The semicarbazone crystallized as heavy needles from water, mp 153–158° (lit.[12] mp 155°).

The *p*-nitrobenzoate crystallized from petroleum ether (bp 20–40°), mp 64–66°.

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.84; H, 5.88; N, 4.81. Found: C, 61.58; H, 5.83; N, 4.65.

C. 2-Methyl-2-hydroxymethylcycloheptanone (10).—Application of above general procedure produced an extremely viscous oil from epoxy alcohol **7**. Gas chromatographic analysis indicated the presence of only 15% of the desired keto alcohol **10** (see below).

II. Reaction with Acidic Alumina. General Procedure.—A mixture of 1 g of Merck acid-washed alumina in 20 ml of dry benzene was refluxed with stirring under a Dean–Stark trap for 12 hr. The solution was cooled slightly, and 1 mmole of epoxy alcohol was added. The resulting mixture was then refluxed with stirring for the specified period of time, cooled, and filtered. The alumina was washed with methylene chloride, the combined filtrate and washings were concentrated *in vacuo*, and the residual oil was analyzed by gas chromatography.

A. 2-Methyl-2-hydroxymethylcyclohexanone (9).—Employment of the above general procedure with a 2-hr reaction time, produced keto alcohol **9** in 52% yield as measured by gas chromatography.

B. 2-Methyl-2-hydroxymethylcycloheptanone (10).—The rearrangement of epoxy alcohol **7** was performed on a preparative scale. Thus, refluxing a benzene solution of 15.6 g (0.10 mole) of **7** with alumina overnight produced 11.9 g of a pale yellow oil, containing 7.65 g (49%) of keto alcohol **10** by gas chromatography. Distillation afforded 5.1 g (32.7%) of **10** as a colorless oil, bp 120–123° (8 mm). The semicarbazone melted at 148.5–150.5° after two recrystallizations from water.

Anal. Calcd for $C_{10}H_{19}N_3O_2$: C, 56.31; H, 8.98; N, 19.70. Found: C, 56.20; H, 9.03; N, 19.64.

The semicarbazone was hydrolyzed by warming in 10% sulfuric acid on a steam bath for 15 min. The reaction mixture was cooled and extracted with chloroform. The combined extracts were washed with saturated sodium chloride solution, dried, concentrated, and distilled to afford the pure keto alcohol **10**: bp 134–134.2° (16 mm); $n^{24.9}D$ 1.4827; ν_{max}^{neat} 3460, 2941, 2874, 1701, 1471, 1453, 1047, 1026 cm^{-1}.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.33. Found: C, 68.94; H, 10.37.

α-Amino Alkanoic and Alkenoic Acids with Perfluoroalkyl Terminal Segments[1]

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α-Amino acids bearing perfluoroalkyl groups were synthesized from perfluoroalkyl-substituted alkanoic acids by α bromination and α amination. Addition of 1-iodoperfluoropropane to ethyl alkenylacetamidomalonates and subsequent reactions gave alkenyl- and alkylmalonic acids having perfluoropropyl and acetamido substituents. The facile formation of γ lactones from such propenylacetamidomalonic acids was observed. Decarboxylation and hydrolysis then gave 5-perfluoropropyl-4-hydroxy-2-aminopentanoic acid, which readily re-formed the γ-lactone when converted to an N-trifluoroacetyl derivative. Synthesis of an heptafluoro-α-aminodecanoic acid from 1-iodoperfluoropropane and ethyl 4-pentenylacetamidomalonate was successfully demonstrated. High yields were secured in each step.

Free-radical addition of iodoperfluoroalkanes to alkenoic acids was used to prepare a series of long-chain iodoalkanoic acids having the general structure R_F-$CH_2CHI(CH_2)_nCOOH$, where R_F was a perfluoroalkyl group of one to ten carbons and n was an integer including 0–14. From these compounds the corresponding alkenoic acids [$R_FCH{=}CH(CH_2)_nCOOH$] and alkanoic acids [$R_F(CH_2)_{n+2}COOH$] were synthesized.[2]

$$R_FI + CH_2{=}CH(CH_2)_nCOOR \xrightarrow{R\cdot} RC_FH_2CHI(CH_2)_nCOOR$$

$$R_FCH_2CHI(CH_2)_nCOOR \xrightarrow[\text{alcohol}]{KOH} R_FCH{=}CH(CH_2)_nCOOH$$

$$\xrightarrow{HCl,\ Zn/\text{alcohol}} \quad \xrightarrow{H_2/Pt}$$

$$R_F(CH_2)_{n+2}COOH$$

The yields in each step were excellent with the exception of R_FI addition to acrylate esters where telomerization and low conversion resulted.[2,3] Very little is known about the corresponding α-amino acids bearing a terminal perfluoroalkyl group. Various alternative routes were explored in order to define a satisfactory procedure for the syntheses of these novel and potentially useful compounds.

Results

Two complementary methods were studied in some detail. The terminally fluorinated alkanoic acid prepared by the sequence given above was brominated and then aminated by standard procedures.[4,5] In each case the R_F group was perfluoropropyl, chosen for convenience and because of the availability of *n*-perfluoropropyl iodide.

$$R_F(CH_2)_nCH_2COOH + Br_2 \xrightarrow{PCl_3} R_F(CH_2)_nCHBrCOOH$$

$$R_F(CH_2)_nCHBrCOOH + NH_3 \xrightarrow[0°]{C_2H_5OH} R_F(CH_2)_nCHNH_2COOH$$

$$n = 2, 3$$

The yield of α-bromo acids (70%) was somewhat better than that of the α-amino acids (50–60%), but improvement in the latter undoubtedly could be made in view of the reported yield[5] of 95% for unfluorinated acids by this method. Displacement of bromine by azide ion also would appear to be useful.[6] The new α-amino acids were readily characterized, though they were very slightly soluble in water and were difficult to recrystallize. The N-trifluoroacetyl derivative was obtained in excellent yield by the method of Weygand and Geiger.[7]

(1) This work was carried out, in part, at the Illinois Institute of Technology during the summers of 1964 and 1965 under the National Science Foundation College Teacher Research Participation Program. Helpful discussions with Dr. Robert Filler are acknowledged.

