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

The Syntheses of ω-Trifluoromethyl Amino Acids. II.[1,2] Their Microbiological Activities

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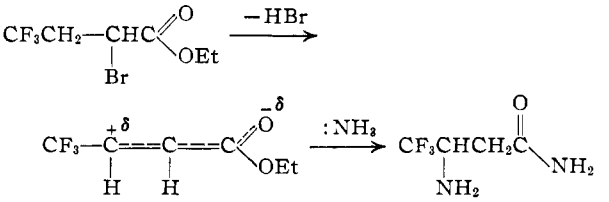
The syntheses of 5,5,5-trifluoronorvaline, 6,6,6-trifluoronorleucine and 5-methyl-6,6,6-trifluoronorleucine are described. These amino acids, all containing a terminal CF_3 group, were tested for their antimetabolic activity. 5,5,5-Trifluoronorvaline was found to be a very potent inhibitor on the growth of *E. coli*.

The syntheses of amino acids containing the trifluoromethyl group were undertaken because of the possible unique behavior that such a grouping might exhibit in biological systems. The CF_3 group is approximately the same size as the CH_3 group; therefore the relative size and configuration of the natural amino acid is duplicated to a very large extent. The important difference is that one has now created a center of high electron density by replacing the hydrogen atoms of a CH_3 group by the highly electronegative fluorine atoms. This part of the molecule now may participate in forming strong hydrogen bonds with enzymes and thereby blocking a metabolite from forming an enzyme-substrate complex. Another attractive feature of this group is its relative non-toxicity[3] as compared to mono- and difluoro analogs which are toxic and unstable.[4] Previous work with monofluorinated derivatives of tyrosine and phenylalanine as growth inhibitors has shown them to be highly toxic.[5]

Syntheses

4,4,4-Trifluoro-3-aminobutyramide.—It was demonstrated[6] previously that nucleophilic reagents attack the β-carbon of ethyl 4,4,4-trifluorocrotonate. This held true for the addition of hydrogen bromide, with or without promoters, and for aqueous or gaseous ammonia. In order to circumvent these difficulties it was decided to prepare ethyl 2-bromo-4,4,4-trifluorobutyrate by the bromination of 4,4,4-trifluorobutyric acid and treating the α-bromo ester with ammonia to yield the α-amino amide.

4,4,4-Trifluorobutyric acid was refluxed with bromine and phosphorus trichloride[7] for several hours. The addition of a large excess of anhydrous ethyl alcohol to the reaction mixture resulted in a 43% yield of the α-bromoester. Treatment of the bromoester with an excess of concentrated ammonia gave a 42% yield of the β-amino amide, which was identical with a sample prepared previously[6] by reaction of ammonia with ethyl 3-bromo-4,4,4-trifluorobutyrate. Undoubtedly both reactions proceed by the initial elimination of hydrogen bromide to give ethyl 4,4,4-trifluorocrotonate followed by the addition of ammonia.[6] Similar results have been observed in substitution reactions of α-bromosuccinates.[8]



5,5,5-Trifluoronorvaline.—This amino acid was prepared by the following method: 4,4,4-trifluorobutyric acid was treated with benzoyl chloride[9] to give a 75% yield of 4,4,4-trifluorobutyryl chloride which was converted immediately to the carbazole amide. Reduction of this sterically hindered amide with lithium aluminum hydride at −10° resulted in an 83% yield of 4,4,4-trifluorobutyraldehyde.[10] Treatment of the aldehyde with ammonium chloride and sodium cyanide followed by hydrolysis with hydrobromic acid gave a poor yield of 5,5,5-trifluoronorvaline.

An alternate synthesis involved the following reaction scheme: ethyl 4,4,4-trifluorobutyrate was reduced, in 75% yield, to 4,4,4-trifluorobutanol by lithium aluminum hydride. The alcohol was oxidized to the aldehyde by slowly adding the alcohol to a hot solution of sodium dichromate and distilling the aldehyde from the reaction mixture as it was formed. This method[11] gave a 56% yield of 4,4,4-trifluorobutyraldehyde. The aldehyde was treated with ammonium carbonate and sodium cyanide to form the hydantoin which was hydrolyzed directly with barium hydroxide to give a 30% yield of 5,5,5-trifluoronorvaline.[12]

6,6,6-Trifluoronorleucine.—4,4,4-Trifluorobutanol was converted to the iodide by the elegant method of Schechter and Stone[13] which utilizes 95% phosphoric acid and potassium iodide to generate hydrogen iodide *in situ*. The iodide obtained in 77% yield was condensed with diethyl formamidomalonate, using sodium hydride as the condensing

(1) Presented before the 126th National Meeting of the American Chemical Society, New York, September 13, 1954.

