10-Fluoro-3-methyldecanoyl Chloride.—10-Fluoro-3-methyldecanoic acid (6.0 g., 0.029 mole) was added dropwise to boiling thionyl chloride (4.8 g., 0.040 mole). The resultant mixture was heated for an additional two hours on a steam-bath. Fractional distillation of the product gave 10-fluoro-3-methyldecanoyl chloride (5.3 g., 81.5%), b.p. 112–114° (1.5 mm.), $n^{25}D$ 1.4410.

Anal. Calcd. for $C_{11}H_{20}ClFO$: C, 59.32; H, 9.05; Cl, 15.93. Found: C, 59.38; H, 9.04; Cl, 15.98.

11-Fluoro-4-methylundecanoic Acid (V).—A solution of 10-fluoro-3-methyldecanoyl chloride (5.3 g., 0.024 mole) in anhydrous ether (25 ml.) was added to a stirred ethereal solution of diazomethane (5.9 g., 0.14 mole) cooled in an ice-bath. Stirring was continued for three hours in the cold and then for three hours at 20–25°. The ether was removed *in vacuo* at 20–25°. The residual diazomethyl ketone, a bright yellow liquid, was dissolved in dioxane (100 ml.) and was added dropwise with stirring to a mixture of freshly prepared silver oxide (2 g.), sodium carbonate (5 g.) and sodium thiosulfate (3 g.) in water (200 ml.) at 70°. The mixture was stirred at 70° for two hours with occasional addition of fresh silver oxide. The temperature was then raised to 90° for 10 hours. The black silver residue was removed by filtration, and the filtrate was acidified with dilute nitric acid. The resultant solution was extracted with ether and separated into neutral and acidic fractions. After drying over sodium sulfate and removal of the ether, the acidic fraction was distilled through a short Vigreux column to yield 11-fluoro-4-methylundecanoic acid (1.4 g., 27%), b.p. 150–151° (0.2 mm.), $n^{25}D$ 1.4393.

Anal. Calcd. for $C_{12}H_{23}FO_2$: C, 66.02; H, 10.61. Found: C, 66.02; H, 10.60.

18-Fluoro-10-methyloctadecanoic acid (VI) has been previously described.[3]

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LONDON, ONTARIO, CANADA

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

Toxic Fluorine Compounds. XVII.[1] Some 1-Fluoroalkanes, ω-Fluoroalkenes and ω-Fluoroalkynes

BY F. L. M. PATTISON AND J. J. NORMAN

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Some 1-fluoroalkanes (*n*-alkyl fluorides), ω-fluoroalkenes and ω-fluoroalkynes were prepared for biochemical studies, and for use as intermediates in the synthesis of other compounds. The even-chain 1-fluoroalkanes are very toxic. Whereas no clear-cut conclusions could be drawn regarding the biochemical breakdown of 1-alkenes, evidence was obtained for ω-oxidation of 1-fluoroalkanes, and, less convincingly, for hydration of 1-alkynes to the corresponding methyl ketones. Ethyl ω-fluorolactate, $FCH_2CH(OH)COOEt$, the preparation of which is described, was found to be non-toxic.

The three classes of monofluorinated hydrocarbons described in this paper were prepared for toxicological studies, and hence to obtain information regarding the breakdown *in vivo* of the unfluorinated analogs. ω-Oxidation had previously been postulated[2] in the biological degradation of certain fluoroketones; it was recognized that the study of 1-fluoroalkanes would provide additional evidence for this mechanism. The results presented here are in conformity with the suggestion. In an earlier report[3] was mentioned the toxicity of 11-fluoro-1-undecene; the inference was drawn that the alkene was converted to the intermediate 11-fluoro-1,2-undecanediol,[4] which in turn was oxidized with loss of one carbon atom. The toxicities of the ω-fluoro-1-alkenes presented below do not tally with this simple mechanism. In regard to the biological fate of the 1-alkynes, hydration to the corresponding methyl ketones was considered most likely; the toxicity figures shown in Table II, supplemented by some studies of citric acid accumulation, lend support for this prediction.

(1) Part XVI, THIS JOURNAL, **79**, 2308 (1957); issued as DRB Report No. SW-37.

(2) R. R. Fraser, J. E. Millington and F. L. M. Pattison, *ibid.*, **79**, 1959 (1957).

(3) F. L. M. Pattison, *Nature*, **174**, 737 (1954).

(4) F. L. M. Pattison, *ibid.*, **172**, 1139 (1953).

Preparation

The majority of the 1-fluoroalkanes were prepared from alkyl halides or alkyl sulfonates by treatment with potassium fluoride in diethylene glycol.[5–10] Special procedures, for example the cleavage of an alkyl *p*-toluenesulfonate with silver fluoride in acetonitrile, were used in a few instances, but none proved superior to the two above-mentioned methods, both of which already have been described. All the 1-fluoroalkanes have been prepared previously in other laboratories.

The ω-fluoroalkenes listed in Table I were prepared from ω-haloalkenes or from ω-methanesulfonoxyalkenes[10] by treatment with potassium fluoride in diethylene glycol. All four members were prepared by the former method, while 5-fluoro-1-pentene was obtained also by the latter method.[10]

(5) F. W. Hoffmann, THIS JOURNAL, **70**, 2596 (1948).

(6) F. W. Hoffmann, *J. Org. Chem.*, **15**, 425 (1950).