(2) N. O. Brace, *J. Org. Chem.*, **27**, 4491 (1962).

(3) N. O. Brace, *ibid.*, **27**, 3027, 3033 (1962).

(4) J. F. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1961, p 2382.

(5) S. Birnbaum, S. C. Fu, and J. P. Greenstein, *J. Biol. Chem.*, **203**, 333 (1953).

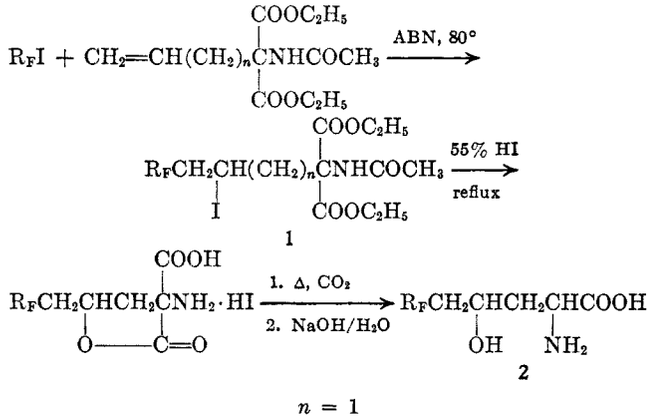
(6) H. M. Walborsky and M. E. Baum, *J. Org. Chem.*, **21**, 538 (1956).

(7) F. Weygand and R. Geiger, *Chem. Ber.*, **89**, 647 (1956).

$$R_F(CH_2)_nCHNH_2COOH + (CF_3CO)_2O \xrightarrow{CF_3COOH} R_F(CH_2)_nCH(NHCOCF_3)COOH$$

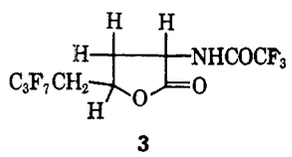
$n = 3$

Because of the inevitable loss of material in this five-step process from the costly R_FI, it seemed preferable to introduce the perfluoro group as near to the final reaction as possible. Accordingly R_FI was added to ethyl alkenyl-α-acetamidomalonates, prepared by the alkylation of the readily available α-acetamidomalonic ester with allyl bromide or with 5-bromo-1-pentene.[8,9] This is similar to the previously reported reaction of *n*-perfluoropropyl iodide with ethyl allylmalonate[10] or the reaction with ethyl 4-pentenylmalonate reported herein. These syntheses were chosen for study because of the possible difficulties involved in the first instance by lactone formation,[11,12] and to demonstrate in the second case the steps of a successful procedure. Free-radical addition of R_FI



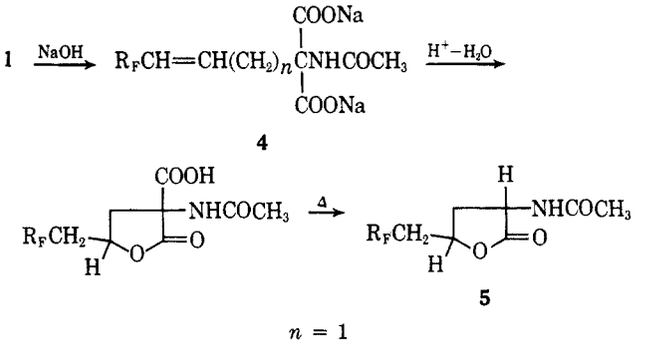
$n = 1$

to ethyl allylacetamidomalonate occurred normally, but the product isolated from an attempted reduction of **1** by hydrogen iodide turned out to be 2-amino-4-hydroxy-6,6,7,7,8,8,8-heptafluorooctanoic acid (**2**) apparently derived from the lactone.[12] The lactone was re-formed when the N-trifluoroacetamido derivative was prepared in trifluoroacetic acid as shown above.[13] After repetitive crystallization two substances were isolated having identical infrared spectra and the same elemental composition. These were evidently the expected *cis* and *trans* isomers of lactone **3**.



3

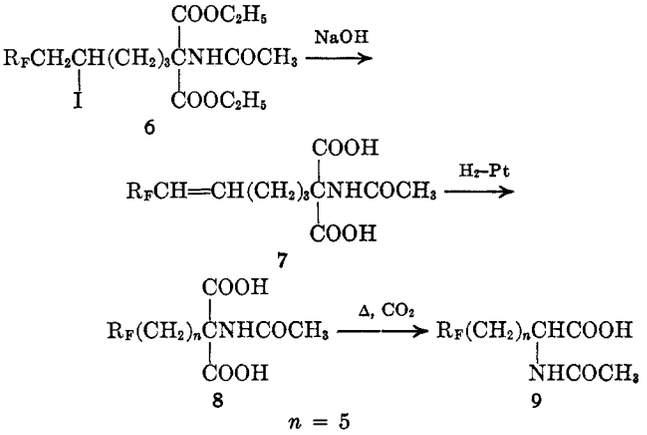
The infrared spectrum showed the NH band at 3380, no carboxyl group bands, the γ-lactone band[11] at 1780, and the $NHCOCF_3$ band at 1720 cm^{-1}. A similar result occurred subsequent to alkaline hydrolysis of the adduct **1**. As the sodium salt of the α-acetamidomalonic acid **4** was acidified, the unsaturated malonic acid lactonized and when heated lost carbon dioxide.



