reached quantitatively on the basis of the titration data (Fig. 3). In its simplest form the equilibria involved must be of the form

$$\text{denaturation}\quad N + xH^+ \underset{}{\overset{\text{instantaneous}}{\rightleftarrows}} NH_x \xrightarrow{k_1} DH_x$$

$$\text{regeneration}\quad DH_x - xH \rightleftarrows D \xrightarrow[k_2]{} N$$

where N and D are native and denatured protein, respectively; and x is the number of equivalents of $[H^+]$ involved in the trigger reaction. It is important to note that x is not necessarily 36; the kinetic data suggest a much smaller number (2.5) of groups which affect the stability of N. Furthermore it is not necessary to assume that N and NH_x, or D and DH_x are characterized by the same ϵ. It is only necessary that the ratios $[N]/[NH_2]$ and $[D]/[DH_2]$ be the same in equilibrium mixtures of all four components, as they are in pure native or pure denatured protein at the same pH, so that the ratios measured by the absorption measurements are $([N] + [NH_2])/([D] + [DH_2])$ rather than $[N]/[D]$.

It is attractive to inquire how the combination of 2.5 equivalents (average) of H^+ results in a rapid doubling of the groups available to combine with acid, and in the spectroscopic and solubility changes which follow. Without contradicting conclusions drawn from X-ray data and molecular constants, we may consider the ferrihemoglobin molecule to consist in a singly folded flat molecular fabric, with the prosthetic groups on the inner surface of the fold, and acid-binding groups distributed uniformly over both surfaces of each disc.[9] Combination with H^+ of an average of 2.5 COO^- groups per molecular unit of folded fabric may then cause opening of the fold, and separation of the inner surfaces; thus the COO^- groups on the inner surfaces become available to combine with H^+. At the same time, but either more slowly or only after combination with H^+, the molecular rearrangements which affect the absorption, take place. Aggregation of the fabric units into the large particles of insoluble denatured protein takes place only after COOH groups are ionized again by removal of H^+. If the COOH groups are not completely ionized (pH range near 4) all the changes are reversed and orderly refolding of single units gradually occurs, and no precipitation results. If all the COOH groups dissociate, including those that participate in bonding the discs, orderly folding is less likely to occur than the building up into large aggregates that is always possible when polyvalent units are involved.

In view of the demonstration by Gralén[10] that hemoglobin is dissociated into units of half the normal molecular weight (two hemes per unit) at pH values above those studied in this paper, the folded units postulated above must be thought of as containing only two hemes each.

CAMBRIDGE, MASS.

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[9] A folded fabric is indicated rather than paired flat discs, since the regeneration reaction, as well as the denaturation reaction, is first order.

[10] N. Gralén, *Biochem. J.*, **33**, 1907 (1939).

[CONTRIBUTION NO. 35 OF CENTRAL RESEARCH DEPARTMENT, MINNESOTA MINING & MANUFACTURING COMPANY]

The Chemistry of the Perfluoro Acids and their Derivatives. V. Perfluoropropionic Acid

BY DONALD R. HUSTED AND ARTHUR H. AHLBRECHT

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A number of derivatives of perfluoropropionic acid have been prepared and their properties determined. Data are reported for the first time on the anhydride, acid chloride, methyl, ethyl and isopropyl esters, dihydro amine and dihydro alcohol. Many compounds containing the perfluoroethyl group, C_2F_5–, differ sharply in chemical or physical properties from the adjoining compound containing one CF_2 group more, or one CF_2 group less.

We started our investigation of the properties of the perfluorinated acids and their derivatives with perfluorobutyric acid. Numerous derivatives were made from that acid, and were reported earlier.[1] As the other perfluoro acids became available it was desirable to make the corresponding derivatives from these acids in order to study changes in properties as affected by changes in fluorocarbon chain length. In making these comparisons a number of derivatives of perfluoropropionic acid were prepared. The syntheses and properties of some of these derivatives are reported in this paper.