(7) G. H. Jeffery, J. Leicester, W. A. T. Macey and A. I. Vogel, *Chemistry & Industry*, 1045 (1954).

(8) Private communications from Dr. A. I. Vogel, The Woolwich Polytechnic, London, S.E. 18 (August 1 and December 11, 1956); A. I. Vogel, J. Leicester and W. A. T. Macey, *Org. Syntheses*, **36**, 40 (1956).

(9) W. F. Edgell and L. Parts, THIS JOURNAL, **77**, 4899 (1955).

(10) F. L. M. Pattison and J. E. Millington, *Can. J. Chem.*, **34**, 757 (1956).

The ω-fluoroalkynes[3] were prepared either by treatment[11] of the appropriate ω-fluoroalkyl bromides and iodides[12] with sodium acetylide, or by fluorination of the corresponding ω-chloroalkynes[13,14] with potassium fluoride in ethylene glycol or diethylene glycol. By the former method were prepared 5-fluoro-1-pentyne, 6-fluoro-1-hexyne, 7-fluoro-1-heptyne and 8-fluoro-1-octyne, while the latter method yielded 5-fluoro-1-pentyne, 6-fluoro-1-hexyne, 9-fluoro-1-nonyne, 1,4-difluoro-2-butyne and 1-fluoro-4-chloro-2-butyne.

Properties

Chemical.—As has been noted by other workers,[7,8,15] 1-fluoroalkanes are very stable liquids. It is unfortunate that the early misconception[16] regarding the instability of monofluoro aliphatic compounds has persisted for so long. Notwithstanding the growing number of stable monofluoro aliphatic compounds reported in the literature during the last ten years, two recent reviews[17,18] still repeat Henne's observation that a single fluorine atom in an aliphatic compound causes instability. Of some three hundred primary monofluoro compounds prepared in the course of our study of toxic materials, only a handful have proved to be unstable and, in these few instances, the instability was associated almost exclusively with some other functional group in the molecule.

The ω-fluoro-1-alkenes reacted readily with performic acid[19] to yield the corresponding ω-fluoro-1,2-alkanediols; by this means were prepared 5-fluoro-1,2-pentanediol and 11-fluoro-1,2-undecanediol; the former was converted without purification into 4-fluorobutanal.[20] 3-Fluoro-1,2-propanediol was more conveniently prepared by hydrolysis of epifluorohydrin.[21,22] The latter was obtained in 50% yield by fluorination of epichlorohydrin in a stainless steel autoclave at 215–225° using anhydrous potassium fluoride. In most runs, the maximum pressure developed was 190–210 p.s.i., but in one instance, unaccountably, the pressure rose to 3000 p.s.i., with almost total loss of product; it is therefore essential that this reaction be carried out in a pressure vessel equipped with an emergency pressure relief device. Both epifluorohydrin and 3-fluoro-1,2-propanediol on oxidation with nitric acid afforded ω-fluorolactic acid; the crude acid was esterified prior to purification.

(11) K. N. Campbell and B. K. Campbell, *Org. Syntheses*, **30**, 15 (1950).

(12) F. L. M. Pattison and W. C. Howell, *J. Org. Chem.*, **21**, 748 (1956).

(13) W. R. Taylor and F. M. Strong, THIS JOURNAL, **72**, 4263 (1950).

(14) R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 2100 (1950).

(15) W. K. R. Musgrave, *Quart. Revs. (London)*, **8**, 331 (1954).

(16) A. L. Henne and T. Midgley, THIS JOURNAL, **58**, 882 (1936).

(17) M. Stacey in "Progress in Organic Chemistry," Vol. 2, Editor J. W. Cook, Butterworths Scientific Publications, London, England, 1953, p. 29.

(18) P. Tarrant in "Fluorine Chemistry," Vol. 2, Editor J. H. Simons, Academic Press, Inc., New York, N. Y., 1954, p. 213.

(19) D. Swern, G. N. Billen, T. W. Findley and J. T. Scanlan, THIS JOURNAL, **67**, 1786 (1945); D. Swern, G. N. Billen and J. T. Scanlan, *ibid.*, **68**, 1504 (1946).

(20) J. F. K. Wilshire and F. L. M. Pattison, *ibid.*, **78**, 4996 (1956).

(21) E. Gryszkiewicz-Trochimowski, A. Sporzynski and J. Wnuk, *Rec. trav. chim.*, **66**, 413 (1947).

(22) I. L. Knunyants, O. V. Kil'disheva and I. P. Petrov, *J. Gen. Chem., U.S.S.R.*, **19**, 87 (1949) [Engl. translation].

The ω-fluoro-1-alkynes formed copper, silver and mercuric salts; the last of these served as a convenient means of characterization. The ω-fluoro-1-alkynes tended to lose fluorine in the presence of reactants such as sodamide and Grignard reagents,[23] rather than undergoing the reactions characteristic of the non-fluorinated alkynes. Thus, the reaction of 6-fluoro-1-hexyne with sodamide resulted in an indeterminate mixture of products, and with ethylmagnesium bromide followed by carbon dioxide produced fluorine-free polymers. Whereas 1,4-difluoro-2-butyne was stable, 1-fluoro-4-chloro-2-butyne decomposed extensively when distilled at atmospheric pressure.

