[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

Synthesis and Reduction of Difluorodecanoic Acid Derivatives

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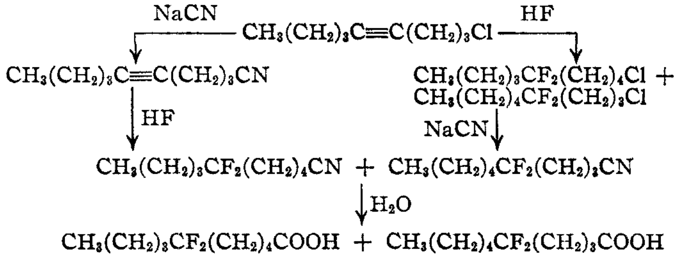
In this paper we describe the synthesis of 5,5- and 6,6-difluorodecanoic acids (mixture of isomers) and some reactions of their derivatives. The synthetic scheme is indicated below.



The starting compound, 1-chloro-4-nonyne, was best prepared by alkylation of 1-hexyne with 1-chloro-3-bromopropane using lithium amide in liquid ammonia. Of the two succeeding alternate paths, addition of hydrogen fluoride to the acetylenic nitrile proved superior.[2] In each case a mixture of isomeric difluoro compounds was obtained as was expected since the chloro or cyano groups were too far removed from the triple bond to cause directed addition. Because of the stability of the fluorinated compounds it is certain that CF_2 groups are present. The mixtures thus obtained were carried through to the corresponding difluoro acids, no attempt being made to separate pure individuals in any case.

Of particular interest are certain reduction reactions carried out in order to prepare the corresponding difluorodecanols. High pressure catalytic hydrogenation over copper chromite caused complete decomposition. Bouveault–Blanc reduction[3] was partly successful but considerable amounts of fluoride ion were detected in the reaction mixture. Reduction of the thiol esters by lithium aluminum hydride[4] gave the desired alcohol but the best method involved desulfurization of the thiol esters with Raney nickel.[5]

Experimental[6]

1-Chloro-4-nonyne.—Lithium amide, prepared in two liters of liquid ammonia from 42 g. (6 moles) of lithium, in presence of 1.8 g. of ferric nitrate nona-hydrate as catalyst, as described for sodamide by Greenlee and Henne[7] was treated with 492 g. (6 moles) of 1-hexyne[8] and then 946 g. (6 moles) of 1-chloro-3-bromopropane was added and allowed to react during fourteen hours.[9] Lithium amide, prepared and used *in situ*, was found to give higher yields of 1-chloro-4-nonyne than either sodium or potassium amide. After addition of 320 g. of ammonium chloride and subsequent evaporation of most of the ammonia, about 1500 ml. of water was added. Extraction with ether removed the organic product which was subsequently purified by fractional distillation. The yield of 1-chloro-4-nonyne boiling at 100–106° (23 mm.), $n^{20}D$ 1.4595, was 515.5 g. (54.2%). Approximately 180 g. of 1-hexyne was recovered, together with 51 g. of still residue.

4,4- and 5,5-Difluoro-1-chlorononane (Mixture of Isomers).—The addition of hydrogen fluoride to 1-chloro-4-nonyne was accomplished by adding a solution of 79 g. (0.5 mole) of 1-chloro-4-nonyne in 60 ml. of dry ether during one and three-fourths hours to a stirred mixture of 37 g. of dry ether and 83 g. (4.1 moles) of hydrogen fluoride in an ice-cooled stainless steel flask. After stirring for eight hours in the cold, the reaction mixture was poured on ice and extracted with ether. The ether extract was washed with 5% sodium hydroxide solution until free from acid and dried over calcium chloride. On distillation two fractions of incompletely fluorinated product were obtained: 37 g., b. p. 85–95° (11 mm.), $n^{20}D$ 1.4312; and 7 g., b. p. 95–105° (11 mm.), $n^{20}D$ 1.4297; together with 37.5 g. of heavy oil as still residue. The partly fluorinated material, 211 g., from a number of runs, was again treated with hydrogen fluoride (27 g.) at 0° as above, followed by stirring at room temperature overnight, to yield two fractions, 87 g., b. p. 87–92° (11 mm.), $n^{20}D$ 1.4232 and 84 g., b. p. 92–97° (11 mm.), $n^{20}D$ 1.4235. These completely fluorinated fractions were combined for conversion to the nitrile (see below). There was a still residue of 30.5 g. The pure chlorodifluorononane foams badly when redistilled.

Anal. Calcd. for $C_9H_{17}F_2Cl$: F, 19.1. Found: F, 19.7.