(2) Previous publication, H. M. Walborsky and M. Schwarz, THIS JOURNAL, **75**, 3241 (1953).

(3) These data were kindly furnished by Dr. R. G. Jones of the Eli Lilly Co. and will be reported elsewhere.

(4) (a) R. N. Haszeldine and A. G. Sharpe, "Fluorine and its Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 83 and 89; (b) M. Stacey, "Progress in Organic Chemistry," Vol. II, Academic Press, Inc., New York, N. Y., 1953, p. 29; (c) A. L. Henne in H. Gilman, "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 956.

(5) P. D. Boyer, R. J. Evans and P. H. Phillips, *J. Pharmacol. and Exper. Therap.*, **73**, 176 (1941); M. D. Armstrong and J. D. Lewis, *J. Biol. Chem.*, **188**, 91 (1951); **190**, 461 (1954).

(6) (a) H. M. Walborsky and M. Schwarz, THIS JOURNAL, **75**, 3241 (1953); (b) E. T. McBee, O. R. Pierce and D. D. Smith, *ibid.*, **76**, 3722 (1954).

(7) P. Bagard, *Bull. soc. chim.*, [4] **1**, 310 (1907).

(8) J. Volhard, *Ann.*, **242**, 157 (1887).

(9) H. C. Brown, THIS JOURNAL, **60**, 1325 (1938).

(10) V. M. Micovic and M. F. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

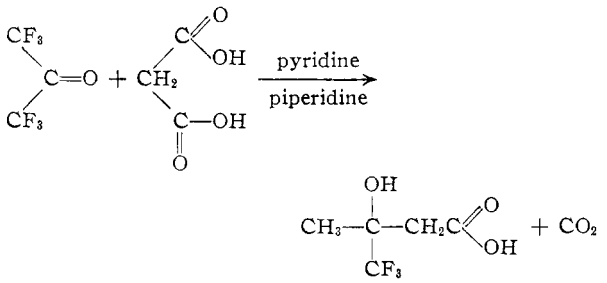
(11) A. L. Henne, R. L. Pelley and R. M. Alm, THIS JOURNAL, **72**, 3370 (1950).

(12) D. O. Holland and J. H. Naylor, *J. Chem. Soc.*, 3503 (1952).

(13) H. Schechter and H. Stone, *J. Org. Chem.*, **15**, 491 (1950).

agent,[14] to give a 59% yield of diethyl (4,4,4-trifluorobutyl)-formamidomalonate. Hydrolysis of the condensation product with 10% hydrochloric acid gave a 35% yield of 6,6,6-trifluoronorleucine.

5-Methyl-6,6,6-trifluoronorleucine.—Trifluoroacetone[15] was condensed with malonic acid using pyridine as a solvent and piperidine as the catalyst. The reaction proceeds smoothly at room temperature with the evolution of carbon dioxide. The product isolated from this reaction was not the expected 3-methyl-4,4,4-trifluorocrotonic acid[16] but the 3-hydroxy-3-methyl-4,4,4-trifluorobutyric acid.[17]



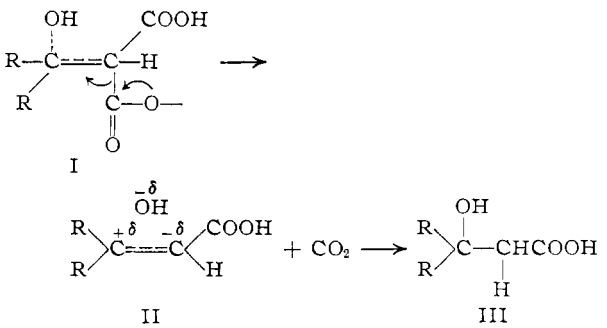
Difficulty was encountered in the dehydration of 3-hydroxy-3-methyl-4,4,4-trifluorobutyric acid. A low yield of 3-methyl-4,4,4-trifluorocrotonic acid was obtained using the method of Brandenberger and Galat.[18] A 75% yield was obtained using phosphoric acid as the dehydrating agent.[6b] The olefinic acid was reduced with palladium-on-charcoal and hydrogen to the saturated acid and then with lithium aluminum hydride to 3-methyl-4,4,4-trifluorobutanol. The Shechter and Stone[13] procedure was utilized to convert the alcohol to the corresponding iodide. The iodide was condensed with diethyl formamidomalonate and, without isolation, the condensation product was hydrolyzed with hydrochloric acid to yield the desired 5-methyl-6,6,6-trifluoronorleucine.