$n = 1$

The products **4** and **5** as isolated were insoluble in dilute sodium bicarbonate solution. Compound **5** also showed the band for a γ-lactone in its infrared spectrum at 1780 cm^{-1}. It would have been preferable to reduce the unsaturated malonic acid sodium salt in solution.[14]

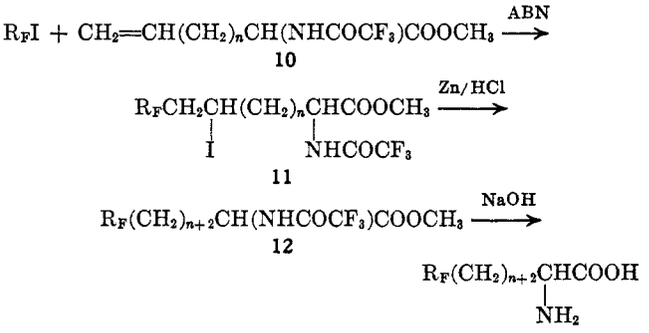
By contrast, the steps attempted above proceeded without difficulty when applied to the synthesis of 2-acetamido-8,8,9,9,10,10,10-heptafluorodecanoic acid.



$n = 5$

The adduct **6** obtained in 81% conversion from ethyl 4-pentenylacetamidomalonate, gave upon alkaline hydrolysis in 96% yield the unsaturated malonic acid **7**. Hydrogenation of **7** over platinum at 45 psi gave **8** in quantitative yield. A toluene or xylene solution of **8** at the boil deposited insoluble **9**.

Yet to be preferred is a reaction sequence in which the amino group is relatively easy to regenerate and which requires a minimum of steps after the addition of R_FI. Such is afforded by the following scheme.



Unsaturated amino acids have been synthesized in a few cases.[9,12] The N-trifluoroacetyl derivatives of the saturated analogs undergo ready hydrolysis in aqueous alkali.[4] The N-trifluoroacetylamino acid methyl esters (**10**) are volatile and may be purified by distillation.[15]

(8) H. R. Snyder, J. F. Shelton, and C. D. Lewis, *J. Am. Chem. Soc.*, **67**, 310 (1945).

(9) N. F. Albertson, *ibid.*, **68**, 450 (1946).

(10) N. O. Brace, to E. I. du Pont de Nemours and Co., U. S. Patent 3,145,222 (Aug 18, 1964).

(11) N. O. Brace, *J. Org. Chem.*, **29**, 1247 (1964).

(12) H. L. Goering, S. J. Cristol, and K. Dittmer, *J. Am. Chem. Soc.*, **70**, 3310, 3314 (1948).

(13) M. F. Ansell and M. H. Palmer, *J. Chem. Soc.*, 2640 (1963).

(14) Zinc reduction of **1** should also be studied as a feasible method for the synthesis of α-amino acids.

(15) F. Weygand and E. Csendes, *Angew. Chem.*, **64**, 136 (1952).

A one-step zinc reduction of adduct **11** appears feasible,[2,3] or an alkaline solution of the unsaturated amino acid may be hydrogenated over platinum oxide as was done previously.[12] Careful acidification would be expected to precipitate the saturated amino acid, leaving sodium iodide and other salts in solution.

6-Heptenoic acid was prepared from ethyl acetamidocyanoacetate and 5-bromo-1-pentene by the method of Albertson.[9] In further studies the sequence outlined above will be explored as a route to fluorinated α-amino acids.

Experimental Section

5-Bromo-1-pentene from Peninsular ChemResearch Inc. was redistilled twice, separating a cut, bp 126–127°, $n^{24}D$ 1.4620 [lit. bp 125.6, $n^{20}D$ 1.4632,[16] and bp 74–76° (125 mm), $n^{20}D$ 1.4624[17]]. The corresponding data[18] for 5-bromo-2-pentene are bp 121.7°, $n^{20}D$ 1.4695. Gas chromatographic analysis showed only one main component (6-ft Carbowax 20 M column at 90 or 135°). 1-Iodoperfluoropropane (bp 41°) from Columbia Organic Chemicals Co. or Pierce Chemical Co. was distilled on occasion or was used as received. Vinylacetic acid (3-butenoic acid) from Peninsular ChemResearch Inc. was redistilled and the cut [bp 86–87° (34 mm), $n^{25}D$ 1.4229] was used. Ethyl acetamidomalonate (mp 95–96°, from ligroine and carbon tetrachloride) and ethyl acetamidocyanoacetate (mp 132–133°, from water) were obtained from Winthrop Chemical Co. and were recrystallized before use. These solids were stored in a desiccator over phosphorus pentoxide. Unless otherwise indicated the liquids were distilled in a 16-in. spinning-band column (column A).

5,5,6,6,7,7,7-Heptafluoroheptanoic Acid.—A Carius tube was charged with vinylacetic acid (8.6 g, 0.10 mole), azobisisobutyronitrile (ABN, 0.33 g, 0.002 mole), and 1-iodoperfluoropropane (60.0 g, 0.20 mole, 30 ml). At −70° the tube was evacuated, filled with nitrogen and evacuated twice, and sealed *in vacuo*. The tube was heated in an oil bath at 67° for 24 hr, cooled, and opened. 1-Iodoperfluoropropane (30 g) was removed and the residue (33.3 g, 87% yield) of crude 3-iodo-5,5,6,6,7,7,7-heptafluoroheptanoic acid was used for a zinc reduction.