Our original supply of acid for this investigation was obtained by distillation of the forerun from the electrolytic preparation of perfluorobutyric acid. For later work, the acid was obtained by the electrolytic fluorination of propionic acid.[2] This acid forms a hydrate, containing about 10% water, boiling at 108.5°. Pure perfluoropropionic acid is easily obtained from the hydrate upon distillation from a little phosphorus pentoxide. The small amounts of anhydride formed are removed as the low-boiling fraction.

The preparation of perfluoropropionic anhydride itself is easily accomplished by adding an excess of phosphoric anhydride to the acid, refluxing the mixture for several hours and then recovering the anhydride by distillation. The acid chloride is conveniently prepared by the reaction of the anhydrous acid with benzoyl chloride. The amide is prepared by addition of anhydrous ammonia to an ether solution of the ethyl or methyl ester, or by the reaction of the acid chloride with ammonia. The

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[1] D. R. Husted and A. H. Ahlbrecht, 116th American Chemical Society Meeting, Atlantic City, N. J., September, 1949, Fluorine Symposium Paper No. 17, page 10K; paper for publication in preparation.

[2] E. Kauck, A. Diesslin, J. H. Simons, 116th American Chemical Society Meeting, Atlantic City, N. J., September, 1949, Paper No. 15, page 9K; *Ind. Eng. Chem.*, **43**, 2332 (1951).

1,1-dihydroperfluoropropyl alcohol may be produced by lithium aluminum hydride reduction of the anhydrous acid with the production of some aldehydrol as a by-product. The procedure for the isolation of the aldehyde has already been described.[3]

1,1-Dihydroperfluoropropylamine is produced by the lithium aluminum hydride reduction of the corresponding amide. The preparation of the perfluoroisocyanate has been described elsewhere.[4]

Compounds containing the perfluoroethylalkyl group, C_2F_5, appear to mark a transition point in the physical and chemical properties in the series of some of the perfluoroalkyl derivatives. For example, 1,1-dihydroperfluoroethylamine boils higher than ethylamine[5] and the 1,1-dihydroperfluoropropylamine boils higher than the corresponding hydrocarbon propylamine whereas the next higher member of the series, 1,1-dihydroperfluorobutylamine,[1] boils lower than the corresponding hydrocarbon amine. At least one reaction of the 1,1-dihydroperfluoroamines, the reaction with alkyl bromides, gives different products under the conditions used for those containing a perfluoropropyl, $C_3F_7^-$, or longer group than it does for the one containing only a trifluoromethyl, CF_3– group.[6] The acyl azide, $C_2F_5CON_3$,[4] of this acid appears to be quite explosive as is also the acyl azide of the first member of the series, perfluoroacetyl azide, CF_3CON_3.[7] During distillation or attempted rearrangement to the isocyanate both azides exploded. In contrast to this behavior, acyl azides of perfluorobutyric acid and of higher perfluoro acids were found to be stable enough to rearrange quite smoothly to give a satisfactory yield of the perfluoroisocyanate.

Perfluoropropionamide and the longer chain perfluoroamides give different type products, namely perfluoroalkyl bromides, when subjected to the Hofmann hypohalite degradation,[6] than does perfluoroacetamide, which produces perfluoroethane[8] by the same reaction.

The azeotrope of the acid and water boils higher than the acid, thus resembling trifluoroacetic acid and in sharp contrast to the azeotrope of perfluorobutyric acid and water which boils 22° below the acid. An additional point of contrast is the high concentration of acid in the acid–water azeotrope (91.8%) as contrasted with the low concentration (28%) in the perfluorobutyric acid–water azeotrope.

Among the alcohols[6] a sharp break also occurs in the chemical properties. An example is the formation of ethyl trifluoroethyl ether on refluxing the appropriate mixed alcohols with sulfuric acid, while under the same reaction conditions 1,1-dihydroperfluorobutanol was recovered unreacted.

