle of *Dichapetalum toxicarium*. Other ω-fluoro unsaturated acids have been prepared, including the isomeric *trans*-acid (ω-fluoro-elaidic acid). The toxicities of all new ω-fluoro compounds have been determined; the results, interpreted in terms of previously reported metabolic routes, provide additional evidence for the catabolism of aliphatic halides, nitriles and acids.

Dichapetalum toxicarium (*Chailletia toxicaria*, Don), a glabrous shrub occurring in Sierra Leone, produces a hard and woody fruit which is extremely toxic to warm-blooded animals. The powdered fruit has been used for killing rats; the common name of "ratsbane" has therefore been coined for the shrub. It is also known as "broke back" from its effect in producing paralysis of the lower limbs. The pharmacological, medical and historical aspects of the plant have recently been reviewed.[4] It has been widely used locally as an arrow poison, for poisoning enemy water supplies and, by witch doctors, for terrorizing the native population.

Peters and colleagues have concluded,[5] on the basis of nuclear magnetic resonance, infrared spectroscopy and ozonolysis, that the toxic principle is ω-fluoro-oleic acid. It was in order to confirm this conclusion that the following synthesis was undertaken, starting from 8-fluoro-octyl bromide

$$F(CH_2)_8Br + NaC{\equiv}CH \longrightarrow F(CH_2)_8C{\equiv}CH + I(CH_2)_7Cl \longrightarrow$$
$$F(CH_2)_8C{\equiv}C(CH_2)_7Cl + NaCN \longrightarrow$$
$$F(CH_2)_8C{\equiv}C(CH_2)_7CN \longrightarrow$$
$$F(CH_2)_8C{\equiv}C(CH_2)_7CONH_2 \longrightarrow$$
$$F(CH_2)_8C{\equiv}C(CH_2)_7COOH \longrightarrow$$
$$F(CH_2)_8CH{=}CH(CH_2)_7COOH(cis)$$

Because 8-fluoro-octyl bromide[6] is expensive and time-consuming to prepare, the entire synthesis was first carried out on a trial basis starting from the more readily available 6-fluorohexyl bromide.[6] This led to 16-fluoro-*cis*-9-hexadecenoic acid (ω-fluoropalmitoleic acid), an interesting compound in its own right and one which provided a ready source of 16-fluorohexadecanoic acid (ω-fluoropalmitic acid). The toxicities of these acids are discussed later.

8-Fluoro-octyl bromide, previously prepared[6] in low yield from 1,8-dibromo-octane by partial halogen exchange, was obtained in 89% yield from 8-fluoro-octanol[7] by treatment with phosphorus tribromide. Conversion of the fluorobromide to 10-fluoro-1-decyne was accomplished in 60% yield by reaction with sodium acetylide in xylene–dimethylformamide[8]; the use of organic solvents for the preparation of sodium acetylide and for its subsequent reaction with ω-fluoroalkyl halides is more convenient than the older procedure[9] involving liquid ammonia. An even more convenient procedure involves the very recently introduced[10] lithium acetylide stabilized as the ethylenediamine complex; use of this material obviates the need for gaseous acetylene and gives a higher yield of product. Thus, 6-fluorohexyl chloride gave 8-fluoro-1-octyne in 71% yield. This is the only method which gives high yields of 1-alkynes directly from chlorides; however, the use of bromides is usually preferable because of a lower reaction temperature, and because the chlorides and resultant 1-alkynes have very similar boiling points.

Previous work[9] had indicated that the ω-fluoro-1-alkynes, in the presence of reactants such as sodamide and Grignard reagents, tended to give fluorine-free mixtures rather than form the expected ω-fluoroacetylides. In initial attempts to convert 10-fluoro-1-decyne to 1-chloro-17-fluoro-8-heptadecyne, preformed lithium amide in liquid ammonia was examined as the reagent; no reaction occurred, and unchanged starting materials were recovered. However, by using lithium amide formed *in situ*[11] from pure metallic lithium in liquid ammonia, 10-fluoro-1-decyne and 1-chloro-7-iodoheptane gave the required chlorofluoroheptadecyne in 89.4% yield. Reaction of this last compound with sodium cyanide in dimethyl sulfoxide[12] produced the corresponding nitrile in 93.5% yield.

Preliminary work using 15-cyano-1-fluoro-7-pentadecyne had indicated the difficulty of hydrolyzing this type of nitrile, because the triple bond is susceptible to strongly acidic reagents and the fluorine to vigorous alkaline treatment. Methanolysis was therefore examined, using absolute methanol saturated with hydrogen chloride; but, in the course of the reaction, the triple bond was also affected, forming methyl 9(10)-chloro-16-fluoro-9-hexadecenoate, $F(CH_2)_6CH{=}CCl(CH_2)_7COOCH_3$ (or the 10-isomer). Subsequent attempts at methanolysis using methanol and concentrated sulfuric acid resulted in concomitant hydration of the triple bond, giving methyl 16-fluoro-9(10)-oxohexadecanoate. The desired 16-fluoro-9-hexade-

(1) Part XVII. F. L. M. Pattison and J. J. Norman, *J. Am. Chem. Soc.*, **79**, 2311 (1957).

(2) Presented in part at the 140th Natl. Meeting of the American Chemical Society, Chicago, Ill., September, 1961.