Physical.—All the 1-fluoroalkanes listed in Table II have been prepared and examined independently by Vogel and co-workers.[7,8] Since the physical constants obtained were essentially the same in both laboratories, it was mutually agreed that the details would be presented in a forthcoming publication by these workers rather than by us. Physical constants and analytical results of the ω-fluoroalkenes and ω-fluoroalkynes and of some precursors and derivatives are shown in Table I.

Toxicological.—The most striking feature of the figures listed in Table II is the very high toxicity of the 1-fluoroalkanes, and more particularly of the members containing an even number of carbon atoms. They are indeed among the most toxic of the ω-fluoro-compounds; this fact, coupled with their relatively high volatility, emphasizes the need for caution in their manipulation. The hazardous nature of the 1-fluoroalkanes, recorded here for the first time, is the more surprising when contrasted with the outstanding stability of the members, and points a warning to industrial workers who may encounter these materials as by-products in commercial processes.

The alternation in toxicity of the 1-fluoroalkanes indicates the existence of a biochemical degradative mechanism akin to that of the ω-fluorocarboxylates.[24] A reasonable interpretation of this observation consequently points to initial ω-oxidation of the 1-fluoroalkanes, resulting in the formation of ω-fluorocarboxylates containing the same number of carbon atoms ($F(CH_2)_nCH_3 \rightarrow F(CH_2)_nCOOH$); the fluoro-acids, once formed, would then be degraded by β-oxidation.[25] In support of this is the marked similarity in toxicity between the 1-fluoroalkanes, particularly those containing an even number of carbon atoms, and the corresponding ω-fluorocarboxylates.[24] Further evidence in favor of the ω-oxidation mechanism is supplied by high citric acid levels found in animals poisoned by the even chain 1-fluoroalkanes, indicat-

(23) We also have reported loss of fluorine in Grignard reactions involving ω-fluoroalkylmagnesium halides; F. L. M. Pattison and W. C. Howell, *J. Org. Chem.*, **21**, 879 (1956). In a related investigation, we have shown loss of fluorine from 1-fluorohexane by treatment with alkylmagnesium halides; W. J. Cott and F. L. M. Pattison, unpublished results.

(24) F. L. M. Pattison, S. B. D. Hunt and J. B. Stothers, *J. Org. Chem.*, **21**, 883 (1956).

(25) I. G. Walker and J. M. Parker have suggested convincingly that oxidative attack on the 1-fluoroalkanes may occur not only at the end but also in the middle of the chain; this theory, based on studies of citric acid accumulation,[26] will be discussed in a forthcoming publication by these workers.

TABLE I

PHYSICAL CONSTANTS AND ANALYTICAL RESULTS

Compound	Formula	B.p. °C.	Mm.	$n^{25}D$ or m.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
5-Fluoro-1-pentene[a]	$F(CH_2)_3CH=CH_2$	61–62	745	1.3748	68.16	68.18	10.29	10.44
6-Fluoro-1-hexene[b]	$F(CH_2)_4CH=CH_2$	91.5	740	1.3874				
11-Fluoro-1-undecene	$F(CH_2)_9CH=CH_2$	84–85	11	1.4236	76.68	76.35	12.29	12.21
1,4-Difluoro-2-butene	$FCH_2CH=CHCH_2F$	73	740	1.3670	52.17	52.44	6.57	6.75
Epifluorohydrin[c]	FCH_2CHCH_2O	83–84	742	1.3679				
3-Fluoro-1,2-propanediol	$FCH_2CH(OH)CH_2OH$	100–101	10	1.4220	38.30	38.40	7.44	7.22
					20.21[d]	20.1[d]		
11-Fluoro-1,2-undecanediol[e]	$F(CH_2)_9CH(OH)CH_2OH$			42–43	64.08	64.03	11.16	11.12
Ethyl ω-fluorolactate	$FCH_2CH(OH)COOEt$	74	12	1.4076	44.12	44.16	6.66	6.85
3,5-dinitrobenzoate[f]	$FCH_2CH(OCOC_6H_3(NO_2)_2)COOEt$			91–91.5	43.64	43.81	3.33	3.30
5-Fluoro-1-pentyne[g]	$F(CH_2)_3C\equiv CH$							
Mercury derivative[f]	$(F(CH_2)_3C\equiv C)_2Hg$			118.5–119	32.38	32.34	3.24	3.29
6-Fluoro-1-hexyne	$F(CH_2)_4C\equiv CH$	106–106.5	745	1.4058	72.00	72.25	9.00	9.09
Mercury derivative[f]	$(F(CH_2)_4C\equiv C)_2Hg$			81–81.5	36.14	36.16	4.04	4.18
7-Fluoro-1-heptyne	$F(CH_2)_5C\equiv CH$	131–131.5	748	1.4103	73.69	73.41	9.65	9.72
Mercury derivative[h]	$(F(CH_2)_5C\equiv C)_2Hg$							
Copper derivative[i]	$F(CH_2)_5C\equiv CCu$			122–123.5[j]	47.58	47.43	5.70	5.58
					35.96[k]	35.99[k]		
8-Fluoro-1-octyne	$F(CH_2)_6C\equiv CH$	77–78	50	1.4165	74.96	75.05	10.23	10.37
Mercury derivative[f]	$(F(CH_2)_6C\equiv C)_2Hg$			66.5–67	42.23	42.04	5.28	5.11
9-Fluoro-1-nonyne[l]	$F(CH_2)_7C\equiv CH$	66–66.5	12	1.4192	76.05	75.98	10.56	10.57
Mercury derivative[f]	$(F(CH_2)_7C\equiv C)_2Hg$			54.5–55	44.77	44.57	5.80	5.79
1,4-Difluoro-2-butyne[l]	$FCH_2C\equiv CCH_2F$	87–88	742	1.3884	53.33	52.93	4.50	4.98
1-Fluoro-4-chloro-2-butyne[l]	$FCH_2C\equiv CCH_2Cl$	54.5–55	50	1.4455	33.28[m]	32.92[m]		