A 500-ml flask was fitted with a magnetic stirring bar, a reflux condenser, dropping funnel, and gas inlet tube. Absolute ethanol (200 ml) was saturated with hydrogen chloride, 5.0 g of zinc (30–60 mesh) was added at 60°, and the crude iodo ester (above) in 50 ml of ethanol was added slowly (1 hr). As needed, 5-g portions of zinc (total 25 g) and intermittent hydrogen chloride additions were made to maintain foaming, over a 3-hr period. Water was added to the alcohol solution, and the liquid was extracted with benzene and ether. The organic extract was dried over magnesium sulfate and distilled. A forerun had bp 37–119° (140 mm), $n^{25}D$ 1.3838, 2.2 g; and ethyl 5,5,6,6,7,7,7-heptafluoroheptanoate distilled, bp 120–121° (140 mm), $n^{25}D$ 1.3449, 16.8 g (68% of theory), leaving a residue of 3.0 g.

The ester (15.0 g, 0.063 mole) was hydrolyzed in aqueous solution (60 ml) containing 5.6 g (0.10 mole) of potassium hydroxide on the steam bath for 4 hr. While cooling in an ice bath, hydrochloric acid (10 ml) was added. A heavy oil separated, which was extracted twice with chloroform (25 ml), and dried over magnesium sulfate. 5,5,6,6,7,7,7-Heptafluoroheptanoic acid distilled (without a column) at bp 210–212°, 11.2 g, $n^{25.5}D$ 1.3435 (86% of theory).

Anal. Calcd for $C_7H_7F_7O_2$: C, 32.8; H, 2.74; F, 51.9. Found: C, 32.48; H, 2.88; F, 51.62.

2-Bromo-5,5,6,6,7,7,7-heptafluoroheptanoic Acid.—5,5,6,6,7,7,7-Heptafluoroheptanoic acid (10.0 g, 0.039 mole), bromine (6.4 g, 0.041 mole, 2.4 ml), and phosphorus trichloride (0.2 ml) were placed in a 100-ml flask fitted with a Dry Ice reflux condenser connected at the top to a water trap. Isopropanol and Dry Ice kept the condenser at −10 to −20°. The reaction mixture was stirred by a magnet bar, and was heated in an oil bath on a thermostatically controlled hot plate. The reflux temperature rose from 91 to 112° over a 2-hr period and after 6 hr most of the bromine was used. The bath temperature finally reached 142°. Ether was added to the cold mixture and the liquid was extracted with cold water and with cold 5% sodium bicarbonate solution. Benzene (25 ml) was added to break the emulsion which formed. The organic extract was dried (magnesium sulfate) and distilled in a Claisen flask, bp 142–158° (12 mm), 9.2 g (71% of theory). 2-Bromo-5,5,6,6,7,7,7-heptafluoroheptanoic acid was redistilled in a 4-in. helices-packed column: bp 134–137° (8 mm), $n^{26}D$ 1.3765, 4.1 g; and bp 137° (8 mm), $n^{26}D$ 1.3820, 2.9 g.

Anal. Calcd for $C_7H_6BrF_7O_2$: C, 25.1; H, 1.80. Found: C, 24.76; H, 1.89.

5,5,6,6,7,7,7-Heptafluoro-2-aminoheptanoic Acid.—2-Bromo-5,5,6,6,7,7,7-heptafluoroheptanoic acid (5.0 g, 0.015 mole) was dissolved in 100 ml of anhydrous ethanol and ammonia from a cylinder bubbled in while cooling in an ice–salt bath at 1 to −1°. The temperature inside rose to 10° and fell to 0° during 0.5 hr. The flask was protected by a Drierite-filled tube. After 3 days the yellow solution was evaporated by a rotary evaporator (Roto-Vac) to dryness. The solid, warmed with 75 ml of ethanol, gave 1.7 g of insoluble 2-amino-5,5,6,6,7,7,7-heptafluoroheptanoic acid, mp 242–243° dec. Recrystallized from 100 ml of 95% ethanol, it gave 0.8 g, mp 266–267° dec. The filtrate evaporated to dryness gave a second crop from 30 ml of 50% ethanol, 0.4 g, mp 262–263° dec. The filtrate now gave only an oil when cooled or evaporated. The yield of product was 52% of theory. The amino acid gave a positive ninhydrin test.

Anal. Calcd for $C_7H_8F_7NO_2$: C, 31.0; H, 2.97; N, 5.18. Found: C, 30.75; H, 2.98; N, 5.52.

Ethyl 6,6,7,7,8,8,8-Heptafluoro-2-carbethoxyoctanoate.—1-Iodoperfluoropropane was previously added to ethyl allylmalonate.[10] The reaction was repeated. From 0.15-mole amounts 67.4 g or a 90% yield of crude ethyl 2-iodo-4,4,5,5,6,6,6-heptafluorohexylmalonate was obtained. An infrared spectrum was identical with that of a previously distilled sample. A zinc reduction of this material was carried out as described above. The product distilled at bp 102° (2.5 mm), $n^{25}D$ 1.3746, 35.1 g, and 2.4 g, $n^{25}D$ 1.3782, 74% of theory. A residue of 7.1 g remained.

6,6,7,7,8,8,8-Heptafluorooctanoic Acid.—Hydrolysis of ethyl 6,6,7,7,8,8,8-heptafluoro-2-carbethoxyoctanoate (49.8 g, 0.135 mole) was done in 330 ml of 90% ethanol containing 32.0 g (0.57 mole) of potassium hydroxide. The liberated acid was extracted into ether and the (dry) ether solution was filtered through alumina and charcoal in a chromatography tube in an unsuccessful attempt to remove a yellow impurity. The acid (35.9 g, 85% of crude yield) was heated in a flask using a 4-in. helices-packed column for 0.5 hr up to a pot temperature of 190° (100 mm) and distilled, bp 162° (88 mm), 24.0 g (77% yield). It was carefully fractionated in a 24-in. spinning-band column (column B). Fractions I [bp 76–100° (4.0 mm), 1.0 g] and II [bp 102° (4.0 mm), 2.4 g (partially crystalline)] were yellow in color; fraction III [bp 105° (4.0 mm), 16.7 g] was crystalline, mp 33–34.5°.