(3) F. L. M. Pattison and R. E. A. Dear, *Nature*, **192**, 1284 (1961).

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(8) T. F. Rutledge, *ibid.*, **22**, 649 (1957); **24**, 840 (1959).

(9) F. L. M. Pattison and J. J. Norman, *J. Am. Chem. Soc.*, **79**, 2311 (1957).

(10) Foote Mineral Co., Route 100, Exton, Pa.

(11) M. S. Newman, M. W. Renoll and I. Auerbach, *J. Am. Chem. Soc.*, **70**, 1023 (1948).

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TABLE I

PROPERTIES OF ω-FLUORO-OLEIC ACID (NATURAL AND SYNTHETIC) AND OF ω-FLUORO-ELAIDIC ACID

		ω-Fluoro-oleic acid		ω-Fluoro-elaidic acid	Interpretation
		Natural	Synthetic		
M.p., °C.		12.4–13.5	15.8–16.8	53–54	
$n^{25}D$		1.4616	1.4598	..	
Infrared, cm.$^{-1}$[a]		3530	3525	3500	O—H stretching
		..	..	3030	C—H stretching of RCH=CHR′(*trans*)
		3007	3005	..	C—H stretching of RCH=CHR′(*cis*)
		2934	2933	2915	C—H stretching of CH_2
		2859	2859	2841	
		2670	2662	2667	Bonded O—H stretching
		1710	1710	1704	C=O stretching
		1465	1464	1462	C—H deformation of CH_2
		1432	1432	1435	
		1413	1413	1412	C—O stretching and O—H in-plane deformation
		1286	1285	1285	CH_2 vibration
		1048	1046	1043	C—F stretching
		1012	1015	1000	
		..	..	972	C—H out-of-plane deformation of RCH=CHR′(*trans*)
		945	942	945	O—H out-of-plane deformation
		726	726		C—H out-of-plane deformation of RCH=CHR′(*cis*)
N.m.r., c.p.s.[b]	ν^e	258	259	260	FCH_2—
	J_{HF}	47	47	47	
	J_{HH}[d]	5.9[e]	5.9[e]	5.9	
	ν^c	317	316	318	—CH=CH—
	J_{HH}[d]	3.6	3.6	3.6	

[a] Determined in CCl_4 using a Beckman IR-7 infrared spectrophotometer. [b] Determined using a Varian 60 Mc./sec. V-4302B spectrometer. [c] c.p.s. from tetramethylsilane. [d] Spin–spin interaction with adjacent methylene group. [e] Sheppard[5] gives J_{HF}, 48; J_{HH} (FCH_2–), 6.1; J_{HH} (–CH:CH–), 3.6.

cynoic acid was eventually obtained in 75.6% yield by methanolysis using methanol and *p*-toluenesulfonic acid, followed by alkaline hydrolysis of the intermediate ester.

Attempts to prepare ω-fluorostearolic acid by this last procedure gave inconsistent results. Hence recourse was made to the reaction of nitriles with hydrogen peroxide and potassium hydroxide in acetone solution,[13] a procedure which has been applied successfully[14] to the conversion of acetylenic nitriles to the corresponding amides; ω-fluorostearolamide was thus obtained in 77.4% yield. Hydrolysis of the amide was attempted by the following means: (a) treatment with nitrous acid (unsuccessful), (b) treatment with nitrosonium fluoroborate ($NO^+BF_4^-$) in tetramethylene sulfone[15] (amide hydrolyzed but triple bond also attacked), (c) treatment with aqueous potassium hydroxide (partially successful), and (d) treatment with alcoholic potassium hydroxide (successful). Although alcoholic potassium hydroxide will cause elimination of fluorine from compounds such as fluoroacetic acid, its effect on long chain ω-fluoro acids is less harsh[5]; ω-fluorostearolic acid was thus obtained in 94.5% yield. The method was then applied successfully to the C_{16}-fluoronitrile, forming 16-fluoro-9-hexadecynoic acid.

After this method had been completed, the direct alkaline hydrolysis of ω-fluorostearolonitrile was examined, using essentially the same conditions as those employed for the amide. Alcoholic potassium hydroxide (10%) thus formed ω-fluorostearolic acid in 66% yield. This procedure is more convenient, but gives a lower over-all yield than the above two-step process (73%).

Stereospecific hydrogenation of ω-fluorostearolic acid using Lindlar catalyst[16] formed ω-fluoro-oleic acid in excellent yield. The over-all yield from 8-fluoro-octyl bromide was 36.5%. Proof of structure of ω-fluoro-oleic acid has already been described,[3] based on its infrared and proton resonance spectra and its hydrogenation to ω-fluorostearic acid.[17,18] Its physical properties are in good agreement with those determined for the naturally occurring acid provided by Peters[5] (Table I).[3]

