[CONTRIBUTION FROM THE MORLEY CHEMISTRY LABORATORY, WESTERN RESERVE UNIVERSITY]

The Reaction of *N*-Perfluoroalkylurethans with Diazomethane[1]

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N-*n*-Perfluoropropyl- and *N*-*n*-perfluoroheptylurethans have been treated with diazomethane to give the corresponding *N*-methyl-*N*-*n*-perfluoroalkylurethans in yields of 12% and 19%, respectively. Side reactions occurred involving the *N*-α-difluoromethylene group which in the case of *N*-*n*-perfluoropropylurethan led to the formation of *N*-carbethoxyfluoromethylpentafluoroethyl ketimine in 14% yield. *N*-Methyl-*N*-*n*-perfluoropropylurethan reacted with excess lithium aluminum hydride to give methyl-1,1-dihydroperfluoropropylamine and dimethyl-1,1-dihydroperfluoropropylamine. *N*-Carbethoxyfluoromethylpentafluoroethyl ketimine was hydrolyzed in aqueous hydrochloric acid to yield 1,3,3,4,4,4-hexafluoro-2-butanone hydrate.

Amines containing both a perfluoroalkyl group and an alkyl group were unknown when the present work was initiated. Recently[3] a procedure has been developed to convert carbylamine chlorides to secondary amines containing one trifluoromethyl group. However, the only three representative amines reported were hydrolytically unstable, and no derivatives were synthesized. Since some of the derivatives might be of greater stability than the parent amines, their preparation would be of possible pharmaceutical value as well as of theoretical interest.

Tertiary amines containing only one completely fluorinated alkyl group have never been reported.* Such amines would serve as intermediates for the synthesis of perfluoroalkyl analogs of choline, an interesting antimetabolite. The reduction of *N*-alkyl-*N*-perfluoroalkylurethans with lithium aluminum hydride offers a possible synthetic route to the necessary tertiary amines.

N-Alkyl-*N*-perfluoroalkylurethans have never been prepared. Since these compounds would serve not only as possible intermediates for the preparation of perfluoroalkyl analogs of choline but also would be the first derivatives reported of monoperfluoroalkyl secondary amines, their synthesis has been undertaken in the present work.

The alkylation of the readily available *N*-perfluoroalkylurethans by conventional means has failed.[4] However, the strong electron-withdrawing effect of the perfluoroalkyl group conceivably might render the amidic hydrogen of the parent urethans sufficiently acidic to react with diazomethane. Although simple aliphatic amides fail to react with diazomethane, some cyclic lactams do undergo methylation with the reagent.[5]

Treatment of ethyl-*N*-*n*-perfluoropropyl- and ethyl-*N*-*n*-perfluoroheptylurethans with diazomethane has now been found to give the corresponding ethyl *N*-methyl-*N*-*n*-perfluoroalkylcarbamates in yields of 12% and 19%, respectively, of isolated pure products. These are minimum yields for during the multiple distillations necessary to obtain pure samples, much decomposition occurred. Apparently this is the first successful alkylation of an aliphatic amide with diazomethane.[5]

The structures of the methylated urethans were substantiated by elemental analyses and the infrared absorption spectra (Fig. 1), which exhibited an *N*,*N*-disubstituted amidic band at 5.8 μ and an absence of the N—H stretching peak characteristic of the parent *N*-perfluoroalkylurethans.

Conclusive structure proof was obtained by reduction of ethyl *N*-methyl-*N*-*n*-perfluoropropylcarbamate with lithium aluminum hydride to give dimethyl-1,1-dihydroperfluoropropylamine, isolated as its hydrochloride, in 19% yield. In addition, a 23% yield of methyl-1,1-dihydroperfluoropropylamine was obtained by the familiar cleavage of the carbon to nitrogen bond often encountered in such reductions.[6]

$$CF_3CF_2CF_2N(CH_3)-C(=O)-OC_2H_5 + LiAlH_4 \longrightarrow CF_3CF_2-CH_2-N(CH_3)_2$$

The reduction of the α-difluoromethylene function has been encountered before.[7] It has been proposed that such reduction might involve preliminary loss of hydrogen fluoride followed by reduction of the carbon to nitrogen double bond. In the present work, the replacement of the amidic hydrogen by a

* NOTE ADDED IN PROOF. A recent paper has appeared describing the synthesis of such amines. R. J. Harder and W. C. Smith, *J. Am. Chem. Soc.*, **83**, 3422 (1961).