[a] Hoffmann[28] reports b.p. 61.9–62.1°. [b] Hoffmann[28] reports b.p. 91–92° and $n^{25}D$ 1.3869. [c] Redemann, *et al.*,[29] report b.p. 83.5–84° (753 mm.) and $n^{20}D$ 1.3693; Knunyants, *et al.*,[22] report b.p. 85–86.4° and $n^{20}D$ 1.3730. [d] Fluorine, %. [e] Previously reported.[20] [f] Recrystallized from 95% ethanol. [g] The free alkyne was not isolated. [h] The mercury salt is liquid at room temperature; f.p. *ca.* 15°. The copper derivative is therefore more convenient for characterizing 7-fluoro-1-heptyne. [i] Recrystallized from acetone. [j] Accompanied by extensive decomposition. [k] Copper, %. [l] Because of the very small quantity isolated, physical constants should be regarded only as approximate. [m] Chlorine, %.

ing[26] the ultimate formation of fluoroacetate. In short, ω-oxidation provides a satisfactory explanation of the toxicity results of the 1-fluoroalkanes[25] and of the fluoromethyl alkyl ketones described earlier.[2]

The four ω-fluoroalkenes listed in Table II are all toxic, irrespective of the length of their carbon chains. Hence no clear-cut conclusions can be drawn from these figures regarding the biochemical fate of the alkene grouping. The earlier suggestion[3] that the alkene group was oxidized to the diol and then to the aldehyde ($-CH=CH_2 \rightarrow -CH(OH)-CH_2OH \rightarrow -CHO$) clearly requires modification because of the high toxicity of 6-fluoro-1-hexene; hence a competitive metabolic route, such as ketone[2] formation ($-CH=CH_2 \rightarrow -CH(OH)CH_3 \rightarrow -COCH_3$), also may be available. That the diols, once formed, are indeed oxidized to aldehydes or acids with loss of one carbon atom is supported by the two figures presented in Table II.

Ethyl ω-fluorolactate was found to be non-toxic, as was expected from the low toxicity of the closely related fluoropyruvic acid.[27] This result thus provides evidence that 3-fluoro-1,2-propanediol (toxic) forms some metabolite other than fluorolactate (non-toxic), and at the same time implies that in general α-glycols are not oxidized to the corresponding α-hydroxyacids; this implication is therefore consistent with the oxidative cleavage of α-glycols postulated above.

The alternation in toxicity shown by the ω-fluoro-1-alkynes indicates that the alkyne grouping is attacked *in vivo*. From a comparison of the toxicity pattern of the ω-fluoro-1-alkynes with that previously described for the ω-fluoroalkyl methyl ketones,[2] it is suggested that hydration of the alkyne grouping may be the initial step in its degradation

TABLE II

TOXICITY RESULTS

Compound	Formula	L.D. 50 for mice (intraperitoneal), mg./kg.
1-Fluorohexane	$CH_3(CH_2)_5F$	1.7
1-Fluoroheptane	$CH_3(CH_2)_6F$	35
1-Fluoroöctane	$CH_3(CH_2)_7F$	2.7
1-Fluorononane	$CH_3(CH_2)_8F$	21.7
1-Fluorodecane	$CH_3(CH_2)_9F$	1.7
1-Fluoroundecane	$CH_3(CH_2)_{10}F$	15.5
1-Fluorododecane	$CH_3(CH_2)_{11}F$	2.5
5-Fluoro-1-pentene	$F(CH_2)_3CH=CH_2$	5.4
6-Fluoro-1-hexene	$F(CH_2)_4CH=CH_2$	2.8
11-Fluoro-1-undecene	$F(CH_2)_9CH=CH_2$	9.3
1,4-Difluoro-2-butene	$FCH_2CH=CHCH_2F$[a]	6.1
3-Fluoro-1,2-propanediol	$FCH_2CH(OH)CH_2OH$[a]	16.8
11-Fluoro-1,2-undecanediol	$F(CH_2)_9CH(OH)CH_2OH$[b]	1.75
Ethyl ω-fluorolactate	$FCH_2CH(OH)COOEt$[c]	>100
1-Hexyne	$CH_3(CH_2)_3C\equiv CH$	>100
6-Fluoro-1-hexyne	$F(CH_2)_4C\equiv CH$	5.7
7-Fluoro-1-heptyne	$F(CH_2)_5C\equiv CH$	53
8-Fluoro-1-octyne	$F(CH_2)_6C\equiv CH$	7.5
9-Fluoro-1-nonyne	$F(CH_2)_7C\equiv CH$	79

[a] For comparison, FCH_2COOH has L.D. 50, 6.6 mg./kg.[24] [b] For comparison, $F(CH_2)_9CHO$ has L.D. 50, 1.95 mg./kg.[20] and $F(CH_2)_9COOH$ has L.D. 50, 1.5 mg./kg.[24] [c] The high L.D. 50 is consistent with the relatively non-toxic nature of $FCH_2COCOOH$.[27]

(26) R. A. Peters, *Proc. Roy. Soc.* (*London*), **B139**, 143 (1952).