Although the spectroscopic results strongly indicated that the naturally occurring acid was *cis* and not *trans* (notably the absence of a band in the 970 cm.$^{-1}$ region of the infrared which is specific and diagnostic for a *trans*-alkene), final confirmation of the configuration required the synthesis and examination of ω-fluoro-elaidic acid. Stereospecific *trans* reduction of alkynes is usually accomplished by means of sodium in liquid ammonia. Replacing sodium by lithium and using stearolic acid as a model, it was found that no reduction occurred at atmospheric pressure, but that if the reaction was carried out under pressure at room temperature in an autoclave, elaidic acid was formed in 97.5% yield. This then constitutes one of the best methods for preparing elaidic acid in terms of convenience, yield and purity of the final product; moreover, the procedure seems to be widely applicable to the stereospecific partial reduction of acetylenes in general to the *trans* isomer. When the method was applied to ω-fluorostearolic acid, however, considerable loss of fluorine occurred, resulting in a mixture containing elaidic acid and ω-fluoro-elaidic acid. Attempted separation of the mixture, using a variety of techniques, was unsuccessful. Hence, an alternative procedure, involving elaidinization[19] of ω-fluoro-oleic acid, was examined. Preliminary work using oleic acid and selenium at 220–225° for one hour gave elaidic acid in satisfactory yield; 10-fluorodecanoic acid[17] under these

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TABLE II

TOXICITY RESULTS

Compound	LD_{50} (mice, intraperitoneal) mg./kg. (95% confidence limits)	Compound	LD_{50} (mice, intraperitoneal) mg./kg. (95% confidence limits)
$F(CH_2)_8C{\equiv}CH$	5.21 (2.74–9.46)		
$F(CH_2)_8C{\equiv}C(CH_2)_7Cl$	>94	$F(CH_2)_6C{\equiv}C(CH_2)_7Cl$	~100
$F(CH_2)_8C{\equiv}C(CH_2)_7CN$	>94	$F(CH_2)_6C{\equiv}C(CH_2)_7CN$	>100
$F(CH_2)_8C{\equiv}C(CH_2)_7COOH$	2.83 (2.26–3.54)	$F(CH_2)_6C{\equiv}C(CH_2)_7COOH$	3.99 (3.08–5.16)
$F(CH_2)_8CH{=}CH(CH_2)_7COOH(cis)$	2.36 (1.88–2.97)	$F(CH_2)_6CH{=}CH(CH_2)_7COOH(cis)$	1.40 (1.12–1.74)
$F(CH_2)_8CH{=}CH(CH_2)_7COOH(trans)$	1.22 (1.16–1.30)		
$F(CH_2)_8CH_2CH_2(CH_2)_7COOH$[a]	3.07 (2.16–4.37)	$F(CH_2)_6CH_2CH_2(CH_2)_7COOH$	3.36 (2.58–4.36)
		$F(CH_2)_6CH{=}CCl(CH_2)_7COOH$[b]	3.80 (2.50–6.14)

[a] Previously reported as 5.7 mg./kg.[17]; the value quoted in this table has been determined recently. [b] Or the 10-chloro isomer.

conditions was recovered unchanged, indicating that the C–F bond had survived intact. Treatment of ω-fluoro-oleic acid was then attempted and ω-fluoro-elaidic acid was obtained in 74.6% yield. Physical properties, the significance of which has been discussed previously,[3] are shown in Table I.

It is clear, from the figures presented in Table I, that there can be little doubt that the toxic principle of *Dichapetalum toxicarium* is indeed ω-fluoro-oleic acid. This acid is only the second naturally occurring organic fluorine compound to be characterized, the first being fluoroacetic acid (*Dichapetalum cymosum* and *Acacia georginae*). It is not improbable that there is some biogenetic relationship between these two fluorine compounds, but proof of this point will require further study.

Toxicity results of new compounds are shown in Table II. 10-Fluoro-1-decyne, being an ω-fluoro-1-alkyne containing an even number of carbon atoms,[9] was found to be toxic, as expected.

The metabolic fate of the non-terminal acetylenic link is under study by us, using the ω-fluorine atom, with its characteristic toxicological properties, as a "tag." A few comments can be given at the moment regarding the various acetylenic compounds in Table II. (a) The two ω-chloro compounds, $F(CH_2)_nC{\equiv}C(CH_2)_7Cl$, contain an odd number of carbon atoms and are non-toxic. This is the same result as was found for the corresponding saturated analogs, $F(CH_2)_mX$,[6] which were considered to be cleaved hydrolytically and then oxidized (*e.g.*, $F(CH_2)_5Cl \rightarrow F(CH_2)_5OH \rightarrow F(CH_2)_4COOH \rightarrow F(CH_2)_2COOH$); thus, the toxic fluoroacetic acid cannot be formed. (b) The two nitriles, $F(CH_2)_nC{\equiv}C(CH_2)_7CN$ contain an even[20] number of carbon atoms and are non-toxic; this too conforms with the results given by the corresponding saturated members, $F(CH_2)_mCN$,[21] which cannot give rise to fluoroacetic acid (*e.g.*, $F(CH_2)_5CN \rightarrow F(CH_2)_4COOH$ (+ HCN) $\rightarrow F(CH_2)_2COOH$). (c) The two ω-fluoroalkynoic acids, $F(CH_2)_nC{\equiv}C(CH_2)_7COOH$, contain an even number of carbon atoms and are very toxic; once again, this is consistent with the results given by the corresponding saturated ω-fluorocarboxylic acids, $F(CH_2)_mCOOH$.[18] In short, the acetylenic link appears to have little or no effect on the metabolic breakdown of these long-chain compounds; if oxidation and cleavage of the acetylenic link were in fact the main degradative step, then the six compounds discussed in this paragraph should all be equally toxic.