Increasing the time of contact of 1-chloro-4-nonyne with hydrogen fluoride (twenty-four hours) and allowing the temperature to rise to 7° during the latter part of this time (eight to twelve hours) afforded lower yields of fluorinated product and a larger amount of polymeric residue. The substitution of dimethyl or diisopropyl ether for ethyl ether as solvent gave slightly lower yields of fluorinated product.

5-Decynenitrile.—1-Chloro-4-nonyne (100 g., 0.63 mole) was refluxed, with stirring, with a solution of 123 g. of sodium cyanide in 175 ml. of water and one liter of ethanol for eighteen hours. After removal of nearly all of the alcohol under reduced pressure the residue was poured into water and extracted with ether. From the ether solution there was obtained 70 g. (74.5%) of 5-decynenitrile, b. p. 106–8° (5 mm.), $n^{20}D$ 1.4540.

5,5- and 6,6-Difluorodecanenitriles (Mixture of Isomers).—A solution of 202 g. (1.36 moles) of 5-decynenitrile in 140 ml. of ether was added to 268.5 g. (13.4 moles) of hydrogen fluoride in 106 g. of ether at 0° during two hours as described for 1-chloro-4-nonyne. The reaction flask was then placed in a vacuum-jacketed bath at 6° and stirring was continued for seventeen hours while allowing the temperature to rise to 18°. This was followed by four hours of stirring at 29°. From the washed and dried ether solution there was obtained 10 g. of fore-run, b. p. below 112° (5 mm.), 141 g. of incompletely fluorinated nitrile, b. p. 112–118° (5 mm.), $n^{20}D$ 1.4230, and 78 g. of crystalline still residue. A second treatment of 151 g. of

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[2] Compare Henne and Plueddeman, THIS JOURNAL, **65**, 587 (1943).

[3] Ziegler and Hechelhammer, *Ann.*, **528**, 114 (1937).

[4] Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947); Finholt, Bond and Schlesinger, *ibid.*, **69**, 1199 (1947).

[5] Jeger, *et al.*, *Helv. chim. acta*, **29**, 784 (1946).

[6] All fluorine analyses were carried out as described by Renoll, THIS JOURNAL, **68**, 1159 (1946).

[7] Greenlee and Henne, "Inorganic Syntheses," McGraw-Hill Book Company, New York, N. Y., **1946**, Vol. II, p. 128.

[8] Purchased from the Farchan Laboratories, Cleveland, Ohio.

[9] Henne and Greenlee, THIS JOURNAL, **67**, 484 (1945).

the crude fluorinated nitrile in 85 ml. of ether with 160 g. (8 moles) of hydrogen fluoride in 65 g. of ether at 0°, followed by stirring for five hours at 25° gave a product consisting of 1 g. of fore-run, b. p. below 111.5° (5 mm.), $n^{20}D$ 1.4178, 135 g. of completely fluorinated nitrile, b. p. 111.5–118° (5 mm.), $n^{20}D$ 1.4145 and 15 g. of residue.

The crystalline still residue was hydrolyzed to difluorodecanoic acid by refluxing with potassium hydroxide in aqueous ethanol. From 176 g. of residue there was obtained 106 g. of acid.

1-Chloro-4,4- and 5,5-difluorononane mixture was converted to 5,5- and 6,6-difluorodecanenitrile mixture by sodium cyanide in 60% yield, as described for 1-chloro-4-nonyne. Approximately one-third of the starting material remained unreacted after twenty hours.

Difluorodecanoic Acid.—Hydrolysis of 265 g. (1.4 moles) of the nitrile by refluxing with a solution of 240 g. of potassium hydroxide in 1580 ml. of ethanol and 316 ml. of water, with stirring, for twenty-seven hours gave 274 g. (94%) of difluorodecanoic acid, b. p. 125–131° (2 mm.). When recrystallized from Skellysolve-B it melted at 44–46°, with softening at 40°.

Anal. Calcd. for $C_{10}H_{18}F_2O_2$: neut. equiv., 208; F, 18.3. Found: neut. equiv., 210; F, 18.4.

Taking into account the acid obtained by hydrolysis of the difluorodecanenitrile still residue (18%), the over-all yield of acid from 5-decynenitrile was 65%.

The **acid chloride** was prepared from the acid and excess thionyl chloride in 98% yield, b. p. 103–106° (4 mm.).

Ethyl Difluorodecanoate.—Esterification of 21 g. (0.1 mole) of difluorodecanoic acid with 25 ml. of ethanol in 150 ml. benzene, using *p*-toluenesulfonic acid as catalyst, gave 23 g. (97.4%) of ester, b. p. 107.5–108.5° (4 mm.), $n^{20}D$ 1.4126.