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(2) Public Health Service Research Assistant. From the thesis to be submitted by Donald Yamashiro to the Graduate School of Western Reserve University in partial fulfillment of the requirements for the Ph.D. degree. Presented at the New York Meeting of the American Chemical Society, September 1960.

(3) K. A. Petrov and A. A. Neĭmysheva, *Zhur Obshcheĭ.*, **29**, 2169 (1959).

(4) R. L. Dannley and M. Lukin, *J. Org. Chem.*, **22**, 268 (1957).

(5) R. Gompper, *Ber.*, **93**, 187 (1960).

(6) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948).

(7) R. L. Dannley and R. G. Taborsky, *J. Org. Chem.*, **22**, 77 (1957).

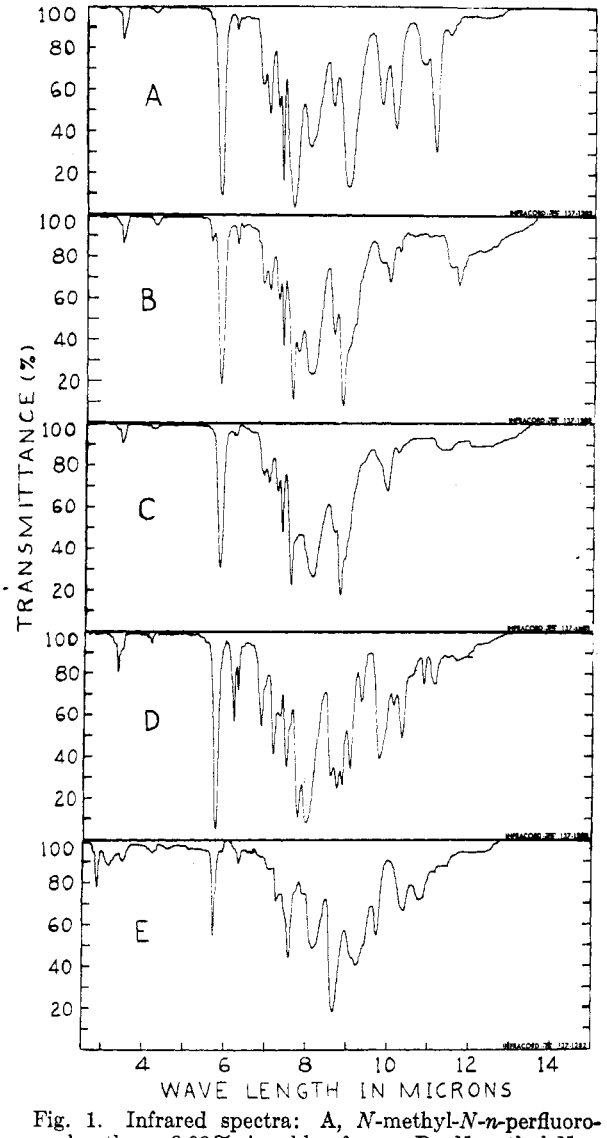
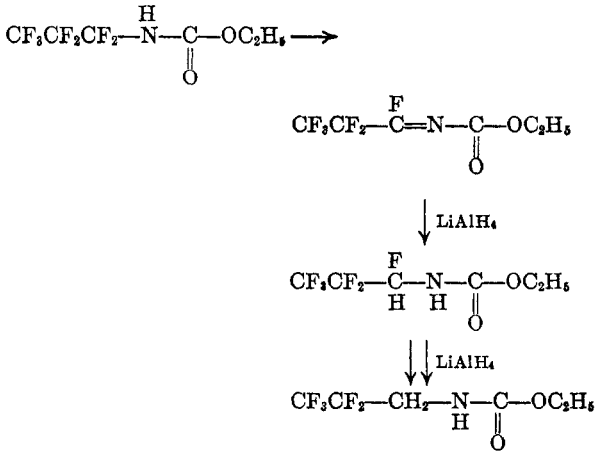
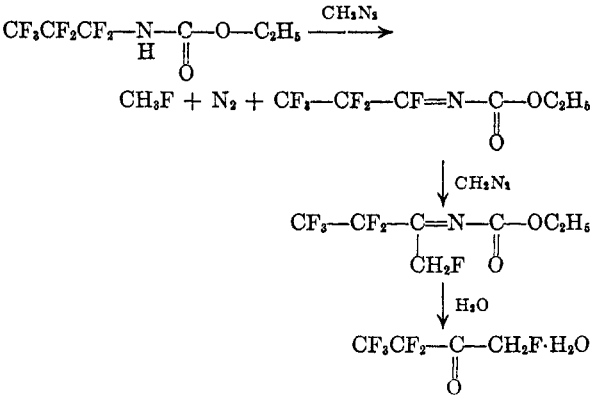