The three ω-fluoroalkenoic acids, $F(CH_2)_nCH{=}CH(CH_2)_7COOH$ (ω-fluoro-oleic, ω-fluoro-elaidic and ω-fluoropalmitoleic acids) show approximately the same toxicological pattern as that of the saturated ω-fluorocarboxylic acids, $F(CH_2)_mCOOH$. That ω-fluoro-elaidic acid is about twice as toxic as ω-fluoro-oleic acid indicates that the β-oxidation process may be favored by the *trans* configuration. The presence and location of one or more double bonds in a fatty acid has been reported to have little or no effect on the overall β-oxidation process[22]; in support of this, compounds having the following formulas all gave rise to benzoic acid *in vivo:* $C_6H_5CH{=}CHCOOH$, $C_6H_5CH_2CH_2CH{=}CHCOOH$, $C_6H_5CH_2CH{=}CHCH_2COOH$ and $C_6H_5CH{=}CHCH{=}CHCOOH$. The high toxicity of 9-(10)-chloro-16-fluoro-9-hexadecenoic acid implies that the chlorine atom is not inhibiting or blocking the β-oxidation process.

Experimental[23]

Many of the compounds described in this paper have been analyzed by gas chromatography. This method has been particularly useful in determining the extent to which a particular reaction has proceeded. Earlier analyses were carried out on a Barber–Coleman model 10 argon ionization chromatograph (by kind permission of Dr. K. K. Carroll of the Collip Medical Research Laboratory). More recently an Aerograph A-350 dual-column, temperature-programming model has been used. Best results were obtained using a 12 ft. × 0.25 inch column packed with 20% w./w. diethylene glycol succinate supported on 60/80 mesh regular firebrick. C_{16}-Compounds were generally analyzed at a temperature of 185°; for C_{18}-compounds, a temperature of 210° gave optimum results. ω-Fluoro compounds were found to have a retention time approximately 2.7 times that of the non-fluorinated analogs; this relationship has been observed previously.[5]

8-Fluoro-octyl Bromide (Improved Procedure[6]).—8-Fluoro-octanol[7] (47 g., 0.32 mole) was added dropwise with stirring to phosphorus tribromide (45 g., 0.165 mole) cooled in an ice-brine bath (−5°). Addition was complete in 35 minutes, at the end of which time the cooling bath was removed and the reaction mixture allowed to attain room temperature. After stirring for 3 hours at room temperature the reaction was completed by warming in an oil-bath at 120° for an additional hour. When cool, the reaction mixture was poured into water and extracted with ether. The extracts were washed successively with water, 10% sodium carbonate solution, and water. After drying over calcium chloride and removal of the ether, the product was fractionated to yield 59.5 g. (89%) of 8-fluoro-octyl bromide, b.p. 98–101° (11 mm.).

6-Fluorohexyl bromide[6] was prepared in 86% yield from 6-fluorohexanol[7] by the same procedure.

10-Fluoro-1-decyne.—Sodium dispersion[24] (50% in xylene, 20 g., 0.44 g.-atom of sodium) was suspended in dry xylene (240 ml.) in a 1-liter three-necked flask fitted with a stirrer, dropping funnel, condenser and a sintered-glass inlet. A slow stream of nitrogen was passed through the apparatus while the temperature was raised to 105° with stirring. The condenser was fitted with a calcium chloride drying tube, the exit of which was directly connected to the fume hood exhaust. The nitrogen flow was stopped and purified acetylene[8] was passed into the hot suspension, which rapidly turned dark brown and then gradually became lighter, passing through various shades of gray, until after 2.5 hours a chalk-white suspension was present. The acetylene flow was stopped and the flask and contents were

(20) The total carbon chain includes the CN.

(21) F. L. M. Pattison, W. J. Cott, W. C. Howell and R. W. White, *J. Am. Chem. Soc.*, **78**, 3484 (1956).

(22) A. J. Quick, *J. Biol. Chem.*, **77**, 581 (1928); R. T. Williams, "Detoxication Mechanisms," Chapman and Hall Ltd., London, 1959, p. 379.

(23) (a) The microanalyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. (b) Melting points are uncorrected. (c) Infrared results were obtained using a Beckman IR-7 or a Beckman IR-5A infrared spectrophotometer.

(24) Sodium dispersion (8 μ particle size) was kindly donated by U. S. Industrial Chemicals Co., 1275 Section Rd., Cincinnati, O., and appeared to be of excellent quality and uniformity; the 50% excess used in this experiment is probably an unnecessarily high safety margin.

allowed to cool. Redistilled dimethylformamide (160 ml.) was added, giving a total volume of diluent of 400 ml. (40% v./v. dimethylformamide), and 8-fluoro-octyl bromide (59 g., 0.28 mole) was added dropwise with vigorous stirring at room temperature. Addition was complete in 35 minutes and the mixture was stirred overnight (a total of 13.5 hours). Water (100 ml.) was added slowly to decompose the excess sodium acetylide and the resultant dark brown mixture was washed with two 200-ml. portions of water to remove dimethylformamide. Gas chromatographic analyses showed that all dimethylformamide was removed by this procedure. Distillation of the organic residue gave 26.2 g. (60.1%) of 10-fluoro-1-decyne, b.p. 81–82° (10 mm.), $n^{25}D$ 1.4250, d^{20}_4 0.877; principal bands of infrared spectrum (CCl_4, cm.$^{-1}$): 3344 (≡C—H, s), 2959 and 2882 (C—H, s), 2128 (C≡C, w), 1462 and 1437 (C—H, m), 1052 and 1013 (C—F, s), 633 (≡C—H, s).