(27) I. Blank, J. Mager and E. D. Bergmann, *J. Chem. Soc.*, 2190 (1955).

(28) F. W. Hoffmann, *J. Org. Chem.*, **14**, 105 (1949).

(29) C. E. Redemann, S. W. Chaikin, R. B. Fearing, G. J. Rotariu, J. Savit and D. van Hoesen, THIS JOURNAL, **70**, 3604 (1948).

(—C≡CH → —$COCH_3$); the fact that the fluoroalkynes are all rather less toxic than the corresponding fluoroketones may indicate, however, that hydration is not the sole metabolic route. Ultimate formation of fluoroacetate from 6-fluoro-1-hexyne and from 7-fluoro-1-heptyne was shown by citric acid accumulation in the tissues of poisoned animals. That both the even *and* odd members caused citric acid accumulation is a unique point in common between the fluoroalkynes and the fluoroalkyl methyl ketones; moreover, with both classes, the accumulation was greater with the even chain members (on a molar basis). While the toxicity pattern and citric acid levels are thus in substantial agreement with the hydration of the alkyne grouping to the corresponding methyl ketone, independent work is still required to confirm or disprove this postulate.

Experimental[30]

Intermediates.—The ω-fluoroalkyl halides were prepared as described previously.[12] The ω-chloroalkyl iodides were prepared from ω,ω'-dichloroalkanes.[31] 5-Bromo-1-pentene[32] was prepared from 5-hydroxy-1-pentene using phosphorus tribromide; 6-bromo-1-hexene[33] and 11-bromo-1-undecene[34] were prepared similarly from 6-hydroxy-1-hexene[35] and 11-hydroxy-1-undecene,[36] respectively. 1,4-Dichloro-2-butene was purchased commercially.[35] 5-Chloro-1-pentyne[37] was prepared from 5-hydroxy-1-pentyne[38] by treatment with thionyl chloride; the other ω-chloro-1-alkynes were prepared from the appropriate ω-chloroalkyl iodides using sodium acetylide in the usual way.[11] 1,4-Dihydroxy-2-butyne was kindly donated by General Aniline and Film Corporation, 435 Hudson St., New York 14, N. Y. Potassium fluoride and diethylene glycol were purified as described previously.[39]

1-Fluoroalkanes. (a) From *n*-Alkyl Chlorides and Bromides.—The following example is representative of the general method. For the lower members, continuous removal[5,6] of the product gave satisfactory results.

1-Fluoroundecane.—A mixture of anhydrous potassium fluoride (15.0 g., 0.26 mole), diethylene glycol (80 g.) and 1-chloroundecane (34.0 g., 0.18 mole) was heated at 135° for 23 hours with vigorous stirring; the period of heating may be reduced, with slight diminution of yield. The mixture was cooled and diluted with an equal volume of water. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer and extracts were treated with bromine in ether until a faint orange color persisted, and then were washed successively with water, aqueous sodium carbonate and water again. The product, after being dried over sodium sulfate and removal of the ether, was fractionally distilled, yielding 1-fluoroundecane (15.0 g.), b.p. 102–102.5° (23 mm.), $n^{25}D$ 1.4131, and then unchanged 1-chloroundecane (9.0 g.). Gryszkiewicz-Trochimowski, *et al.*,[21] report b.p. 90° (12 mm.). The yield, calculated on reacted 1-chloroundecane, was 66%.

Anal. Calcd. for $C_{11}H_{23}F$: C, 75.80; H, 13.30. Found: C, 75.61; H, 13.03.

By essentially the same procedure were prepared: **1-fluorohexane** (52% yield, from 1-bromohexane, isolated by continuous removal at atmospheric pressure), **1-fluoroheptane** (39% yield, from 1-chloroheptane, isolated by continuous removal under reduced pressure), **1-fluoroöctane** (48% yield, from 1-bromoöctane, isolated by continuous removal under reduced pressure), **1-fluorononane** (31% yield, from 1-chlorononane, isolated by dilution with water) and **1-fluorododecane** (57% yield, from 1-bromododecane, isolated by dilution with water).

(b) From *n*-Alkyl Methanesulfonates.—This previously described procedure[10] was used for the preparation of **1-fluorohexane** (67% yield) and **1-fluorodecane** (48% yield).

ω-Fluoroalkenes and Derivatives. 5-Fluoro-1-pentene.—A mixture of anhydrous potassium fluoride (61.0 g., 1.05 moles) and diethylene glycol (200 g.) was heated to 110° in a three-necked flask equipped with a thermometer, a mercury-seal stirrer and a distillation assembly. 5-Bromo-1-pentene (104.8 g., 0.703 mole) was then added dropwise to the stirred mixture; after about half the quantity had been added, a colorless liquid began to distil at a b.p. of 55–70°. The heating was continued until distillation ceased. The product (35.9 g.) was found to be free of acid, and was therefore fractionated directly through a Todd still, giving 25.8 g. (42%) of a colorless, sweet-smelling liquid. **5-Fluoro-1-pentene** may also be obtained from the corresponding methanesulfonoxyalkene.[19]