Fig. 1. Infrared spectra: A, *N*-methyl-*N*-*n*-perfluoropropylurethan, 0.99% in chloroform; B, *N*-methyl-*N*-*n*-perfluoroamylurethan, 1.01% in chloroform; C, *N*-methyl-*N*-*n*-perfluoroheptylurethan, 0.94% in chloroform; D, *N*-carbethoxyfluoromethylpentafluoroethyl ketimine, 1.07% in chloroform; E, 1,3,3,4,4,4-hexafluoro-2-butanone hydrate, 1.0% in chloroform



methyl group excluded such an elimination of hydrogen fluoride and yet reduction of the α-difluoromethylene function occurred: therefore a direct displacement of the fluorine atoms by lithium aluminum hydride must be possible. The preliminary elimination of hydrogen fluoride as a reaction path in the reduction of the parent urethan is not excluded however.

In fact, a competing side reaction which occurred during the methylation of the parent urethan apparently did involve hydrogen fluoride elimination. In each reaction of a perfluoroalkylurethan with diazomethane, excessive consumption of the alkylating reagent was observed. From the reaction of ethyl *N*-*n*-perfluoropropylcarbamate with diazomethane a 14% yield of *N*-carbethoxyfluoromethylpentafluoroethyl ketimine was isolated. The structure of this product was established by the elemental analysis and the infrared spectrum (Fig. 1), which exhibited peaks at 5.75 μ and 6.18 μ characteristic of carbonyl and C=N groups. The N—H stretching peak was completely absent. Additional structure proof consisted of hydrolysis to 1,3,3,4,4,4-hexafluoro-2-butanone hydrate. The nature of this hydrolysis product was determined by elemental analysis and the infrared spectrum (Fig. 1), which showed peaks at 5.71 μ and 3.85 μ characteristic of ketonic carbonyl and O—H groups. In the spectra of both the ketimine and ketone, as well as 2-fluoroethanol (a typical reference compound), was found a peak at 6.30 μ, tentatively assigned to the CH_2F group. The following is a possible reaction sequence for the formation of these products:



The loss of hydrogen fluoride from the urethan would yield an imidyl fluoride which by a reaction analogous to a Nierenstein,[8] type would be converted to a fluoromethyl ketone.

Now that proof had been obtained that under mild conditions hydrogen fluoride could be eliminated from an *N*-perfluoroalkylurethan, a major difference in hydrolytic stability could be predicted between these parent urethans and their methylated analogs. This has now been found to be true.

(8) G. Olah and S. Kuhn, *Ber.*, 89, 864 (1956).

The treatment of ethyl *N*-methyl-*N*-*n*-perfluoropropylcarbamate with water for thirty minutes at 100° gave an extremely faint fluoride ion test, and hydrolysis of the *N*-α-difluoromethylene unit was estimated to be less than 1%. In contrast, ethyl *N*-*n*-perfluoropropylcarbamate, when shaken with water for one minute at room temperature, gave a very strong fluoride ion test.

The present work has demonstrated again the lability of fluorine atoms alpha to a nitrogen atom and some of the factors governing this behavior. It is concluded that the reduction of *N*-alkyl-*N*-*n*-perfluoroalkylurethans with lithium aluminum hydride is not a promising route to tertiary amines containing one perfluoroalkyl group.