Anal. Calcd. for $C_{10}H_{17}F$: C, 76.87; H, 10.97. Found: C, 76.48; H, 11.07.

8-Fluoro-1-octyne[9] was prepared similarly from 6-fluorohexyl bromide; b.p. 52–53° (15 mm.), $n^{25}D$ 1.4178; infrared maxima (CCl_4, cm.$^{-1}$): 3322 (≡C—H, s), 2941 and 2865 (C—H, s), 2119 (C≡C, w), 1458 and 1433 (C—H, m), 1049 and 1029 (C—F, s), 630 (≡C—H, s).

8-Fluoro-1-octyne[9] was also prepared using lithium acetylide complexed with ethylenediamine. Dimethyl sulfoxide (100 ml.), dried over calcium hydride, was placed in a three-necked 250-ml. flask fitted with a nitrogen inlet tube, a dropping funnel, a stirrer and a condenser. The whole experiment was carried out in a nitrogen atmosphere with rigorous exclusion of moisture. Lithium acetylide complex[10] (19.6 g., 0.2 mole based on 96% purity and a lithium acetylide content of 33.4%) was added rapidly with stirring, forming a pale brown solution. 6-Fluorohexyl chloride (27.7 g., 0.2 mole) was added dropwise with vigorous stirring. During the addition the temperature of the mixture was held at 25° by external cooling. The mixture was stirred for a further 3 hours at room temperature, and then was acidified with hydrochloric acid (50 ml. of 50:50 concentrated hydrochloric acid–water) to hydrolyze any unreacted lithium acetylide. The mixture was poured into water (200 ml.) and was extracted three times with ether (100 ml.). The extracts were washed with water, dried (calcium sulfate) and distilled to give recovered 6-fluorohexyl chloride (1.3 g.) and 8-fluoro-1-octyne (17.3 g., 71.2% based on reacted 6-fluorohexyl chloride), b.p. 154.5–155°, $n^{25}D$ 1.4166 (lit.[9] 77–78° (50 mm.), $n^{25}D$ 1.4165).

1-Chloro-17-fluoro-8-heptadecyne.—The following procedure was adapted from those of Ahmad and Strong,[25] and Huber.[26] Lithium[27] (1 g., 0.14 g.-atom) was added to liquid ammonia (250 ml.) containing ferric nitrate (0.05 g.). After stirring for 30 minutes, a dark-brown suspension of lithium amide[28] was present. 10-Fluoro-1-decyne (9 g., 0.058 mole) was added dropwise and with vigorous stirring over a period of 40 minutes and stirring was continued for a further 3 hours. 1-Chloro-7-iodoheptane[29] (15 g., 0.058 mole) was added over 1 hour, and stirring was continued for a further 4 hours. Ammonium chloride (5 g.) was added to neutralize any unreacted amide and the ammonia was allowed to evaporate. Water (100 ml.) was added to dissolve the inorganic salts. The product was thoroughly extracted with ether, washed with water and dried over sodium sulfate before distillation, which gave recovered fluorodecyne (5.4 g.) and 1-chloro-17-fluoro-8-heptadecyne (16.7 g.); this represents a conversion of 55.1% and a yield of 89.4%; b.p. 137° (0.25 mm.), $n^{25}D$ 1.4610, d^{20}_4 0.969; principal infrared peaks (CCl_4, cm.$^{-1}$): 2941 and 2874 (C-H, s), 1464 and 1433 (C-H, m), 1050 and 1010 (C-F, m), 651 (C-Cl, w).

Anal. Calcd. for $C_{17}H_{30}ClF$: C, 70.68; H, 10.47; Cl, 12.28. Found: C, 70.56; H, 10.38; Cl, 12.42.

15-Chloro-1-fluoro-7-pentadecyne was prepared similarly in 70.5% yield, b.p. 113° (0.15 mm.), $n^{25}D$ 1.4598, d^{20}_4 0.956. The infrared spectrum was very similar to that of the previous compound.

Anal. Calcd. for $C_{15}H_{26}ClF$: C, 69.07; H, 10.05; Cl, 13.60. Found: C, 68.90; H, 10.13; Cl, 13.76.

1-Cyano-17-fluoro-8-heptadecyne (ω-Fluorostearolonitrile).—Dimethyl sulfoxide was dried over calcium hydride, and sodium cyanide was dried overnight at 120°. Sodium cyanide (3.6 g., 0.073 mole) was suspended in dimethyl sulfoxide (25 ml.), and the suspension was warmed with stirring to 90° in an oil-bath; most of the cyanide dissolved at this temperature. 1-Chloro-17-fluoro-8-heptadecyne (16.7 g., 0.059 mole) in dimethyl sulfoxide (25 ml.) was added over a period of 20 minutes, and the ensuing mixture was stirred and heated at 135–140° for 30 minutes. After cooling, the reaction mixture was poured into water and extracted with ether. The extracts were washed with dilute hydrochloric acid to hydrolyze any isocyanide. Washing with water, drying (sodium sulfate), and distillation gave the nitrile (15.05 g., 93.5%), b.p. 166–168° (0.25 mm.), $n^{25}D$ 1.4578; infrared maxima (CCl_4, cm.$^{-1}$): 2941 and 2874 (C—H, s), 2252 (C≡N, w), 1464 and 1433 (C—H, m), 1048 and 1009 (C—F, m).