Thus, it is apparent that perfluoropropionic acid is an important member of the family of perfluoroaliphatic acids, many of its derivatives having properties differing in kind as well as in degree from the other members of the family, sometimes resembling the higher members of the series and sometimes resembling the corresponding derivative containing a trifluoromethyl CF_3– group.

Physical data in the form of the infrared absorption spectral curves (Figs. 1 and 2) and Debye–Scherrer X-ray fine powder patterns[10] are presented to facilitate the identification of these compounds when they occur in very small amounts.

Work is continuing on derivatives of this acid and will be reported at a later date.

Experimental

The Purification of Perfluoropropionic Acid.—Crude perfluoropropionic acid[2] was distilled through a packed fractionating column giving as a first cut, the pure acid boiling at 95.5° (738.5 mm.).[9] A higher boiling cut at 108.5° (734.5 mm.) containing approximately 9.8% water was also obtained. When other perfluorinated acids were also present, purification could most easily be accomplished by adding phosphorus pentoxide in an amount equal to about 1% of the weight of the acid and slowly fractionating the liquid. The low-boiling anhydrides distilled off first followed by the pure perfluoropropionic acid. Failure to remove all water present complicates the separation and decreases the yield of the acid; properties: C_2F_5COOH, b.p. 95.5° (738.5 mm.), $n^{20}{}_D$ 1.2838, $d^{20}{}_4$ 1.561; $C_2H_5COOH \cdot H_2O$ azeotrope, b.p. 108.5° (734.5 mm.), $n^{25}{}_D$ 1.3010, $n^{20}{}_D$ 1.3035.

Anal. Calcd. for $C_3HO_2F_5$: F, 57.8; C, 21.96; neut. equiv., 164.04. Found: F, 57.8; C, 22.0; neut. equiv., 164. Calcd. for $C_2H_3O_3F_5$; neut. equiv., 182.04 (for monohydrate); H_2O, 9.9. Found: neut. equiv., 180; H_2O, 9.8.

Infrared absorption spectral curve (Fig. 1) of the pure acid showed the presence of a carbonyl (1780 cm.$^{-1}$) and a hydroxyl group (3100 cm.$^{-1}$). The sodium salt was prepared by the exact neutralization of the acid by sodium hydroxide. The three most prominent lines in the Debye–Scherrer X-ray fine powder pattern are: I, 5.08, V.S.; II, 11.35, S.; III, 4.68, S.[10]

Perfluoropropionic Anhydride.—A mixture of 46 g. of the perfluoro acid and 10 g. of phosphorus pentoxide was placed in a flask fitted with a 6-plate fractionating column topped by a total reflux fractionating head. The mixture was refluxed for several hours, or conveniently overnight, then the distillation of the anhydride was started. A small amount of low-boiling forerun was removed and the pure anhydride collected, b.p. 69.8–70° (735 mm.), $n^{25}{}_D$ 1.2721. If further purification was necessary it was accomplished by distillation over fresh phosphorus pentoxide; yield 25 g. (57.5%).

Anal. Calcd. for $C_6O_3F_{10}$: C, 23.3; neut. equiv., 155. Found: C, 23.1; neut. equiv., 155.

The infrared absorption spectral curve showed the presence of a double carbonyl and no hydroxyl group (Fig. 1).

Perfluoropropionyl Chloride.—A mixture of 100 g. (0.608 mole) of perfluoropropionic acid and 112.5 g. (0.8 mole) of benzoyl chloride was placed in a 500-ml. flask fitted with a water-cooled reflux condenser connected to a Dry Ice–acetone cooled trap with the outlet protected from atmospheric moisture. The mixture was allowed to reflux overnight. The next morning, about 50 ml. of material had collected in the Dry Ice cooled trap. This liquid was purified by distillation in a low temperature still. The product was pure perfluoropropionyl chloride, b.p. 5° (739.5 mm.).

Anal. Calcd. for C_3OClF_5: mol. wt., 182.47; neut.