6-Fluoro-1-hexene.—A mixture of anhydrous potassium fluoride (18.0 g., 0.3 mole), diethylene glycol (70 g.) and 6-bromo-1-hexene (30.0 g., 0.18 mole) was heated at 90° for two hours with vigorous stirring. The pressure was then slowly reduced until a steady, slow rate of distillation resulted. Toward the end of the reaction, the heating was increased and the pressure further reduced until distillation ceased. The residue was heated at 120° for an additional hour at atmospheric pressure, and then was cooled, diluted with water and extracted with ether. The extracts were added to the distillate, and the combined liquids were washed successively with water, aqueous sodium carbonate and water again. The product, after drying over sodium sulfate and removal of the ether, yielded 6-fluoro-1-hexene (5.2 g.) and then unchanged 6-bromo-1-hexene (9.0 g.). The yield, calculated on reacted 6-bromo-1-hexene, was 40%.

11-Fluoro-1-undecene.—A mixture of 11-bromo-1-undecene (62.0 g., 0.28 mole), anhydrous potassium fluoride (33.6 g., 0.58 mole), diethylene glycol (60 g.) and butyl carbitol (60 g.) was heated at 180° for six hours with vigorous stirring. After cooling overnight, the mixture was diluted with water (200 ml.). The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer and extracts were washed and dried, and yielded on fractionation 21.0 g. (46%) of 11-fluoro-1-undecene.

1,4-Difluoro-2-butene.—A mixture of anhydrous potassium fluoride (70.0 g., 1.2 moles), diethylene glycol (150 g.) and 1,4-dichloro-2-butene (46.0 g., 0.37 mole) was heated at 115° for 2.5 hours with continuous stirring. The resultant mixture was cooled, diluted, separated, extracted, dried and fractionated as above, yielding 20.2 g. (60%) of 1,4-difluoro-2-butene. A higher fraction, suspected of being 1-fluoro-4-chloro-2-butene, was found to be unstable.

Epifluorohydrin.—In an electrically heated, stainless-steel autoclave, fitted with a stirrer and an emergency pressure relief device (a rupture disk leading to a fume-hood), was placed a mixture of commercial epichlorohydrin (783 g., 8.5 moles) and anhydrous potassium fluoride (700 g., 12.1 moles). The temperature was raised to 215–225° and maintained in that range for 5.5 hours. The maximum pressure developed was 210 p.s.i. The liquid was distilled from the autoclave leaving only the solids behind. The combined distillates from two identical runs (1165 g.) were fractionated through a Todd still, giving 342 g. of epifluorohydrin and 736 g. of recovered epichlorohydrin. The yield based on reacted epichlorohydrin was 50%.

As mentioned in the Discussion, a serious pressure hazard developed during one run, under apparently identical conditions. When the temperature reached 225°, the pressure had reached 440 p.s.i. The heating was stopped immediately, but within five minutes the temperature had risen spontaneously to 252° and the pressure had passed 1000

(30) (a) The majority of the microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J., and by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. (b) The melting points and boiling points are uncorrected.

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p.s.i. and was rising rapidly. Within another five minutes, the temperature was >255° and the pressure was 3000 p.s.i. The total distillate from 737 g. of epichlorohydrin consisted of 25 g. of a brown liquid. It is therefore essential that the reaction be carried out in a pressure vessel equipped with an emergency pressure relief device.

3-Fluoro-1,2-propanediol.—Epifluorohydrin (20.0 g., 0.213 mole), 10% sulfuric acid (2 ml.) and water (16 ml.) were heated under reflux on a steam-bath for one hour. The solution was allowed to cool, and then was neutralized with solid sodium carbonate. The water was removed under reduced pressure, and the residue was distilled twice, yielding 3-fluoro-1,2-propanediol (18.3 g., 76%).

5-Fluoro-1,2-pentanediol and **11-fluoro-1,2-undecanediol** have been described earlier.[20]

Ethyl ω-Fluorolactate.[40]—Water (58 ml.) and concentrated nitric acid (20 ml.) were placed in a 500-ml. flask fitted with a reflux condenser, a mercury-seal stirrer and a dropping funnel. Epifluorohydrin (58.0 g., 0.76 mole) was added dropwise over 15 minutes to the dilute nitric acid, heated on a steam-bath. A further 100 ml. of concentrated nitric acid was then added, and the mixture was heated for three hours and left overnight at room temperature. Water and nitric acid were distilled off under reduced pressure. The oxalic acid formed during the oxidation was removed by the addition of hot water (1 l.) and then powdered calcium carbonate until effervescence ceased (*ca.* 70 g.). The precipitate was removed by filtration under vacuum at 60°, and the filtrate was acidified with 100 ml. of concentrated hydrochloric acid. The fluorolactic acid was isolated by continuous extraction with ether. Esterification by azeotropic distillation with ethanol and benzene gave ethyl ω-fluorolactate (40.0 g., 39%) as a colorless liquid.

The **3,5-dinitrobenzoate**, recrystallized from 95% ethanol, had m.p. 91–91.5°. Dr. Rivett reported[40] the ***p*-bromophenacyl** ester to have m.p. 126°, the ***p*-nitrobenzoate** to have m.p. 67–67.5°, and the **benzoate** to be an oil.