Anal. Calcd. for $C_{18}H_{30}FN$: C, 77.36; H, 10.82; N, 5.01. Found: C, 77.29; H, 10.77; N, 4.79.

15-Cyano-1-fluoro-7-pentadecyne was prepared by the same procedure in 87.7% yield; b.p. 134–136° (0.15 mm.), $n^{25}D$ 1.4551, d^{20}_4 0.917. The infrared spectrum was very similar to that of the previous compound.

Anal. Calcd. for $C_{16}H_{26}FN$: C, 76.45; H, 10.42. Found: C, 76.46; H, 10.34.

9(10)-Chloro-16-fluoro-9-hexadecenoic Acid.—15-Cyano-1-fluoro-7-pentadecyne (3.14 g., 0.0125 mole) was dissolved in absolute methanol (50 ml.) and anhydrous hydrogen chloride was passed in. The solution immediately became warm and refluxing began. A white solid precipitated and coagulated on further refluxing. After 2 hours the gas flow was stopped and the mixture was gently refluxed for a further 2 hours. The mixture was cooled, poured into water and extracted with ether. The extract was washed with sodium bicarbonate solution and then with water. After removal of the ether, the crude ester was hydrolyzed to the free acid with 10% aqueous sodium hydroxide. Acidification, extraction and distillation gave 3.05 g. (79.5%) of 9(10)-chloro-16-fluoro-9-hexadecenoic acid, b.p. 165° (0.075 mm.), $n^{25}D$ 1.4657; principal bands of infrared spectrum (CCl_4, cm.$^{-1}$): 2933 and 2865 (C—H, s), 2667 (O—H, m), 1709 (C=O, s), 1661 (C=C, w), 1462 and 1431 (C—H, m), 1412 (C—O and O—H, m), 1282 (CH_2, m), 1047 (C—F, m), 939 (O—H, m), 670 (C—Cl, w).

Anal. Calcd. for $C_{16}H_{28}ClFO_2$: C, 62.63; H, 9.20. Found: C, 62.29; H, 9.46.

16-Fluoro-9(10)-oxohexadecanoic Acid.—Attempted methanolysis of 15-cyano-1-fluoro-7-pentadecyne using 50:50 methanol–sulfuric acid (w./w.) resulted in considerable charring. After alkaline hydrolysis, the keto-acid was obtained in low yield, m.p. 60.5–61°. The sharpness of the melting point is consistent with a 1:1 eutectic of the 9- and 10-isomers.[30] The triple bond probably reacts as if it were symmetrically substituted, since the fluoro and carboxyl substituents are too remote to have any directing influence.

Anal. Calcd. for $C_{16}H_{29}FO_3$: C, 66.64; H, 10.14. Found: C, 66.93; H, 10.04.

16-Fluoro-9-hexadecynoic Acid.—15-Cyano-1-fluoro-7-pentadecyne (1.56 g., 0.0062 mole), *p*-toluenesulfonic acid (1.19 g., 0.0062 mole), methanol (0.25 g., 0.31 ml., 0.0078 mole) and benzene (10 ml.) were refluxed for 24 hours, poured into water, extracted with ether and the extracts were dried over a mixture of sodium sulfate and potassium carbonate. Removal of the ether yielded a pale yellow semi-solid mixture, which was refluxed and stirred for 14 hours with 10% aqueous sodium hydroxide (15 ml.). Acidification, extraction and removal of the ether gave 1.08 g. of the required product as a pale yellow crystalline solid (75.6%). Unreacted nitrile (0.23 g.) was recovered. Two recrystallizations from aqueous methanol afforded colorless acicular crystals, m.p. 43–43.5°. The infrared spectrum was very similar to that of ω-fluorostearolic acid (see below).

Anal. Calcd. for $C_{16}H_{27}FO_2$: C, 71.07; H, 10.07. Found: C, 71.40; H, 10.14.

18-Fluoro-9-octadecynoamide (ω-Fluorostearolamide).—1-Cyano-17-fluoro-8-heptadecyne (2 g., 0.0072 mole) was dissolved in acetone (50 ml.), 40% potassium hydroxide (1.5 ml., *ca.* 0.01 mole) and 4% hydrogen peroxide (38 ml.). The mixture was stirred at 50° for 24 hours. During this period the solution turned from water-white to a pale straw color. On pouring into water a voluminous white precipitate separated. The mixture was neutralized with dilute hydrochloric acid and then extracted with chloroform. Evaporation of the chloroform gave a pale yellow solid which had a strong odor of mesityl oxide (from acetone and KOH). Three recrystallizations from methanol gave 1.65 g. (77.4%) of the desired amide as white crystals, m.p. 85–86°; infrared maxima ($CHCl_3$, cm.$^{-1}$): 3509 and 3425 (free N—H, m), 3344 and 3195 (bonded N—H, m), 2941 and 2865 (C—H, s), 1672 (C=O, s), 1595 (C—N and N—H, m), 1466 and 1435 (C—H, m), 1391 (amide, m), 1114 (m), 1050 and 1001 (C—F, m).