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(3) D. R. Husted and A. H. Ahlbrecht, 118th American Chemical Society Meeting, Chicago, Ill., September, 1950, Fluorine Symposium Paper No. 36, page 20L; THIS JOURNAL, **74**, 5422 (1952).

(4) A. H. Ahlbrecht, D. R. Husted, T. S. Reid and G. H. Smith, Jr., *ibid.*, not yet published; (a) T. S. Reid and G. H. Smith, Jr., 116th Meeting, American Chemical Society, Atlantic City, N. J., September 18, 1949, Fluorine Symposium Paper No. 16, page 9K.

(5) H. Gilman and R. G. Jones, THIS JOURNAL, **65**, 1458 (1943).

(6) A paper covering this reaction is in preparation.

(7) Private communication to this Laboratory by Professor McBee, *cf.* W. Huckel, *Nachr. Akad. Wiss., Göttingen, Math.-Physik Klasse*, 36 (1946); *C. A.*, **43**, 6793 (1949).

(8) E. Gryszkiewicz-Trochimowski, A. Sporzynski and A. Wnuk, *Rec. trav. chim.*, **66**, 426 (1947).

(9) R. N. Haszeldine, *Nature*, **166**, 192 (1950), reports a different method of preparation for this acid.

(10) For the full Debye–Scherrer X-ray fine powder pattern order Document 3721 from American Documentation Institute, % Library of Congress, Washington 25, D. C., remitting $1.00 for microfilm (images 1 inch high on standard 35 mm. motion picture film) or $1.00 for photocopies (6 × 8 inches) readable without optical aid.

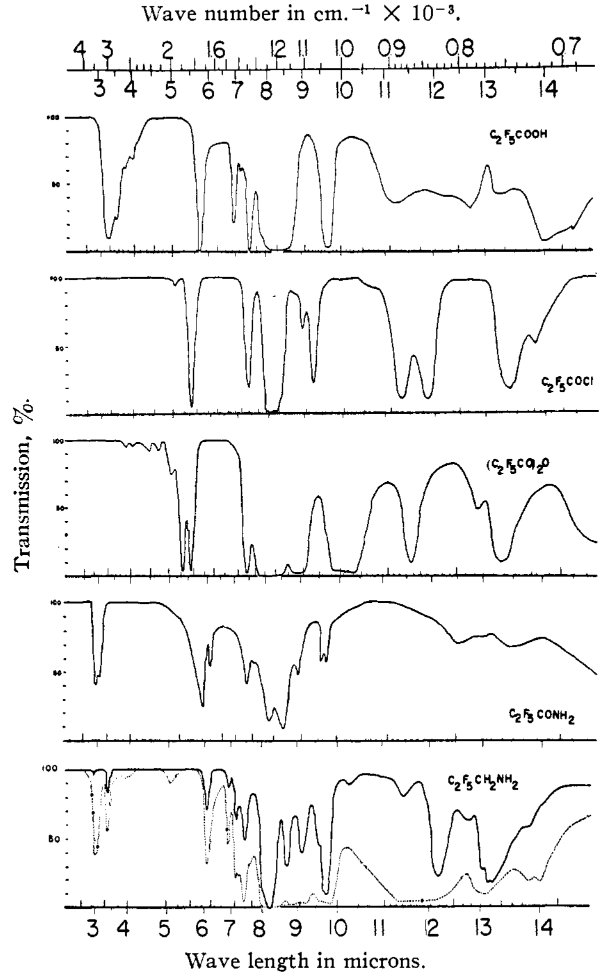

Fig. 1.—C_2F_5COOH, thickness, 0.013 mm.; C_2F_5COCl, 50 mm. pressure, 25 mm. length cell; $(C_2F_5CO)_2O$, thickness, 0.013 mm.; $C_2F_5CONH_2$, Nujol mull of solid; $C_2F_5CH_2NH_2$, solid line, vapor sample, 50 mm. pressure, 25 mm. length; broken line, liquid sample, thickness, 0.013 mm.

equiv., 91.24; Cl, 19.43. Found: mol. wt. (gas density balance), 183, by hydrolysis, 180.3; neut. equiv., 90.7; Cl, 19.77.