(14) J. Shapira, R. Shapira and K. Dittmer, THIS JOURNAL, **75**, 3655 (1953).

(15) R. A. Darral, F. Smith, M. Stacey and J. C. Tatlow, *J. Chem. Soc.*, 2329 (1951).

(16) S. E. Boxer and E. P. Linstead, *J. Chem. Soc.*, 740 (1931).

(17) This observation is of special interest in view of the recent work on the mechanism of this reaction (E. J. Corey, THIS JOURNAL, **74**, 5897 (1952); S. Patai, *et al.*, *ibid.*, **76**, 3446 (1954)). Corey suggests that the reaction proceeds by a process of simultaneous decarboxylative elimination (I–II).



At first sight it would seem that the fact that we obtained smooth decarboxylation and isolated the β-hydroxy acid as the only product, was in direct contrast to Corey's mechanism. This need not be the case since it has been demonstrated previously[3,6] that trifluorocrotonic acid is attacked very readily by nucleophilic reagents; therefore as the decarboxylative elimination occurs (I–II), the hydroxyl group may be forming a loose ion pair with the incipient olefin II, which may then collapse to yield III.

(18) W. Brandenberger and A. Galat, THIS JOURNAL, **72**, 3275 (1950).

Microbiological Assay

5,5,5-Trifluoronorvaline, 6,6,6-trifluoronorleucine and 5-methyl-6,6,6-trifluoronorleucine were tested for their ability to inhibit the growth of *E. coli*, ATCC 9723, and *S. cerevisiae*, strain 139, according to the method of Dittmer, *et al.*[19]

The growth of the yeast strain (7 ml.) was not inhibited by the following amino acids: 6,6,6-trifluoronorleucine (100 μg.), 5-methyl-6,6,6-trifluoronorleucine (100 μg.), 5,5,5-trifluoronorvaline (10 mg.). The growth of *E. coli* was inhibited to 50% of normal by 1.7 μg. of 5,5,5-trifluoronorvaline per 7 ml. of medium. The norleucine analogs were not effective on the growth of *E. coli* up to 100 μg. per 7 ml. of medium.

The reversal of trifluoronorvaline inhibition of *E. coli* was run on 5, 10, 50 and 100 μg. per 7 ml. of medium. Methionine (1 mg.), leucine (1 mg.) and valine (10 mg.) caused complete reversal, while partial reversal was obtained with glutamic acid (10 mg.), isoleucine (10 mg.), tryptophan (10 mg.) and homocystine (1 mg.).

Acknowledgment.—The authors wish to express their sincere appreciation to Miss Mary Lou Kamm for the Microbiological Assay. This investigation was supported by a research grant from the National Cancer Institute, of the National Institutes of Health, Public Health Service.

Experimental[20]

Ethyl 2-Bromo-4,4,4-trifluorobutyrate.—A mixture of 22 g. (0.15 mole) of 4,4,4-trifluorobutyric acid,[6] 28 cc. (0.1 mole) of phosphorus trichloride and 16 cc. (0.45 mole) of bromine was refluxed for twenty hours, concentrated by distillation and the residue was cooled in an ice-bath. To the cooled residue was added 40 cc. of ethyl alcohol and the reaction mixture was then poured into a mixture of ice-water and sodium carbonate. The supernatant oil was extracted with ether and the ether extract washed with sodium bisulfite, sodium carbonate and dried over anhydrous sodium sulfate. The solvent was stripped and the residual oil distilled to yield 16 g. (43%) of product, b.p. 156–157°, $n^{23}D$ 1.3962, d^{20}_4 1.524.

Anal. Calcd. for $C_6H_5F_3BrO_2$: C, 28.93; H, 3.24; Br, 32.09; *MR*, 39.02. Found: C, 28.97; H, 3.18; Br, 31.72; *MR*, 39.28.