Anal. Calcd. for $C_{18}H_{32}FNO$: C, 72.68; H, 10.85. Found: C, 72.83; H, 10.86.

16-Fluoro-9-hexadecynoamide was prepared similarly in 60.5% yield, recrystallized from methanol; m.p. 88.5–89°. The in-

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(26) W. F. Huber, *ibid.*, **73**, 2730 (1951).

(27) Purchased from Lithium Corporation of America, Inc., 1110 Title Insurance Bldg., Minneapolis 1, Minn.

(28) K. W. Greenlee and A. L. Henne, *Inorg. Syntheses*, **2**, 128 (1946).

(29) Prepared in 76% yield by the method of L. Crombie and A. G. Jacklin, *J. Chem. Soc.*, 1622 (1957).

(30) C. C. Cochrane and H. J. Harwood, *J. Org. Chem.*, **26**, 1278 (1961); J. C. Smith and P. D. Thickbroom, *Chem. Ind.* (London), 695 (1962).

frared spectrum was very similar to that of the previous compound.

Anal. Calcd. for $C_{16}H_{28}FNO$: C, 71.33; H, 10.48. Found: C, 71.46; H, 10.56.

18-Fluoro-9-octadecynoic Acid (ω-Fluorostearolic Acid).—ω-Fluorostearolamide (560 mg., 0.0019 mole) was heated under reflux for a period of 90 minutes with 40% potassium hydroxide (12 ml.) in 95% ethanol (30 ml.) (*i.e.*, KOH concentration of 9.8% assuming the content of AR potassium hydroxide to be 85%). Vigorous stirring was maintained throughout. The clear solution was poured into water. No solid separated, indicating that little if any amide remained unchanged. After extraction with 35–60° petroleum ether, the aqueous layer was acidified with dilute hydrochloric acid and extracted with chloroform. The extraction and separation were time-consuming because of the very powerful soap effect. Removal of the chloroform gave 458 mg. of ω-fluorostearolic acid; evaporation of the petroleum ether allowed recovery of 86 mg. of unreacted amide. Based on a consumption of 474 mg. of amide, the yield was 94.5%. Three recrystallizations from aqueous methanol gave colorless needles, m.p. 52–53°; principal infrared maxima (CCl_4, $cm.^{-1}$): 3497 (O—H, w), 2924 and 2857 (C—H, s), 2667 (bonded O—H, m), 1706 (C=O, s), 1462 and 1437 (C—H, m), 1412 (C—O and O—H, m), 1289 (CH_2, m), 1047 and 1005 (C—F, m), 948 (O—H, m).

Anal. Calcd. for $C_{18}H_{31}FO_2$: C, 72.31; H, 10.47. Found: C, 72.50; H, 10.28.

16-Fluoro-9-hexadecynoic acid was prepared similarly from the corresponding amide in 96% yield as colorless crystals from aqueous methanol; m.p. 40–41°; mixed with the above analytical sample, m.p. 41–42°.

18-Fluoro-9-octadecynoic Acid (ω-Fluorostearolic Acid) was obtained also by direct hydrolysis of the corresponding nitrile. 1-Cyano-17-fluoro-8-heptadecyne (226 mg., 0.00081 mole) was stirred and heated under reflux for 90 minutes with 40% potassium hydroxide solution (2 ml.) in 95% ethanol (6 ml.). After being cooled, the solution was poured into water and any neutral material was extracted with petroleum ether. The neutral fraction, after being dried over calcium sulfate, afforded no unchanged nitrile. The aqueous layer was acidified with 2 *N* hydrochloric acid, and the liberated acid was extracted with chloroform. Drying (calcium sulfate) and removal of the solvent yielded 160 mg. (66%) of crude ω-fluorostearolic acid. Recrystallization from aqueous methanol yielded a white crystalline acid, m.p. 52–53°; mixed with the above analytical sample, m.p. 52–53°.

18-Fluoro-*cis*-9-octadecenoic Acid (ω-Fluoro-oleic acid).—Freshly prepared and tested Lindlar catalyst[16] (700 mg.) was suspended in ethyl acetate (15 ml.), and 5% quinoline solution in petroleum ether (1 ml.) was added. Upon saturation with hydrogen at room temperature and atmospheric pressure, no noticeable uptake of hydrogen occurred. ω-Fluorostearolic acid (661 mg., 0.0022 mole) in ethyl acetate (35 ml.) was added, and hydrogenation was started. The theoretical amount of hydrogen was rapidly absorbed (*ca.* 15 minutes). The catalyst was removed by filtration and was washed with ether. The filtrate and washings were shaken with dilute hydrochloric acid to remove the quinoline. After a further water wash, the ether solution was dried over calcium sulfate. Evaporation of the solvent yielded 660 mg. of a pale yellow oil. Gas–liquid chromatography showed no trace of ω-fluorostearic acid nor of residual ω-fluorostearolic acid. The oil was first recrystallized from 35–60° petroleum ether at −30° and subsequently at 2°. After four recrystallizations the m.p. was 15.8–16.8°, $n^{25}D$ 1.4598. Infrared and n.m.r. data are given in Table I.

Anal. Calcd. for $C_{18}H_{33}FO_2$: C, 71.95; H, 11.07; F, 6.32. Found: C, 71.92; H, 11.21; F, 6.16.