EXPERIMENTAL[9]

Dimethyl-1,1-dihydroperfluoropropylamine hydrochloride. A mixture of 5.04 g. (0.0309 mole) of methyl-1,1-dihydroperfluoropropylamine[10] and 4.50 g. (0.0317 mole) of methyl iodide was stirred for 4 hr. at room temperature. After the addition of 100 ml. of 10% sodium hydroxide, the mixture was extracted with three 40-ml. portions of chloroform. The combined chloroform phases were placed over Drierite overnight. After removing the drying agent, the solution was saturated with dry hydrogen chloride while cooling to 0°. The hydrochloride salt of the unchanged amine was removed by filtration and the filtrate evaporated *in vacuo* to a volume of 20 ml. and chilled to 0°. The precipitate which formed was collected to yield 1.75 g. (27% yield) of product, m.p. 190–195°. Three recrystallizations from absolute ethanol–absolute ether gave pure dimethyl-1,1-dihydroperfluoropropylamine hydrochloride, m.p. 203–204° in a sealed capillary.

Anal. Calcd. for $C_5H_9ClF_5N$: C, 28.10; H, 4.25; N, 6.56; neut. equiv., 213.6. Found: C, 28.40; H, 4.04; N, 6.44; neut. equiv., 212.

Reaction of ethyl N-n-perfluoropropylcarbamate with diazomethane. Dry, gaseous diazomethane (0.38 mole) was passed into a stirred solution of 49 g. (0.191 mole) of ethyl *N*-*n*-perfluoropropylcarbamate[4] in 25 ml. of anhydrous ether over a period of 5 hr. while cooling to 0°. After an additional hour of stirring at 0°, the solvent was removed *in vacuo* and the residue subjected to repeated distillations on a 12-in. Nestor and Faust spinning-band column. Two fractions were obtained: I, 6.27 g. (12% yield), b.p. 54–56°/37 mm.; II, 6.76 g. (14% yield), b.p. 60–61°/37 mm. Fraction I, upon redistillation, gave an analytical sample of ethyl *N*-methyl-*N*-*n*-perfluoropropylcarbamate, b.p. 55°/37 mm.

Anal. Calcd. for $C_7H_8F_7NO_2$: C, 31.01; H, 2.97; N, 5.17. Found: C, 31.38; H, 3.07; N, 5.15.

Fraction II, upon redistillation, gave an analytical sample of *N*-carbethoxyfluoromethylpentafluoroethyl ketimine, b.p. 61°/37 mm.

Anal. Calcd. for $C_7H_7F_8NO_2$: C, 33.47; H, 2.81; N, 5.58; mol. wt., 251. Found: C, 34.21; H, 2.72; N, 5.53; mol. wt., 251 (freezing point depression of benzene).

Reaction of ethyl N-n-perfluoroheptylcarbamate with diazomethane. In a manner identical with that described for ethyl *N*-*n*-perfluoropropylcarbamate, 0.183 mole of dry gaseous diazomethane was passed into a solution of 41.3 g. (0.0905 mole) of ethyl *N*-*n*-perfluoroheptylcarbamate[11] in 10 ml. of anhydrous ether. The mixture was stirred for an additional 2 hr. at 0° and 9 hr. at room temperature. The solvent was removed *in vacuo* and the residue subjected to repeated distillations in a 12-in. Nestor and Faust spinning-band column to yield 8.05 g. (19% yield) of product, b.p. 59–61°/2.3 mm. Redistillation gave an analytical sample of ethyl *N*-methyl-*N*-*n*-perfluoroheptylcarbamate, b.p. 60°/2.3 mm.

Anal. Calcd. for $C_{11}H_8F_{15}NO_2$: C, 28.04; H, 1.71; N, 2.97. Found: C, 28.80; H, 1.73; N, 3.02.