Infrared absorption spectral curve showed the presence of a strong CO and CF band, no OH group, no CH group (Fig. 1).

Perfluoropropionamide.—In a flask fitted with a Dry Ice-acetone cooled reflux condenser, was placed 178 g. (1 mole) of methyl perfluoropropionate. Anhydrous ammonia was passed into this with cooling in a Dry Ice-acetone-bath until no more ammonia was absorbed. White crystals were removed from the methanol by filtration and dried in air, m.p. 95°, yield 153 g. (94%). If purification was necessary, the amide was recrystallized from hot methanol solution by cooling to Dry Ice temperatures.

Anal. Calcd. for $C_3H_2NOF_5$: N, 8.56. Found: N, 8.56.

The infrared absorption curve (Fig. 1) showed the presence of a NH_2 group (3400, 1600, 1340 cm.$^{-1}$), C=O group and CF group. The most prominent lines in the Debye-Scherrer X-ray fine powder pattern are 4.75, V.S.; 2.717, S.; 3.87, S.[10]

Methyl Perfluoropropionate.—A mixture of 98 g. (1.0 mole) of concentrated sulfuric acid and 328 g. (2 moles) of perfluoropropionic acid was placed in a flask fitted with a reflux condenser and a dropping funnel. To this was added 68 g. (2.12 moles) of methyl alcohol slowly and with cooling. The mixture was refluxed overnight. In the morning, a small amount of phosphorus pentoxide was added. The reflux condenser was replaced by a distillation head and the mixture distilled. The fraction boiling from 60–61° was collected and redistilled to yield the pure methyl ester, b.p. 61° (739 mm.), n^{25}_D 1.2864, n^{20}_D 1.2884, d^{20}_4 1.393, yield 251 g. (70.6%). The unreacted perfluoropropionic acid was recovered as the sodium salt, amounting to an additional 16% of starting material.

Anal. Calcd. for $C_4H_3O_2F_5$: F, 53.4; C, 26.98; sapn. equiv., 178. Found: F, 53.5; C, 27.3[11]; sapn. equiv., 178.

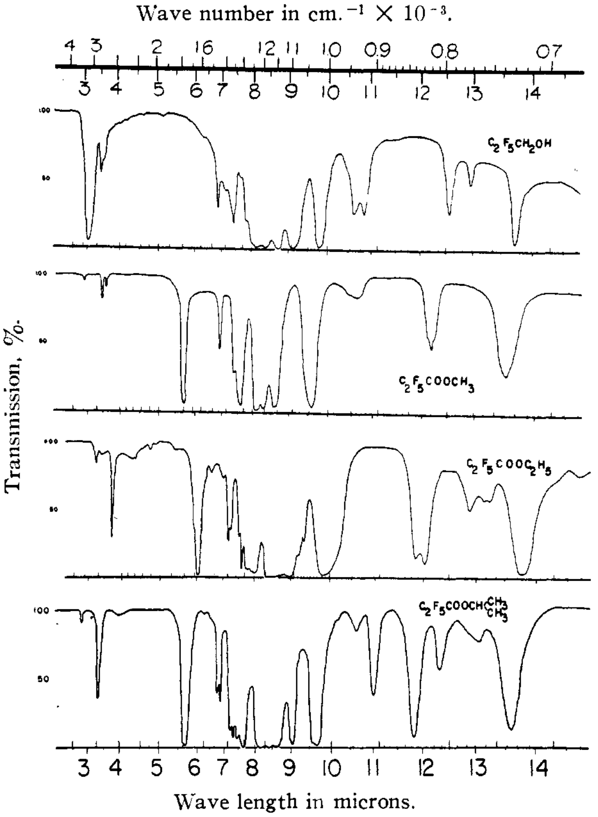

Fig. 2.—$C_2F_5CH_2OH$, thickness, 0.013 mm.; $C_2F_5COOCH_3$, 50 mm. pressure, 25 mm. length; $C_2F_5COOC_2H_5$, thickness, 0.025 mm.; $C_2F_5COOCH(CH_3)_2$, thickness, 0.021 mm.