16-Fluoro-*cis*-9-hexadecenoic acid (ω-fluoropalmitoleic acid) was prepared in a similar manner in 89% yield, m.p. 1–2.5°, $n^{25}D$ 1.4572. The infrared spectrum was very similar to that of ω-fluoro-oleic acid.

Anal. Calcd. for $C_{16}H_{29}FO_2$: C, 70.55; H, 10.73. Found: C, 70.68; H, 10.83.

18-Fluoro-octadecanoic Acid (ω-Fluorostearic Acid).—Platinum oxide (21 mg.) was shaken in ethyl acetate (20 ml.) until no further uptake of hydrogen was observed. The color of the catalyst changed from brown to black. To this was added ω-fluoro-oleic acid (189.2 mg., 0.00063 mole) in ethyl acetate, and hydrogenation was then started. The reaction was complete in 5 minutes. The catalyst was removed by filtration, and the solvent was evaporated to yield 190 mg. of ω-fluorostearic acid (quantitative yield). Recrystallization from aqueous methanol gave a colorless solid, m.p. 77–78°; mixed with an authentic sample,[18,31] m.p. 76–77°.

Anal. Calcd. for $C_{18}H_{35}FO_2$: C, 71.47; H, 11.66. Found: C, 71.40; H, 11.44.

16-Fluorohexadecanoic acid (ω-fluoropalmitic acid) was prepared similarly from 16-fluoro-9-hexadecynoic acid (900 mg., 0.0033 mole) in ethyl acetate (10 ml.), using platinum oxide (200 mg.) in ethyl acetate (20 ml.); yield 690 mg. (76.7%), m.p. 71–72°.

Anal. Calcd. for $C_{16}H_{31}FO_2$: C, 70.03; H, 11.39. Found: C, 70.16; H, 11.59.

Elaidic Acid.—Stearolic acid[32] (10 g., 0.036 mole) was dissolved in tetrahydrofuran (200 ml.) and the resulting solution was cooled to −40° in a Dry Ice–acetone bath. Liquid ammonia (300 ml.) was introduced into a 500-ml. two-necked flask fitted with a Dry Ice–acetone condenser, and lithium (1.0 g., 0.14 g.-atom) was added. When the lithium had completely dissolved (*ca.* 20 minutes) the two solutions were rapidly mixed in a previously cooled 1-liter stainless steel stirred autoclave[33] fitted with a Pyrex liner. After stirring of the mixture overnight at room temperature, the pressure inside the autoclave was released and the ammonia was allowed to evaporate. Water (200 ml.) was added to dissolve the crude ammonium elaidate and the solution was made acid to methyl orange by the addition of 6 *N* sulfuric acid. The organic acid was recovered by thorough extraction with chloroform. Removal of the solvent, after drying over anhydrous sodium sulfate, yielded 9.8 g. (97.5%) of elaidic acid as an off-white amorphous solid, m.p. 40–42°. Recrystallization from light petroleum ether (recovery *ca.* 85%) produced transparent plates, m.p. 44–44.5° (lit.[34] m.p. 44.5°). The identity and purity of the product were proved by mixed m.p. determinations, gas chromatography and infrared spectroscopy.

18-Fluoro-*trans*-9-octadecenoic Acid (ω-Fluoro-elaidic Acid).

(a) **Attempted Reduction of ω-Fluorostearolic Acid.**—Reduction of 2 g. of the acetylenic acid was attempted by the previous procedure. The product contained some ω-fluoro-elaidic acid, as shown by gas chromatography and infrared spectroscopy, but it was contaminated with at least two other materials, one of which had a retention time in the gas chromatograph corresponding to that of elaidic acid. Attempts to separate the mixture (all unsuccessful) included: (1) crystallization, (2) preparative gas chromatography; (3) chromatography on acid-treated Florisil,[35] and (4) reversed phase chromatography on acetylated cellulose.[5]

(b) **Isomerization of ω-Fluoro-oleic Acid.**—ω-Fluoro-oleic acid (521 mg., 0.0017 mole) was mixed with selenium (10 mg.) in a 5-ml. flask, fitted with a nitrogen inlet capillary and an air condenser. After the apparatus had been purged with nitrogen for 30 minutes, the mixture was heated at 220–225° for 1 hour in a stirred oil-bath. Very little darkening occurred. Upon cooling in a stream of nitrogen, white crystals of ω-fluoro-elaidic acid began to appear. The crystals were dissolved in acetone (4 ml.) and allowed to recrystallize at 0°. Filtration and drying gave the pure acid (236.2 mg., 74.6% allowing for 204.5 mg. of recovered ω-fluoro-oleic acid), m.p. 52–53°. Two further recrystallizations raised the m.p. to 53–54°; mixed with ω-fluorostearolic acid, m.p. 40–45°. Infrared and n.m.r. data are given in Table I.

Anal. Calcd. for $C_{18}H_{33}FO_2$: C, 71.95; H, 11.07. Found: C, 72.12; H, 11.16.

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(31) The previously recorded m.p. of 68–69° was obtained after recrystallization from 30–60° petroleum ether. Recrystallization of the originally reported samples[18] from aqueous methanol raised the m.p. to 76–77°. The figure of 77–78° listed above is probably the most accurate and reliable.

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