Anal. Calcd for $C_8H_9F_7O_2$: C, 35.61; H, 3.36. Found: C, 35.33; H, 3.22.

Bromination of 6,6,7,7,8,8,8-Heptafluorooctanoic Acid.—6,6,7,7,8,8,8-Heptafluorooctanoic acid (13.5 g, 0.05 mole), bromine (8.1 g, 0.051 mole, 2.8 ml), and phosphorus trichloride (0.2 ml) were heated as above for 9 hr at 90–137°. Ether (50 ml) was added to the brown solution and shaken with 25 ml of dilute sodium bicarbonate solution; then twice with 25 ml of ice–water. An emulsion formed which was separated with the aid of salt. A *heavy* oil layer also formed which was probably the sodium salt of the acid. It was removed, acidified with hydrochloric acid, and extracted with ether. All ether extracts were dried over magnesium sulfate and distilled in a 4-in. helices-packed column. 2-Bromo-6,6,7,7,8,8,8-heptafluorooctanoic acid distilled, bp 126–128° (5.0 mm) or 118° (1.0 mm), $n^{35}D$ 1.3869, a solid, mp 45–45.4°, 12.2 g (70% of theory). A holdup and residue of 2 g were discarded.

Anal. Calcd for $C_8F_7H_8BrO_2$: C, 27.63; H, 2.32. Found: C, 27.44; H, 2.25.

6,6,7,7,8,8,8-Heptafluoro-2-aminooctanoic Acid.—2-Bromo-6,6,7,7,8,8,8-heptafluorooctanoic acid (11.7 g, 0.034 mole) was dissolved in 150 ml of anhydrous ethanol and cooled to 0° in an ice–salt bath, and ammonia gas was passed in for 0.75 hr. The flask and condenser were protected by a Drierite-filled tube, which was left in place for 3 days. The amino acid was collected and air-dried, 3.0 g, mp 257° dec (sinters at 243°). The filtrate was evaporated down in a Roto-Vac, the solid was taken up in 50 ml of hot ethanol and cooled, and the amino acid was collected, 0.3 g,

(16) M. S. Kharasch and C. F. Fuchs, *J. Org. Chem.*, **9**, 359 (1944).

(17) R. Ya. Levina and E. A. Viktorova, *Vestnik. Moskov. Univ.*, **6**, *No. 2, Ser. Fiz.-Mat. i Estestven Nauk*, No. 1, 89 (1951); *Chem. Abstr.*, **46**, 8605 (1952).

(18) H. L. Goering and S. J. Cristol., *J. Am. Chem. Soc.*, **70**, 3310 (1947).

mp 264–265° dec (sinters at 255°). The filtrate was evaporated again, leaving a soft, tan solid which was completely soluble in water and gave a very foamy solution. Various attempts to recrystallize the solid failed. It seemed probable that it was mostly the ammonium salt of the α-bromo acid. Hence the reaction with ammonia in ethanol was repeated, this time closing the flask while cold with a stopper held in place by a rubber band. In 1 day crystals had formed. After 3 days the solid was collected, 2.63 g, mp 254–256° (sinters at 240°).

The filtrate was evaporated off and the solid was taken up in ethanol and chilled. Two crops (0.3 g) of crystals were collected, mp 244–246° dec (sinters at 241°). Total yield was 6.0 g (62% of theory). The amino acid gave a positive ninhydrin test.

Anal. Calcd for $C_8H_{10}F_7NO_2$: C, 33.7; H, 3.54; N, 4.92. Found: C, 33.53; H, 3.48; N, 5.32.

Ethyl 4-Pentenylmalonate and Ethyl 6,6,7,7,8,8,8-Heptafluorooctylmalonate.—Ethyl malonate (32 g, 0.2 mole) was added to a solution of sodium ethoxide (0.2 mole) in 250 ml of ethanol at 80°. Then 5-bromo-1-pentene (32.8 g, 0.22 mole) was added over a 0.5-hr period, and refluxing was continued for 9 hr. The ethanol and unreacted 5-bromo-1-pentene (strong odor) were distilled off and the residue was treated with water and extracted with carbon tetrachloride three times. The organic layers were dried and distilled in column B. Ethyl malonate (6.9 g) was recovered, along with ethyl 4-pentenylmalonate, bp 121° (7.0 mm), $n^{23}D$ 1.4327, 29.9 g (66% of theory). An infrared spectrum showed that CH_2=CH was present and also a weaker band at 10.30 μ which may be attributed to the presence of some ethyl 3-pentenylmalonate, resulting from isomerization by the strong base.

1-Iodoperfluoropropane (29.6 g, 0.10 mole, 15 ml), ethyl 4-pentenylmalonate (above, 19.9 g, 0.088 mole), and ABN (0.33 g, 0.007 mole) were charged to a 50-ml stainless steel cylinder, cooled to −70°, and evacuated and filled with nitrogen three times. The cylinder was heated in a water bath at 85 ± 5° while shaking occasionally for 6 hr. The cylinder was evacuated through two −70° cold traps. A solid and liquid collected in the first trap. The liquid (15.2 g) was mostly 1-iodoperfluoropropane. The solid (*ca.* 1.0 ml) melted at room temperature and may possibly have been ethyl iodide, ethanol, or water.

While warm the product in the cylinder was poured out (36.0 g). An infrared spectrum showed weak CH_2=CH bands, the 10.30-μ band and new bands at 2.80, 5.85, 6.52, 6.62, 8–9, and 13.8 μ not in the starting material. The product partly crystallized. After cooling to 0° the solid was filtered on a Büchner funnel, rinsed with petroleum ether (bp 67°), and air dried, 2.0 g, mp 119–123° (sinters at 117°). Recrystallization from carbon tetrachloride gave mp 128–132° (sinters at 123°). A second recrystallization gave mp 123–124°. An infrared spectrum of the solid in chloroform solution showed a strong OH band at 2.85, a CH band at 3.30, a very strong C=O band at 5.70, another C=O at 5.85 μ, and numerous higher bands.