3-Amino-4,4,4-trifluorobutyramide.—To 5 g. (0.02 mole) of α-bromoester was added 60 cc. of concentrated ammonium hydroxide and the mixture shaken for four days at room temperature. The solution was evaporated to dryness and the solid residue was triturated with acetonitrile. Evaporation of the acetonitrile gave 1.3 g. (42%) of product, m.p. from acetonitrile and mixed m.p. 120.5–121° (lit.[6a] 120–121°).

4,4,4-Trifluorobutanol.—To a solution of 20 g. of lithium aluminum hydride in 250 cc. of dry ether was added dropwise and with stirring 75 g. (0.44 mole) of ethyl 4,4,4-trifluorobutyrate dissolved in 50 cc. of dry ether. The reaction mixture was refluxed for 24 hr. The excess hydride was decomposed with water and the ether layer decanted and dried over anhydrous sodium sulfate. The solvent was stripped through a 12″ column and the residual oil distilled to yield 42 g. (75%) of product, b.p. 124–125°, $n^{25}D$ 1.3410.

4,4,4-Trifluorobutyl Iodide.—To 54 g. of 95% phosphoric acid was added 54 g. (0.45 mole) of potassium iodide. The mixture was stirred at room temperature and 12 g. (0.1 mole) of 4,4,4-trifluorobutanol was added. The mixture

(19) K. Dittmer, *et al.*, *ibid.*, **70**, 2499 (1948).

(20) Melting points and boiling points are uncorrected.

was heated at 120° for 13 hours, cooled, poured into ice-water and extracted with ether. The ether extract was washed with 20% sodium thiosulfate, saturated solution of calcium chloride and dried over anhydrous sodium sulfate. The solvent was stripped and the residue distilled to yield 16 g. (70%) of iodide, b.p. 126–127°, $n^{23}D$ 1.4326, d^{20}_4 1.851.

Anal. Calcd. for $C_4H_6F_3I$: C, 20.18; H, 2.54; *MR*, 33.39. Found: C, 20.21; H, 2.60; *MR*, 33.16.

Diethyl (4,4,4-Trifluorobutyl)-formamidomalonate.—Diethyl formamidomalonate (10 g., 0.044 mole) was dissolved in 30 cc. of dry benzene and 12.5 g. (0.052 mole) of 4,4,4-trifluorobutyl iodide and 1.3 g. (0.055 mole) of sodium hydride was added. The mixture was refluxed until hydrogen ceased to be evolved. After cooling, the excess sodium hydride was destroyed by methyl alcohol. The mixture was filtered and the solvent was removed *in vacuo* to yield 9 g. (59%) of product, m.p. 87–88° from petroleum ether.

Anal. Calcd. for $C_{13}H_{19}F_3NO_5$: C, 46.00; H, 5.79. Found: C, 46.09; H, 5.84.

6,6,6-Trifluoronorleucine.—The formamidomalonate condensation product (9 g., 0.028 mole) was refluxed with 200 cc. of 17% hydrochloric acid until evolution of carbon dioxide ceased. The mixture was taken to dryness *in vacuo* and the residue extracted with alcohol. The alcohol extract was neutralized with pyridine, which precipitated 6,6,6-trifluoronorleucine. The product was recrystallized from water–alcohol to yield 3 g. (56%) of the amino acid, m.p. 272–274° dec.; R_f (80% butanol–20% acetic acid) 0.76, R_f (65% pyridine–35% water) 0.80.

Anal. Calcd. for $C_6H_{10}F_3NO_2$: C, 38.92; H, 5.44. Found: C, 39.02; H, 5.46.

4,4,4-Trifluorobutyrylcarbazolamide.—To 11.5 g. (0.068 mole) of carbazole was added 12.8 g. (0.08 mole) of crude 4,4,4-trifluorobutyryl chloride (prepared in 75% yield by refluxing the corresponding acid with benzoyl chloride, b.p. 95–115°) and the mixture was refluxed overnight. The deep blue reaction mixture was taken up in 100 cc. of boiling ethyl alcohol and, upon cooling, yielded 13.5 g. (68%) of crude product, m.p. 116–116.5°.