Reaction of ethyl N-n-perfluoroamylcarbamate with diazomethane. By the procedure already described, the reaction of 9.0 g. (0.025 mole) of the urethan with 0.047 mole of diazomethane in 25 ml. of petroleum ether (b.p. 30–60°) was found to produce 2.0 g. (20% yield) of the corresponding methylated urethan, b.p. 44–45.3/3.6 mm., and 0.6 g. (7% yield) of *N*-carbethoxyfluoromethyl-*n*-perfluorobutyl ketimine, b.p. 50.6°/3.6 mm. As judged by its infrared spectrum, the methylated urethan was not free enough of ketimine to justify analysis. The spectrum of the second fraction indicated relatively pure ketimine (Fig. 1) but with only enough sample for one determination, the analysis was unsatisfactory.

Anal. Calcd. for $C_9H_7F_{10}NO_2$: C, 30.78; H, 2.01. Found: C, 28.63; H, 2.05.

Reaction of ethyl N-methyl-N-n-perfluoropropylcarbamate with excess lithium aluminum hydride. A solution of 2.16 g. (0.0080 mole) of the urethan in 10 ml. of anhydrous ether was added dropwise over a period of 25 min. to a stirred, ice-cooled solution of 0.0212 mole of lithium aluminum hydride in 20 ml. of ether. The mixture was stirred an additional 20 min. at 0°, 1 hr. at room temperature, 1.5 hr. with refluxing, and 20 hr. at room temperature. After the slow addition of 1.00 ml. of water, followed by a solution of 3.8 g. of potassium sodium tartrate in 6.0 ml. of water, the mixture was stirred for 4 hr. at room temperature. The ethereal phase was separated, and the aqueous phase was extracted with three 15-ml. portions of ether. The combined ethereal phases were shaken with two 10-ml. portions of 5% hydrochloric acid. The combined aqueous acid phases were made basic with 12 ml. of 10% sodium hydroxide and extracted with three 15-ml. portions of chloroform. After drying the combined chloroform extracts over Drierite, the solution was saturated with dry hydrogen chloride while cooling to 0°. Upon immediate filtration, there was obtained 0.37 g. (23% yield) of product, m.p. 253–256°, which upon recrystallization from absolute ethanol–absolute ether gave methyl-1,1-dihydroperfluoropropylamine hydrochloride, m.p. 263° in a sealed capillary (lit.[10] m.p. 209°). The material sublimed extensively at 209° in an open capillary tube. Conversion to the *p*-nitrobenzamide, m.p. 55–57°, gave no depression of melting point when mixed with an authentic sample of *N*-methyl-*N*-1,1-dihydrcperfluoropropyl-*p*-nitrobenzamide (lit.[10] m.p. 57–58°). The filtrate was evaporated *in vacuo* to a volume of 10 ml., cooled to 0°, and filtered to give 0.33 g. (19% yield) of product, m.p. 186–188°, which upon two recrystallizations from absolute ethanol–absolute ether gave pure dimethyl-1,1-dihydroperfluoropropylamine hydrochloride, m.p. 203–204° in a sealed capillary. Mixture with an authentic sample, prepared as described above, gave no depression of the melting point.

Since the melting point of methyl-1,1-dihydroperfluoropropylamine hydrochloride obtained in this work did not agree with the literature value, a neutralization equivalent was performed to give an observed value of 201 (theory: 199.6).

Hydrolysis of N-carbethoxy-fluoromethylpentafluoroethyl ketimine. A mixture of 19.84 g. (0.079 mole) of *N*-carbethoxyfluoromethylpentafluoroethyl ketimine, 33 ml. of concd. hydrochloric acid, and 50 ml. of water was refluxed with stirring for 22 hr. The upper aqueous phase was separated from the heavy unchanged material and extracted with one 20-ml. and three 10-ml. portions of ether. The combined ethereal phases were washed with 5 ml. of water and placed over Drierite overnight at 0°. Distillation gave 6.30 g.

(9) All melting points and boiling points are uncorrected. All analyses were performed by Huffman microanalytical laboratories, Wheatridge, Colo., except nitrogen analyses which were done in this laboratory by the Kjeldahl method.

(10) R. L. Dannley, R. G. Taborsky, and M. Lukin, *J. Org. Chem.*, **21**, 1318 (1956).

(41% yield) of product, b.p. 68.5–70.5°. The infrared spectrum and analysis corresponded to 1,3,3,4,4,4-hexafluoro-2-butanone hydrate.