The filtrate (an oil) showed only a trace of OH band and a shoulder of the new band at 5.85, but had very strong C=O of the ester at 5.70 μ. It was distilled without a column from an oil bath to remove unreacted ethyl 4-pentenylmalonate, bp 87–118° (1.0 mm), 7.5 g (38% recovery). The residual oil (27.8 g, 54% yield) was chilled to 0°, but no more solid separated. It was mostly ethyl 4-iodo-6,6,7,7,8,8,8-heptafluorooctylmalonate.

A zinc reduction was performed as described previously.[2,10] Distillation without a column gave ethyl 6,6,7,7,8,8,8-heptafluorooctylmalonate, bp 105–112° (1.0 mm), 11.1 g, $n^{26}D$ 1.3830, and bp 120–122° (1.0 mm), 5.7 g, $n^{26}D$ 1.3848 (84% yield). A residue of dark brown solid (3.6 g) remained in the flask which was discarded. It probably contained some of the solid, mp 119–123° (above). The infrared spectrum was consistent. Further investigation of the solid by-product will be required.

Ethyl Allylacetamidomalonate.—The method of Albertson[9] was used. Redistilled allyl bromide (26.6 g, 0.22 mole) was added to a solution of ethyl acetamidomalonate (40.2 g, 0.20 mole) in anhydrous ethanol (200 ml) containing sodium ethoxide prepared by the addition of sodium (4.6 g, 0.20 mole). The reaction mixture was stirred under a nitrogen atmosphere throughout addition and during 20-hr reflux period. Ethanol was distilled from the neutral slurry, the residue was dissolved in water (200 ml), and an oil was extracted into chloroform. Evaporation gave a product as an oil (45.7 g, 90% of theory) which solidified, mp 38–39° (lit.[9] mp 46°). An infrared spectrum was consistent.

Ethyl 4-Pentenylacetamidomalonate.—Reaction of 5-bromo-1-pentene with ethyl acetamidomalonate was carried out on 0.1-mole scale as in the previous section. The oil (18.5 g) eventually recovered after evaporation of benzene and hexane used in an attempted crystallization was 65% of theory. An infrared spectrum showed the CH_2=CH band at 1640 and at 995, NH band at 3420, and CO bands at 1734 (COOH), and 1670 cm^{-1} (CONH). These data are consistent with the anticipated structure. Though this is a new compound its analysis was not secured since purification was not successful.

Ethyl 4-Pentenylcyanoacetamidoacetate and 2-Amino-6-heptenoic Acid.—Synthesis was done as in the section above using recrystallized ethyl acetamidocyanoacetate. Although the allyl derivative[9] and the 3-pentenyl derivative[12] are known, this compound had not been reported. Unfortunately the reaction gave a dark oil (89% of theory) which solidified at 0°, but could not be crystallized. The product had an infrared spectrum similar to ethyl 4-pentenylacetamidomalonate, but a weak band at 965 cm^{-1} appeared.

The product was hydrolyzed to 2-amino-6-heptenoic acid by refluxing in 10% sodium hydroxide solution as done by Albertson.[9] The α-amino acid was obtained as white powder (mp 275–278° dec) in 71% yield. It was recrystallized from water, mp 285–286°.

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.7; H, 9.15. Found: C, 58.52; H, 9.12.

Free-Radical Addition of 1-Iodoperfluoropropane to Ethyl 4-Pentenylacetamidomalonate.—In a 100-ml, round-bottom flask fitted with a nitrogen inlet tube surmounted by a Dry Ice reflux condenser and an addition funnel was placed azobisisobutyronitrile (0.32 g, 0.002 mole) and ethyl 4-pentenylacetamidomalonate (17.5 g, 0.06 mole). The flask was immersed in an oil bath at 71° and stirred by means of a magnet bar while 1-iodoperfluoropropane (23.6 g, 0.08 mole) was added. Refluxing ceased in 3.5 hr. The tan liquid product (40.6 g) showed very weak olefinic absorption bands in the infrared spectrum. 1-Iodoperfluoropropane (8.0 g, 0.026 mole) was added and the reaction mixture was refluxed (74°) for 5 hr. Volatile material (14.1 g) was removed at reduced pressure giving solid **6** (28.2 g, 81% conversion). A small sample recrystallized from benzene and *n*-hexane mixture, mp 75–76°. An infrared spectrum showed none of the olefinic bands present.

Recrystallization of the entire 28.2 g of **6** was not entirely satisfactory. From 20 ml of benzene and 100 ml of *n*-hexane at 0° 15 g (mp 65–73°) was obtained. The filtrate gave on evaporation at 0° 6.0 g, mp 53–80° (sinters at 28°). Recrystallization of the 15 g from methylcyclohexane (105 ml) at 0° gave white solid and yellow lumps, mp 73–76°. Redissolved in benzene, passed down alumina, and chilled, the mixture gave 2.2 g, mp 77–78.5° (sinters at 74°).

Anal. Calcd for $C_{17}H_{23}F_7INO_5$: C, 35.2; H, 4.0. Found: C, 34.85; H, 4.05.

6,6,7,7,8,8,8-Heptafluoro-4-octenylacetamidomalonic Acid (7).—The mother liquor (above) was evaporated off giving 13.0 g and solid adduct (6 g) was added to make a total of about 20 g (*ca.* 0.05 mole) of **6**. Sodium hydroxide (12.0 g, 0.30 mole) as 10% aqueous solution and 20 ml of 95% aqueous ethanol were heated with **6** on a steam bath for 1 hr at reflux. Ethanol was evaporated and the solution was cooled to 10° and acidified with concentrated hydrochloric acid at 0–5° while stirring. After standing overnight **7** was collected, rinsed with two 25-ml portions of water (some dissolved), and dried in air (9.0 g), mp 100–102° dec. The filtrate was extracted with ether. Evaporation gave 4.13 g of low-melting **7**. The total yield of **7** was 96%. An infrared spectrum (Nujol mull) showed NH, COOH, CONH, and CH=CH bands at the anticipated places.