Anal. Calcd. for $C_{16}H_{12}F_3NO_2$: C, 65.97; H, 4.15; N, 4.80. Found: C, 66.05; H, 4.20; N, 4.87.

4,4,4-Trifluorobutyraldehyde. A. Reduction of Carbazole Amide.—The carbazole amide (13.5 g., 0.045 mole) dissolved in 500 cc. of dry ether was reduced at −10° by the addition of 0.42 g. (0.011 mole) of lithium aluminum hydride dissolved in 25 cc. of dry ether. The mixture was allowed to come to room temperature and was stirred for an additional 30 minutes. The excess hydride was decomposed by the addition of *ca.* 1 cc. of water, the ether was decanted and stripped. The residual oil was distilled to yield 4.8 g. (83%) of aldehyde, b.p. 93–97°.

2,4-Dinitrophenylhydrazone, m.p. 189.2–190°.

Anal. Calcd. for $C_{10}H_9F_3N_4O_4$: C, 39.22; H, 2.96; N, 18.30. Found: C, 39.40; H, 2.69; N, 18.45.

B. By Oxidation of 4,4,4-Trifluorobutanol.—To 51 g. (0.42 mole) of concentrated sulfuric acid diluted by 210 cc. of water was added 40 g. (0.36 mole) of 4,4,4-trifluorobutanol. The mixture was heated to 95° in a 3-necked flask fitted with a dropping funnel, sealed stirrer and Claisen distilling head set for downward distillation. Sodium dichromate (41 g., 0.136 mole) dissolved in 130 cc. of water was added dropwise with vigorous stirring to the hot solution. The aldehyde distilled over as it was formed to yield 32 g. of crude product, b.p. 87–90°. Redistillation gave 25 g. (56%) of aldehyde, b.p. 94–97°.

5,5,5-Trifluoronorvaline. A. Strecker Synthesis.—To 1 g. of ammonium chloride and 1 g. of sodium cyanide dissolved in 10 cc. of water was added 1.5 g. (0.01 mole) of trifluorobutyraldehyde. The mixture was shaken at room temperature for seven hours and finally extracted with ether. The ether extract was stripped and residual oil taken up in methanol. The methanol solution was saturated with ammonia gas and allowed to stand at room temperature for four days. The methyl alcohol was evaporated *in vacuo* and the residue refluxed with 45 cc. of 25% hydrobromic acid for three hours. The reaction mixture was evaporated to dryness *in vacuo*, redissolved in 10 cc. of water and again evaporated to dryness. The residue was taken up in methanol and made basic with pyridine which precipitated the amino acid. The product was recrystallized from water–ethanol to yield 79 mg. (4.6%), m.p. 258° dec.

Anal. Calcd. for $C_5H_8F_3NO_2$: C, 35.09; H, 4.71. Found: C, 35.04; H, 4.68.

C. Hydantoin Synthesis.—To a mixture of 3.5 g. (0.07 mole) of sodium cyanide, 16 g. (0.14 mole) of ammonium carbonate in 200 cc. of 50% aqueous alcohol, was added with stirring 7.1 g. (0.97 mole) of triethylamine followed by 8 g. (0.06 mole) of aldehyde. The mixture was stirred overnight at room temperature and the product was diluted with 200 cc. of absolute alcohol. The precipitated sodium carbonate was removed by filtration.

To the aqueous filtrate, 200 cc. of water and 60 g. of barium hydroxide were added and the mixture heated to remove the alcohol and the triethylamine. The mixture finally was refluxed for 30 hours. The hydrolysate was filtered and the solid residue was washed with hot water. The extracts were combined, 12 g. of ammonium carbonate was added and the solution boiled for ten minutes. The precipitated barium carbonate was removed and the filtrate concentrated *in vacuo* to one-third its volume. Acidification to *p*H 6 with acetic acid, addition of ethanol and cooling precipitated 3.1 g. (30%) of product, m.p. 258–258.5° dec., R_f (65% pyridine–35% water) 0.72.

3-Hydroxy-3-methyl-4,4,4-trifluorobutyric Acid.[21]—In a flask equipped with a Dry Ice condenser were placed 24 g. of trifluoroacetone (0.214 mole), 24 g. of malonic acid (0.230 mole), 1 cc. piperidine and 100 ml. of anhydrous pyridine. The reaction mixture was allowed to stand at room temperature for 72 hours during which time carbon dioxide was evolved. The pyridine was stripped *in vacuo* and the residue distilled to yield 30 g. (75%) of product, b.p. 75–76° at 2 mm., m.p. 30°.