ω-Fluoroalkynes.—The following examples are representative of the two general methods. **(a) From ω-Fluoroalkyl Bromides and Iodides. 6-Fluoro-1-hexyne.**—The method was adapted from a previously described procedure.[11] Ferric nitrate (0.3 g. per mole of sodium used) was placed in a 500-ml. flask fitted with a stirrer, a gas inlet tube, and a device for adding sodium.[11] The flask was half-filled with liquid ammonia, and acetylene (scrubbed with concentrated sulfuric acid and dried with calcium chloride) was passed into the system at the rate of 5–10 bubbles per second. After 15 minutes, small pieces of sodium (13.0 g., 0.56 mole) were added to the ammonia solution on a piece of wire at such a rate that metallic sodium solutions were never formed, as indicated by an absence of a blue coloration. The acetylene flow was continued for a further 15 minutes after all the sodium had been added, to decompose any disodium acetylide which might have been formed. 4-Fluorobutyl iodide (100 g., 0.50 mole) was added dropwise to the stirred sodium acetylide solution. The mixture was then stirred for a further five hours to complete the reaction. The volume of the mixture was kept more or less constant by the occasional addition of small portions of liquid ammonia. Ammonium hydroxide (50 ml.) was added to decompose any residual sodium acetylide or sodamide, and the resultant mixture was diluted with water (1 l.). The organic product was isolated by ether extraction. The extracts were washed with dilute hydrochloric acid and then with water, and were dried over calcium chloride. The ether was removed, and the residue was fractionated, yielding 6-fluoro-1-hexyne (44.5 g., 89%) as a colorless, very volatile liquid.

By the above method were prepared **5-fluoro-1-pentyne** (isolated only as the mercury derivative, from 3-fluoropropyl bromide), **7-fluoro-1-heptyne** (53% yield, from 5-fluoroamyl bromide), and **8-fluoro-1-octyne** (63% yield, from 6-fluorohexyl bromide).

(b) From ω-Chloro-1-alkynes. 6-Fluoro-1-hexyne.—Ethylene glycol (200 g.) and anhydrous potassium fluoride (52.0 g., 0.90 mole) were placed in a three-necked flask fitted with a mercury-seal stirrer, a dropping funnel and a distillation assembly. The mixture was heated to 120° and 6-chloro-1-hexyne (42.0 g., 0.36 mole) was added dropwise to the vigorously stirred solution. After about one-third of the chloroalkyne had been added, a liquid, boiling at *ca.* 110°, began to distil. When all the chloroalkyne had been added, the temperature of the mixture was gradually raised to maintain the still-head temperature. The distillate was washed with water and was then dried over calcium chloride. Fractional distillation yielded 6-fluoro-1-hexyne (20.8 g., 57%).

By the above method was prepared **5-fluoro-1-pentyne** (isolated only as the mercury derivative).

9-Fluoro-1-nonyne.—9-Chloro-1-nonyne (2.6 g., 0.016 mole), anhydrous potassium fluoride (1.5 g., 0.026 mole) and diethylene glycol (10 g.) were placed in a sealed tube, 10 cm. long and 16 mm. in diameter. The tube was mounted in a mechanical shaker, and was heated electrically at 120° for 24 hours with vigorous shaking. The contents of the tube, after cooling, were diluted with water. The fluoroalkyne was separated using a hypodermic syringe and was dried over calcium chloride. Fractionation gave crude 9-fluoro-1-nonyne of b.p. 70–80° (25 mm.), which, on refractionation through a microdistillation assembly, yielded the pure fluoroalkyne (0.6 g., 26%).

1,4-Difluoro-2-butyne and 1-Fluoro-4-chloro-2-butyne.—1,4-Dihydroxy-2-butyne was converted to 1,4-dichloro-2-butyne (b.p. 59–60° (13 mm.), $n^{25}D$ 1.5040) in 85% yield using thionyl chloride and pyridine at room temperature. A mixture of anhydrous potassium fluoride (35.0 g., 0.60 mole) and ethylene glycol (200 g.) was heated to 120°, and 1,4-dichloro-2-butyne (49.4 g., 0.41 mole) was added dropwise with vigorous stirring. A brown solid was precipitated, and a very small (*ca.* 5 ml.), two-phase distillate was collected. This was washed with water and dried over calcium chloride. Distillation yielded two fractions, b.p. 70–90° and b.p. 122–130°. The first of these, on fractionation, yielded 1,4-difluoro-2-butyne (0.75 g.), while the second gave 1-fluoro-4-chloro-2-butyne (0.5 g.).

Mercury Derivatives.—Nessler reagent was prepared by dissolving mercuric chloride (66.0 g.) and potassium iodide (163.0 g.) in water (160 ml.) and then adding 10% aqueous sodium hydroxide (125 ml.). The mercury salt was formed by mixing the fluoroalkyne in five volumes of ethanol with an equal volume of Nessler reagent. The white, crystalline precipitate which formed immediately was filtered and recrystallized several times from 95% ethanol. The physical constants and analytical results are listed in Table I. The mercury derivative of 7-fluoro-1-heptyne was found to be liquid at room temperature and to crystallize at *ca.* 15°.

Silver Derivatives.—A 10% solution of the alkyne in alcohol was added to an equal volume of 10% alcoholic silver nitrate solution containing 1% ammonium hydroxide. The insoluble silver salt formed immediately. It was dissolved by gentle heating and crystallized as fine, colorless crystals on cooling. These were filtered and washed with cold alcohol.