Anal. Calcd for $C_{13}H_{14}F_7NO_5$: C, 39.35; H, 3.56; F, 33.5. Found: C, 39.23; H, 3.60; F, 33.52.

6,6,7,7,8,8,8-Heptafluorooctylacetamidomalonic Acid.—Compound **7** (6.5 g, 0.016 mole) in 60 ml of 90% aqueous ethanol at 49 psi (initial) of hydrogen pressure was shaken with 0.20 g of platinum oxide for 20 hr. After filtration, solvent was removed by rotary evaporator and **8** was recovered (6.5 g, 100%), mp 107–108° dec. An infrared spectrum now showed the COOH and CONH bands, but no CH=CH band at 10.30 μ. Dilute potassium permanganate solution was not decolorized by **8**. Compound **8** was insoluble in hot benzene, acetone, or chloroform but dissolved in toluene to which a small amount of 95% ethanol was added. The compound was isolated as the monohydrate.

Anal. Calcd for $C_{13}H_{18}F_7NO_6$: C, 37.5; H, 4.35; F, 31.9. Found: C, 37.5; H, 4.2; F, 31.7.

2-Acetamido-8,8,9,9,10,10,10-heptafluorodecanoic Acid.—Compound **8** (0.50 g, 1.2 mmoles) in 10 ml of toluene was heated to boiling. The compound slowly dissolved with gas evolution, and after 0.5 hr began to precipitate from solution. After 2 hr a small sample of white powder was removed, mp 194–197°, and an infrared spectrum showed the NH band at 3320, the carboxyl group at 1655, the amide carbonyl at 1600, and amide "II" band at 1530 cm^{-1}. The mixture was diluted to 25 ml and the product was brought into solution with a few drops of isopropyl alcohol. Compound **9** (0.144 g, 30% conversion) crystallized, mp 198–200°. Compound **9** was readily soluble in 5% aqueous sodium bicarbonate solution. Successive fractions (0.30 g) containing **8** and **9** were obtained (95% recovery). The sample was isolated as the monohydrate.

Anal. Calcd for $C_{12}H_{18}F_7NO_4$: C, 38.7; H, 4.76; F, 35.65. Found: C, 38.52; H, 4.10; F, 35.3.

2-Amino-4-hydroxy-6,6,7,7,8,8,8-heptafluorooctanoic Acid.—Ethyl allyl acetamidomalonate (22.8 g, 0.088 mole), *n*-heptafluoropropyl iodide (28.0 g, 0.095 mole) and ABN (0.32 g, 0.002 mole), in a 100-ml flask purged with nitrogen and kept at reflux temperature under a Dry Ice reflux condenser, was heated by means of an oil bath at 74–78° for 6 hr. The unreacted R_FI (1.1 g) was pumped off, leaving 49 g (100%) of crude adduct (ethyl 2-iodo-4,4,5,5,6,6,6-heptafluorohexylacetamidomalonate) as a light tan oil which could not be induced to crystallize. Analogous reaction employing ethyl allylacetamidocyanoacetate as olefinic substrate could not be made to take place in several attempts.

Attempted Reduction and Hydrolysis.—Hydrogen iodide (65.6 ml of 50% aqueous solution, 0.44 mole) was added to the oil and the mixture heated under reflux for 5 hr at 70–99°. A solid, crystalline mass was formed. Xylene (35 ml) was added and the foamy mixture was refluxed for 5 hr and the xylene–water azeotrope removed using a Dean–Stark tube. Considerable foaming occurred and it was necessary to separate the xylene and water distillate layers, and evaporate down the water layer to recover part of the product.

The combined aqueous, crystalline salt mixture was brought into solution at 60° in 400 ml of water and 400 ml of 0.05 *N* sodium hydroxide solution was added by buret using a pH meter to bring the pH to 4.0. A precipitate of white solid appeared as the pH was raised above 1.0. The solid was washed with water and dried, 11.8 g, mp 210–216° dec (sinters at 192°). The clear filtrate was taken to a pH of 4.2 by addition of sodium hydroxide solution and evaporated to 500 ml to give solid, 4.2 g, mp 230–231° dec. The filtrate was raised to a pH of 5.0 and evaporated to 200 ml, yielding solid, 0.28 g, mp 210° dec. The total recovery of 2-amino-4-hydroxy-6,6,7,7,8,8,8-heptafluorooctanoic acid was 16.3 g, 63%. One gram was recrystallized from 600 ml of water at the boil. The first crop [0.63 g, mp 234–236° dec (sinters at 227°)] was used for derivatives and an infrared spectrum (Nujol mull). A strong bonded OH at 3000–3300, COOH (salt form) at 1610 and 1590, a strong band at 1510–1530, CF_3 bands at 1170, 1210, and 1220, and bands at 1112, 1108, 1080, 955, and 925 cm^{-1} appeared. Bands not in 2-amino-6,6,7,7,-8,8,8-heptafluorooctanoic acid were observed at 1270, 1450, and 1520 $cm.^{-1}$

Anal. Calcd for $C_8H_{10}F_7NO_3$: C, 31.95; H, 3.36; F, 44.20. Found: C, 32.3; H, 3.38; F, 44.6.