Anal. Calcd. for $C_5H_7F_3O_2$: C, 34.88; H, 4.10. Found: C, 34.32; H, 4.39.

3-Methyl-4,4,4-trifluorocrotonic Acid.[22]—(Attempts to dehydrate the β-hydroxyacid by boric anhydride[20] resulted in small yields.) A mixture of 17.2 g. (0.1 mole) of the β-hydroxyacid and 7.1 g. (0.05 mole) of phosphorus pentoxide was heated on a steam-bath for 4 hours. The reaction mixture was distilled to yield 14.0 g. of crude product. Redistillation yielded 12 g. (78%) of pure material, b.p. 80–84°.

3-Methyl-4,4,4-trifluorobutyric Acid.—One hundred grams (0.65 mole) of 3-methyl-4,4,4-trifluorocrotonic acid was hydrogenated with 3.0 g. of 5% palladium-on-charcoal at an initial pressure of 60 lb. After the theoretical absorption of hydrogen was completed (0.75 hr.), the catalyst was removed by filtration, washed with chloroform, and the combined filtrates distilled to yield 90.5 g. (89%) of product, b.p. 90–91° (25 mm.), $n^{24}D$ 1.3580.

Anal. Calcd. for $C_5H_7F_3O_2$: C, 38.47; H, 4.52. Found: C, 38.64; H, 4.64.

3-Methyl-4,4,4-trifluorobutanol.—To a slurry of 54.5 g. (1.43 moles) of lithium aluminum hydride in 1.4 liters of anhydrous ether was added 100 g. (0.64 mole) of acid in 100 ml. of ether. Upon completion of addition (2.5 hr.), the mixture was refluxed for one hour. Following acidification with dilute sulfuric acid and extraction with ether, the ether extract was dried over anhydrous sodium sulfate. The solvent was stripped and the residue distilled to yield 55.0 g. (61%) of product, b.p. 60–63° (28 mm.).

Anal. Calcd. for $C_5H_9F_3O$: C, 42.25; H, 6.38. Found: C, 41.99; H, 6.37.

Phenylurethan derivative, m.p. 41–42° from chloroform.

Anal. Calcd. for $C_{12}H_{14}F_3NO_2$: C, 55.17; H, 5.40. Found: C, 55.29; H, 5.53.

3-Methyl-4,4,4-trifluorobutyl Iodide.—Phosphoric acid (95%) was prepared from 64.4 g. of 95% phosphoric acid and 14.7 g. of phosphorus pentoxide. Potassium iodide (84.6 g., 0.51 mole) and 3-methyl-4,4,4-trifluorobutanol (40.0 g., 0.28 mole) were added to the 95% phosphoric acid and the mixture was heated at 120° for thirteen hours, cooled, diluted with 1400 cc. of water and extracted with ether. The ether extract was washed with 10% sodium

(21) We are indebted to Dr. M. Schwarz for performing this experiment.

(22) This acid now is commercially available from the Rowland Chemical Co., Gainesville, Florida.

thiosulfate, saturated calcium chloride, water and dried over anhydrous sodium sulfate. The solvent was stripped and the residual oil fractionated through a Wheeler column to yield 23 g. (32%) of product, b.p. 143°, $n^{30}D$ 1.4362.

Anal. Calcd. for $C_5H_8F_3I$: C, 23.83; H, 3.20. Found: C, 23.78; H, 3.32.

5-Methyl-6,6,6-trifluoronorleucine.—To a suspension of 0.70 g. (0.29 mole) of sodium hydride in 12 cc. of anhydrous N,N-dimethylformamide was added 5.5 g. (0.27 mole) of diethyl formamidomalonate. After 10 minutes the solution was filtered and the filtrate added to 7.3 g. (0.29 mole) of 2-methyl-4,4,4-trifluorobutyl iodide dissolved in 2 cc. of dimethylformamide. The mixture was heated at 130° for 0.5 hr. and at 160° for two hours. The solvent was removed *in vacuo* and the residue triturated with ether. The ether extract was stripped and the residue refluxed with 75 cc. of 2:1 hydrochloric acid for 5 hours. The solution was evaporated to dryness *in vacuo* and the solids taken up in ethanol. The ethanolic solution was made basic with pyridine and cooled. The solid which deposited was filtered and recrystallized from water to yield 200 mg. of amino acid, m.p. 254–256° dec.