Ethyl Perfluoropropionate.—The preparation was carried out similarly to that described for the methyl ester in the preceding paragraph, except that phosphorus pentoxide was added to the still-pot during the redistillation. A mixture of 8 g. (0.08 mole) of sulfuric acid and 55 g. (0.33 mole) of perfluoropropionic acid reacted with 11.5 g. (0.25 mole) of ethyl alcohol. Ethyl perfluoropropionate was collected, b.p. 75–75.6° (738.1 mm.), n^{25}_D 1.2988–1.2990, n^{20}_D 1.3002, d^{20}_4 1.299, yield 38 g. (59.1%).

Anal. Calcd. for $C_5H_5O_2F_5$: F, 49.45; C, 31.25; sapn. equiv., 192. Found: F, 49.8; C, 31.2; sapn. equiv., 191 (no F^- lost during saponification).

The infrared absorption spectral curve (Fig. 2) shows the presence of CH and C=O but no OH group.

Isopropyl Perfluoropropionate.—In a container cooled in an ice-bath 75 g. (0.75 mole) of concentrated sulfuric acid was added to 60 g. (1 mole) of isopropyl alcohol. This mixture was added to 82 g. (0.5 mole) of perfluoropropionic acid in a flask with a reflux condenser and heated 20 minutes at 50–60°, then allowed to stand overnight. The bottom layer was removed and distilled from 10 g. of phosphorus pentoxide. The fraction b.p. 75–85° was collected and amounted to 105 g. This was purified by redistillation from 5 g. of phosphorus pentoxide through a 6–8 plate fractionating column. The pure ester has the following physical properties: b.p. 86.5° (741.5 mm.), 41.5° (129 mm.), n^{25}_D 1.3074, n^{20}_D 1.3090, d^{20}_4 1.224 (micro); yield 64 g. (44.6%). The conventional method of isolation of esters by pouring into water, washing and drying, if used for this ester fre-

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[11] Carbon and fluorine by a quartz tube combustion after the method of H. S. Clark, *Anal. Chem.*, **23**, 659 (1951).

quently decreases the yield by half. Propylene has been identified as a by-product of the reaction by boiling point and infrared absorption spectrum.

Anal. Calcd. for $C_6H_7O_2F_5$: F, 46.1; C, 34.9; sapn. equiv., 206. Found: F, 45.8; C, 34.9; sapn. equiv., 206 (no fluoride ion detected on saponification).

1,1-Dihydroperfluoropropylamine.—CAUTION: The use of lithium aluminum hydride is hazardous and precautions must be taken to avoid fire and explosion. Particularly, the handling of lithium aluminum hydride should be under nitrogen atmosphere, and the reaction mixture at all times should be flushed with a nitrogen stream; no oxygen should be present. If the solvent loss is great enough to leave a film of dried solid on the walls of the flask, more ether should be added to bring the level up to at least the original starting volume. Water should be introduced in such a manner that it falls on the liquid and will not run over the sides of the flask where a dry film of lithium aluminum hydride may have collected.