2-Trifluoroacetamido-4-hydroxy-6,6,7,7,8,8,8-heptafluorooctanoic Acid γ-Lactone.—Two trifluoroacetyl derivatives were isolated from 2-amino-4-hydroxy-6,6,7,7,8,8,8-heptafluorooctanoic acid (2.85 g, 0.0095 mole), trifluoroacetic acid (6.0 ml), and trifluoroacetic anhydride (2.78 g, 1.76 ml, 0.0132 mole) according to the procedure used with amino acids.[7] In this instance the solution became very thick at −10° and additional trifluoroacetic acid (3 ml) was added to permit stirring. Extracting with ether gave 1.3 g of soluble product and 2.4 g of insoluble solid (all of the product was soluble in hot toluene). Fractional crystallization from toluene gave, after several repetitions, a solid, mp 115–117.5° and another substance, mp 147–149°. The infrared spectra (Nujol mull) of these compounds were identical. An NH band at 3380 (no COOH band), γ-lactone at 1780, NHCO-CF_3 at 1720, amide "II" band at 1550, 1560, CF_3 at 1220 and 1165, and bands at 1120, 1070, 1080, and 1010 cm^{-1} appeared.

The compounds were insoluble in 5% aqueous sodium bicarbonate solution, but dissolved in 10% aqueous sodium hydroxide solution. Acidifying with dilute hydrochloric acid did not reprecipitate the compound. The product also was recrystallized from carbon tetrachloride containing sufficient acetone to give solution at the boil. The two isomers gave the same elemental analysis; they are therefore the anticipated *cis* and *trans* forms of 2-trifluoroacetamido-4-hydroxy-6,6,7,7,8,8,8-heptafluorooctanoic acid γ-lactone.

Anal. Calcd for $C_{10}H_7F_{10}NO_3$: C, 31.7; H, 2.39; F, 50.05. Found: (mp 115–117.5°): C, 31.80; H, 2.10; F, 50.10. Found (mp 147–149°): C, 31.76; H, 2.15; F, 49.94.

N-Trifluoroacetyl Derivative of 6,6,7,7,8,8,8-Heptafluoro-2-aminooctanoic Acid.—A solution of title compound (0.71 g, 0.0025 mole) in anhydrous trifluoroacetic acid (1.50 ml, 2.3 g, 0.02 mole) was stirred magnetically under a slow nitrogen purge in a flask equipped with a dropping funnel and a Dry Ice reflux condenser. The clear solution was cooled to −15° and 0.43 ml (0.63 g, 0.003 mole) of trifluoroacetic anhydride was added. The temperature was allowed to rise to 25° during 0.5 hr; the trifluoroacetic acid and anhydride pumped off into a −70° trap down to 1 mm, keeping the temperature below 30°. The residue was dissolved in ether and filtered, the ether was evaporated off, and the solid was recrystallized from 15 ml of toluene as needles, 0.535 g, mp 111–113.2°. An additional 0.15 g of product was obtained by successive evaporation of the mother liquor (yield 71%). Recrystallization again from toluene gave platelets (mp 100–102°) but on powdering the melting point reverted to 112.5–113°. In another preparation both crystal forms evidently were produced since the substance started to melt at 100–103° and the remainder melted at 110–103°.

An infrared spectrum run as a mineral oil mull gave the NH band at 3350, COOH (bonded) at 3000–3200, $CF_3C{=}O$ at 1754, COOH at 1722 and 1690, "amide II" at 1560, "III" at 1275, CF_3 at 1220 and 1180, and bands at 1140, 1115, 1040, 1025, 950, 920, 910, 825, 765, 725 (two), and 632 cm^{-1}. The CF_3CO band in $CF_3CONHCH_2COOCH_3$ (10% in CCl_4) was also at 1755 cm^{-1}.

The product was soluble with reaction in 5% aqueous sodium bicarbonate solution and reprecipitated when acidified.

Anal. Calcd for $C_{10}H_9F_{10}NO_3$: C, 31.55; H, 2.38; F, 49.9. Found: C, 31.48; H, 2.18; F, 49.70.

Aqueous Hydrolysis of Ethyl 2-Iodo-4,4,5,5,6,6,6-heptafluorohexylacetamidomalonate (1).—Title compound was prepared as described above. The infrared spectrum showed bands for amide at 3420 and 1675, ester at 1740, absence of olefin bands at 3080, 1640, and 995, a band at 1450, and bands at 1300–1200 cm^{-1}, indicating the correct structure. A solution of 36.2 g (0.065 mole) of compound in 100 ml of alcohol was heated for 0.5 hr with 200 ml of 10% aqueous sodium hydroxide. The clear solution stood for 2 days, and was acidified at 15–18° with concentrated hydrochloric acid. A solid [2.0 g, mp 193–198° dec (sinters at 173°)] precipitated, which appeared to be the desired malonic acid. On standing 4.8 g of solid precipitated (mp 100–107°); after evaporation it yielded 1.8 g, mp 97–185°. The filtrate evaporated in a rotary evaporator gave a solid mixture.

The 4.8-g fraction was treated separately. A sample (0.105 g) in 10 ml of acetone was filtered at the boil, and on cooling gave 0.042 g, mp 98–99°; a second crop gave 0.033 g, mp 93–97°. Infrared spectra of the two samples were identical and showed an NH band at 3300, a γ-lactone band at 1780, the $NHCOCH_3$ band at 1650, and the amide "II" band at 1540 cm^{-1}. The sample was insoluble in 5% sodium bicarbonate solution. The infrared spectrum and properties resembled closely that of the corresponding N-trifluoroacetyl derivative. The reaction products therefore included the unsaturated malonic acid and the γ-lactone of 2-acetamido-4-hydroxy-6,6,7,7,8,8,8-heptafluorooctanoic acid (5).

Anal. Calcd for $C_{10}H_{10}F_7NO_3$: C, 36.87; H, 3.11; F, 40.95. Found: C, 37.00; H, 3.03; F, 41.1.