Anal. Calcd. for $C_7H_{12}F_3NO_2$: C, 42.20; H, 6.07. Found: C, 42.28; H, 6.20.

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

Free Radical Additions Involving Fluorine Compounds. V. Reactions of 1,2-Dibromo-2-chloro- and 1,2-Dichloro-2-iodo-1,1,2-trifluoroethane with Fluoroölefins[1]

BY PAUL TARRANT AND MARVIN R. LILYQUIST

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A study has been made of the reaction of 1,2-dibromo-2-chloro- and 1,2-dichloro-2-iodo-1,1,2-trifluoroethane with various fluoroethenes and fluoropropenes. The iodine compound gives excellent yields of addition products even with olefins which fail to react with the dibromide. The high yields of adducts from these perhaloethanes and the ease with which these addition compounds can be dehydrohalogenated and dehalogenated afford a good synthetic method of preparation of various fluoroölefins and 1,1,2-fluorobutadienes.

Earlier reports from this Laboratory have described the reactions of dibromodifluoromethane,[2] bromochlorodifluoromethane[3] and 1,2-dibromo-2-chloro-1,1,2-trifluoroethane[4] with various olefins. The resulting simple addition products were converted into fluoroölefins by dehydrobromination or into fluorobutadienes by suitable reactions. For example, various 1,1-difluorobutadienes were obtained by heating the adducts of dibromodifluoromethane and propenes with tri-*n*-butylamine and a number of 1,1,2-trifluoro-1,3-alkadienes were obtained from adducts of the perhaloethane.

The preparation of 1,1,2-trifluoro-1,3-butadiene has been carried out earlier in these laboratories[5] by the reactions

$$CF_2Br_2 + CHF{=}CHCH_3 \xrightarrow[\text{peroxide}]{\text{benzoyl}}$$

$$CF_2BrCHFCHBrCH_3 \xrightarrow{R_3N} CF_2{=}CFCH{=}CH_2$$

but, because of the present difficulty in obtaining 1-fluoropropene, this method is not practical for preparing large samples of the diene. The synthesis of 1,1,2-trifluoro-1,3-butadiene recently has been reported by Park, Seffl and Lacher[6] in a six-step process involving the addition of perfluorovinyl iodide to ethene. We wish to report that this butadiene also has been prepared from 1,4-dibromo-2-chloro-1,1,2-trifluorobutane[4] by removal of hydrogen bromide to give $CF_2BrCFClCH{=}CH_2$ which, when treated with zinc, gives $CF_2{=}CFCH{=}CH_2$.

Although 1,2-dibromo-2-chloro-1,1,2-trifluoroethane (I) was found to react readily with most hydrocarbon olefins to give good yields of the addition products, $CF_2BrCFClCH_2CHBrR$, the yields of addition products from olefins containing several fluorine atoms are reduced greatly. For instance, fluoroethene gave a 74% yield of $CF_2BrCFClCH_2CHFBr$, but trifluoroethene gave only 16% of the simple adduct, and 1-chloro-1-fluoroethene and 1,1-difluoropropene failed to form any adduct. It should be noted that increasing amounts of fluorine around the double bond of the olefin led to the formation of larger quantities of two-to-one addition products.

Previous work[4] on the addition of I to hydrocarbon olefins has demonstrated that the $CF_2BrCFCl$ group remains intact during addition reactions so that the proof of structures of the one-to-one adducts from fluoroölefins involves only the problem of the point of attachment of that group to the double bond. The simple products from 1,1-difluoro- and trifluoroethene could have only the structures of $CF_2BrCFClCH_2CF_2Br$ and $CF_2BrCFClCHFCF_2Br$, respectively, since hydrogen bromide was eliminated readily to give olefins. The structure of the adduct from fluoroethene and I was assigned on the basis of the similarity of the reaction to that with dibromodifluoromethane and fluoroethene, which gave an adduct which has been shown to have the formula CF_2BrCH_2CHFBr.[5] The assignment of structures to the higher adducts is consistent with the mechanism which postulates that the alkyl radical attacks the carbon atom of the double bond containing the greater number of hydrogen atoms.

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