To a solution of 51 g. (1.342 moles) of lithium aluminum hydride in 800 ml. of absolute ether was added slowly a solution of 110 g. (0.675 mole) of perfluoropropionamide dissolved in 500 ml. of absolute ether. The reaction was carried out in a flask containing a stirrer, a Dry Ice–acetone cooled condenser and flushed with nitrogen at about 2 c.f.h. throughout the entire reaction. The rate of addition of the ether solution of the amide was such as to maintain a gentle reflux. Stirring was continued for several hours or overnight. The mixture was then cooled with a Dry Ice–acetone-bath and 115 ml. of water added dropwise. (Nitrogen must be flowing through the system. *Explosion shields are recommended.*) Two hundred milliliters of concentrated sulfuric acid (3.75 moles) was added with continued cooling resulting in formation of a white crystalline precipitate. This mixture was evaporated to dryness and the residue dried in a 65° oven. The residue, 568 g. of white solid, was placed in a 3000-ml. flask equipped with a stirrer, a stillhead and a dropping funnel. A solution of 320 g. (8 moles) of sodium hydroxide in 350 ml. of water was added. Distillation of the mixture yielded 67 g. of 1,1-dihydroperfluoropropylamine, b.p. 35–45°, plus about 2 g. liquid collected in a Dry Ice–acetone cooled trap which was connected to the outlet of the still. The contents of the Dry Ice trap were identified as ammonia and pentafluoroethane. The amine was redistilled through a 9-plate semi-micro distillation column and the amine collected, b.p. 49–49.5° (739 mm.), $n^{20}D$ 1.297, d^{20}_4 1.400.

Anal. Calcd. for $C_3H_4NF_5$: N, 9.39. Found: N, 9.4.

The infrared absorption spectral curve showed the presence of an amino group, carbon–hydrogen bond and carbon–fluorine bond (Fig. 1).

1,1-Dihydroperfluoropropylamine Hydrochloride.—Hydrogen chloride was bubbled into a solution of 1 g. of the amine in 50 ml. of anhydrous ether. The white precipitate was air-dried to remove the solvent and volatile reactants; yield 1.1 g., Debye–Scherrer X-ray fine powder pattern,[10] three most prominent lines: I, 3.362, V.S.; II, 4.01, S.; III 4.08, S.

Anal. Calcd. for $C_3H_5NClF_5$: Cl, 19.15. Found: Cl, 19.02.

1,1-Dihydroperfluoropropyl Alcohol.—CAUTION: The same precautions were observed as described for the amine preparation and the same type apparatus used. A solution of 328 g. (2 moles) of perfluoropropionic acid in 800 ml. of dry ether was added to a solution of 80 g. (2.1 moles) of lithium aluminum hydride in 1000 ml. of dry ether with the reaction flask cooled in a Dry Ice–acetone-bath. The rate of addition was such as to maintain a gentle reflux and required about 1 hour. The mixture was stirred for 5 hours at room temperature. Sufficient water (about 40–50 ml.) was then added to decompose the excess lithium aluminum hydride, followed by 250 ml. (4.42 moles) of concentrated sulfuric acid dissolved in ice-water. Two layers formed which were separated and the aqueous layer extracted three times with ether. The ether layer and the ether extracts were combined and the ether removed in a stripping still. The oily residue was distilled through a 9-plate semi-micro fractionating column and a 140-g. fraction boiling 77–81° collected. One hundred milliliters of concentrated sulfuric acid was added to this fraction and the material redistilled. Redistillation through a 15-plate semi-micro fractionating column yielded the pure alcohol, b.p. 80° (748 mm.), yield 85 g. (28.4%), $n^{25}D$ 1.2882, d^{20}_4 1.505 (micro), $n^{20}D$ 1.2900–1.2908, exact value uncertain. The variation may be caused by absorption of water from high humidity atmosphere.

Anal. Calcd. for $C_3H_3OF_5$: F, 63.4; C, 24.0; OH, 11.32. Found: F, 63.2; C, 24.0; (OH, 10.9; H_2O, 0.3—different sample).

The oily residue remaining in the still after removal of the 77–81° fraction contained a substantial amount of alcohol plus the aldehydrol. The aldehyde and a part of the remaining alcohol may be recovered by distillation over concentrated sulfuric acid.[3,12]

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[12] Footnote added after the first submission of the manuscript: The preparations of the three esters were repeated to obtain samples for fluorine analyses which were rerun by a different method.[11] The method of preparation described for the methyl ester was used for all three, except that the two layers produced were separated and only the ester-containing layer distilled (bottom layer for ethyl and methyl, top for isopropyl). The yield by this method is lower, but purification is somewhat simpler.