Reduction of Ethyl Difluorodecanoate.—Hydrogenation of 24 g. (0.1 mole) of ester over copper chromite catalyst (37 KAF)[10] in glass-lined equipment at 250° and 2500 lb. pressure resulted in almost complete decomposition of the ester.

A preliminary distillation of the Bouveault–Blanc[3] reduction product of 23 g. of ethyl ester separated 16 g. of material, b. p. 105–150° (3 mm.), and a small amount of still residue. Redistillation through a small helices-packed column gave 7 g. of 5,5- and 6,6-difluorodecanols (mixture of isomers),[11] b. p. 109–115° (5 mm.).

In order to identify the difluorodecanol, the phenylurethan, m. p. 73.6–74.2°, after recrystallization from Skellysolve-B, was prepared.[12]

Anal. Calcd. for $C_{17}H_{25}NO_2F_2$: F, 12.1. Found: F, 11.6.

Ethyl Thioldifluorodecanoate.—A solution of 120 g. (0.53 mole) of difluorodecanoyl chloride in 200 ml. of dry benzene and 100 g. (1.6 moles) of ethyl mercaptan was treated with 63 g. (0.78 mole) of pyridine in 100 ml. of dry benzene as described by Jeger.[5] The yield of ethyl thioldifluorodecanoate was 91 g. (68%), b. p. 118–121° (2 mm.). Thirty-one grams of difluorodecanoic acid was recovered.

***n*-Butyl Thioldifluorodecanoate.**—From 31 g. (0.14 mole) of difluorodecanoyl chloride, 50 g. (0.55 mole) of *n*-butyl mercaptan, 16.5 g. (0.21 mole) of pyridine, and 75 ml. of benzene there was obtained[5] 24 g. (88.9%) of *n*-butyl thioldifluorodecanoate, b. p. 125–130° (1.5 mm.).

Reductive Desulfurization of Ethyl and *n*-Butyl Thiol Esters.—(a) With Raney nickel[5]: Freshly prepared Raney nickel from 480 g. of Raney alloy[13] was washed by decantation several times with absolute ethanol and covered with 100 ml. of ethanol. A solution of 24–30 g. of the ester in 100 ml. of absolute ethanol was added slowly, with shaking, and agitation continued for one hour longer. Most of the supernatant liquid was decanted from the nickel through filter paper. The nickel residue was washed repeatedly with ethanol in a chromatographic adsorption tube plugged with cotton. The total volume of the combined ethanol solutions was about one liter. Because of foaming encountered in the removal of solvent by distillation, the alcohol solution was allowed to evaporate in an open dish at room temperature. The yield of difluorodecanol, b. p. 112–115° (5 mm.), was 15–18 g. (*ca.* 80%). There was no fore-run or residue in the distillation. It solidified at room temperature and had a pleasant odor.

Anal. Calcd. for $C_{10}H_{20}F_2O$: F, 19.6. Found: F, 18.9.

The reduction with Raney nickel is probably quantitative, but the removal of the last traces of product adsorbed on the nickel is most difficult.[5]

(b) With Lithium Aluminum Hydride: The preparation of lithium aluminum hydride and procedure for use as a reducing agent were as described.[4] A solution of 31 g. of mixed ethyl and butyl thiol esters in 50 ml. of dry ether was added to 50 ml. of an ether solution of lithium aluminum hydride containing 0.00136 mole of $LiAlH_4$ per ml. After removal of solvent, there was obtained 3.5 g. of fore-run, b. p. 103–110° (5 mm.), 17 g. of difluorodecanol, b. p. 110–115° (5 mm.), and 2.5 g. of still residue. All fractions had a mercaptan-like odor. It was obvious that byproducts were formed in this reduction, in contrast to the complete absence of such substances in the Raney nickel reduction.

From 91 g. of ethyl thiol ester and 40 g. of *n*-butylthiol ester there was obtained a total of 78 g. (76%) of difluorodecanol by both reduction methods.

Summary

5,5- and 6,6-difluorodecanoic acids (mixture of isomers) have been synthesized from the corresponding nitrile which was formed by the addition of hydrogen fluoride to 5-decynenitrile. An alternate synthesis from 1-chloro-4,4- and 5,5-difluorononane (mixture of isomers) is described.

5,5- and 6,6-difluorodecanols (mixture of isomers) were prepared in good yield by Raney nickel reduction and by lithium aluminum hydride reduction of the ethyl thiol and *n*-butyl thiol esters.

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(10) Connor, Folkers and Adkins, This Journal, **54**, 1138 (1932).

(11) Referred to hereafter as difluorodecanol.

(12) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 136.

(13) Mozingo, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1941, Vol. 21, p. 15.