Copper Derivatives.—Equimolar quantities of the alkyne and 10% ammoniacal cuprous chloride were mixed and shaken. The insoluble copper salt was filtered, was washed with acetone to remove water, and finally was washed with ether to remove extraneous organic material.

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Synthesis of DL-3,5-Dihydroxy-3-methylpentanoic Acid (Mevalonic Acid)

BY CARL H. HOFFMAN, ARTHUR F. WAGNER, ANDREW N. WILSON, EDWARD WALTON, CLIFFORD H. SHUNK, DONALD E. WOLF, FREDERICK W. HOLLY AND KARL FOLKERS

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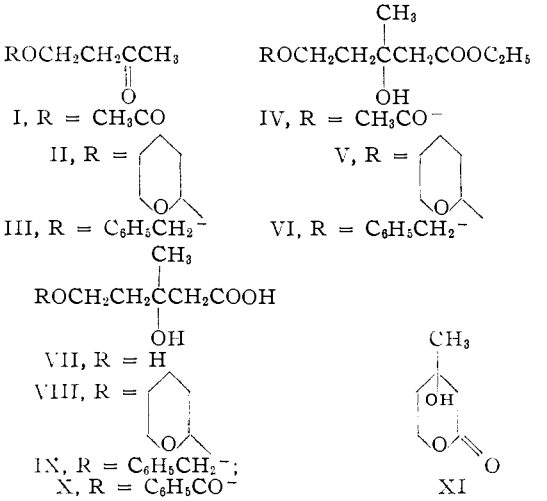
The racemate of a new acetate-replacing factor, DL-3,5-dihydroxy-3-methylpentanoic acid (VII), has been synthesized. The Reformatsky reaction between 4-acetoxy-2-butanone and ethyl bromoacetate gave ethyl 5-acetoxy-3-hydroxy-3-methylpentanoate (IV), which was hydrolyzed by alkali to 3,5-dihydroxy-3-methylpentanoic acid (VII).

A new acetate-replacing factor has been obtained[1] from dried distillers' solubles and has been shown[2] to be 3,5-dihydroxy-3-methylpentanoic acid (XI). The racemate was synthesized[2] from



diethyl 3-hydroxy-3-methylglutarate. This paper describes a new synthesis of DL-3,5-dihydroxy-3-methylpentanoic acid and several of its 5-O-derivatives. In addition, the N,N'-dibenzylethylenediammonium salts of the parent acid and its corresponding 5-O-derivatives are described.

The synthesis was accomplished by a Reformatsky reaction between a 4-O-substituted 4-hydroxy-2-butanone and ethyl bromoacetate to give a hydroxyester, which was hydrolyzed to the corresponding hydroxyacid. Three O-substituted 4-hydroxy-2-butanones were investigated in this reaction. In refluxing ether solution, the best yield (51%) was obtained with 4-acetoxy-2-butanone (I). With the acetal, 4-(2-tetrahydropyranyloxy)-2-butanone (II), the yields were about 20%, while with the ether, 4-benzyloxy-2-butanone (III), the yields were even lower. When the condensation was carried out in refluxing benzene, the yields of hydroxyester were extremely low with both the 4-acetoxy derivative I and the 4-(2-tetrahydropyranyloxy) derivative II.

The hydroxyesters (IV, V, VI) were hydrolyzed with alkali to the corresponding free acids (VII, VIII, IX), which were isolated as oils and purified by conversion to N,N'-dibenzylethylenediammonium salts. Ethyl 5-acetoxy-3-hydroxy-3-methylpentanoate (IV) was hydrolyzed to the corresponding dihydroxyacid VII, which was isolated as an equilibrium mixture of the hydroxyacid and its δ-lactone. The pure lactone XI was isolated from the equilibrium mixture by a short-path distillation. The distilled lactone was crystallized from acetone–ether to yield DL-β-methyl-β-hydroxy-δ-valerolactone (XI), m.p. 27–28°. The acid–lactone mixture was converted by an excess of N,N'-dibenzylethylenediamine in semi-aqueous media into N,N'-dibenzylethylenediammonium-bis-(3,5-dihydroxy-3-methylpentanoate).

Both the lactone XI and the salt of VII are fully active in the *Lactobacillus acidophilus* ATCC 4963 assay.[3]

Ethyl 3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate (V) and ethyl 5-benzyloxy-3-hydroxy-3-methylpentanoate (VI) were hydrolyzed with alkali to the corresponding hydroxyacids (VIII and IX), which formed crystalline N,N'-dibenzylethylenediammonium salts. The acetal derivative, N,N'-dibenzylethylenediammonium-bis-[3-hydroxy-3-methyl-5-(2-tetrahydropyranyloxy)-pentanoate], had 65% of the calculated activity in the L-4963 assay. This derivative is the only one of this series which showed activity in the L-4963 assay. The acetal VIII was converted to the dihydroxyacid VII by acid hydrolysis.

Benzoylation of the 5-hydroxyl group in 3,5-dihydroxy-3-methylpentanoic acid was accomplished in low yield with benzoyl chloride in aqueous alkali. The product, 5-benzoyloxy-3-hydroxy-3-methylpentanoate (X), was isolated as an oil and characterized as the N,N'-dibenzylethylenediammonium salt. This derivative was inactive in the L-4963 assay; alkaline hydrolysis regenerated full activity. Using other acylating reagents, little or none of the 5-acylated products could be isolated. These results indicate that self-acylation to the

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