Anal. Calcd. for $C_4H_4F_6O_2$: C, 24.25; H, 2.03; mol. wt., 198.07. Found: C, 24.58; H, 2.22; mol. wt., 189 (freezing point depression of benzene).

Stability of ethyl N-methyl-N-n-perfluoropropylcarbamate toward hydrolysis to fluoride ion. As a basis for comparison, the alizarin-zirconium test for fluoride ion was found to be sensitive to 0.05 mg. of fluoride ion in 1 ml. of water. A 10-mg. sample of ethyl *N*-*n*-perfluoropropylcarbamate shaken with 1 ml. of water for 1 min. gave a strong positive test for fluoride ion. A 40-mg. sample of ethyl *N*-methyl-*N*-*n*-perfluoropropylcarbamate shaken with 1 ml. of water for 30 min. gave no test for fluoride ion and only a very faintly positive test after an additional 30 min. of heating at 100°. The extent of alpha fluorine hydrolysis was estimated to be less than 1%.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF FLORIDA]

Fluoroolefins. IX. The Reaction of Chlorotrifluoroethylene with Olefins[1]

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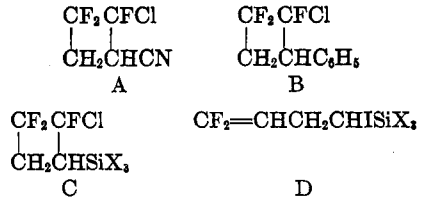
Chlorotrifluoroethylene has been found to react with a variety of olefins to give cyclobutane derivatives. With terminal olefins, addition occurs to give the $-CH_2CF_2-$ structure and a mixture of *cis-trans* isomers is obtained where this type of isomerism is possible. Infrared and nuclear resonance spectra were used to establish the structures of the products. The effects of substituents in the cyclobutane ring on the chemical shift differences between nonequivalent fluorines attached to the ring are found to be approximately additive.

The formation of a variety of cyclobutane derivatives by the reaction of tetrafluoroethylene and unsaturated compounds was reported by Coffman *et al.*[2] in 1949. It is somewhat surprising that the readily available chlorotrifluoroethylene has not been widely employed in cycloalkylation reactions to give a series of similar cyclobutyl derivatives. The dimerization of chlorotrifluoroethylene and similar compounds to substituted cyclobutanes was reported some years ago by Henne and Ruh.[3] Barney and Cairns[4] established the structure of the reaction product of acrylonitrile and chlorotrifluoroethylene as A, while Roberts[5] found that the product from styrene and the fluoroolefin had structure B. Since the completion of our work, Park *et al.*[6] have established that perhaloethylenes react with vinylsilanes; chlorotrifluoroethylene gave compounds such as C while iodotrifluoroethylene gave products represented by D.



The purpose of the present research was to determine the extent of the reaction of chlorotrifluoroethylene with olefins and to determine the structures of the reaction products. Chlorotrifluoroethylene reacted with a wide variety of olefins and good conversions to cyclobutyl derivatives were obtained in several reactions as indicated in Table I. Reactive olefins such as styrene and acrylonitrile gave conversions of 65% while the lowest conversions (7–8%) were obtained with allyl chloride. Tetrafluoroethylene is somewhat more reactive than chlorotrifluoroethylene as the conversion was smaller with the latter and higher reaction temperatures are necessary. The order of reactivity of styrene with various fluoroolefins is as follows, based on conversions: $CF_2{=}CFCl > CF_2{=}CFCN > CF_2{=}CFBr > CF_2{=}CFI \gg CF_2{=}CFCF_3 = CF_2{=}CFH$. No appreciable amounts of cyclobutane derivatives were obtained with the latter olefins. These results are related to the ease with which the individual fluoroolefins form cyclic dimers. For instance, chlorotrifluoroethylene readily gives the cyclic dimer[3] at 200° and even lower while a temperature of 350° is required for the cyclic dimerization of perfluoropropylene in comparable conversion.[7] Perfluoroacrylanitrile gave a 30% conversion to dimer[8] and 100% yield at 230°. It is difficult to explain these results on the basis of electrical or steric factors singly. The differences between the size and electrical effects of the nitrile and trifluoromethyl groups seem too small to account for the rather large

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