crop, m.p. 131–140°, was collected. Recrystallized from ethyl acetate this material formed a mixture of the α- and β-isomers as well-defined crystalline products which were separated mechanically. The long, hair-like needles of the α-isomer obtained in this manner were crystallized from ethyl acetate to give 0.8 g. of methyl α-D-glucofururonoside, m.p. 146–148°, $[\alpha]^{25}D$ +148° (*c* 0.3, water), λ_{max}^{nujol} 5.70 μ; lit.[5] m.p. 148°, $[\alpha]^{23}D$ +149° (*c* 1.0, water).

Anal. Calcd. for $C_7H_{10}O_6$: C, 44.21; H, 5.29. Found: C, 44.20; H, 5.26.

An additional 4.0 g. of the β-isomer, m.p. 137–139°, was obtained in this operation, raising the total yield of purified product to 62%.

Ethyl β-D-Glucofururonoside (IIa, R = C_2H_5).—Treatment of 30.0 g. (0.17 mole) of D-glucuronolactone with anhydrous ethanolic hydrogen chloride as described above gave 30.0 g. (89%) of crude, sirupy glycoside, $[\alpha]^{25}D$ −20° (*c* 1.5, water), λ_{max} 5.62 μ. All attempts to crystallize this material failed.

Anal. Calcd. for $C_8H_{12}O_6$: C, 47.06; H, 5.93. Found: C, 46.86; H, 6.04.

The *p*-nitrobenzoate formed small warts from ethanol, m.p. 201–202°, $[\alpha]^{25}D$ −20° (*c* 0.2, ethanol).

Anal. Calcd. for $C_{22}H_{18}O_{12}N_2$: C, 52.60; H, 3.62. Found: C, 52.86; H, 3.60.

Methyl β-D-Glucofuranoside (IIIa, R = CH_3).—To a stirred solution of 2.71 g. (0.074 mole) of sodium borohydride in 40 ml. of water was added over ten minutes a solution of 12.6 g. (0.0664 mole) of methyl β-D-glucofururonoside in 40 ml. of water. A maximum temperature of 50° was obtained during the addition. The reaction mixture was allowed to stand for ten minutes at 40–45° when the excess reducing agent was quenched with a few drops of dilute sulfuric acid. The solution was then diluted to 200 ml. with distilled water and passed successively through 200 g. of Amberlite IR-120 ion exchange resin (strong cation type) and 200 g. of IR4B resin (weak anion type).[8] The percolate was concentrated under reduced pressure at room temperature to 9.1 g. (71%) of a pale yellow sirup, $[\alpha]^{23}D$ −77° (*c* 3.0, water); lit.[2b] $[\alpha]^{23}D$ −77° (water).

The tetracarbanilate, prepared according to Wolfrom's procedure[9] formed felt-like needles from ethanol, m.p. 218–219°, $[\alpha]^{20}D$ +14° (*c* 2.5, acetone); lit.[9] m.p. 215–217°, $[\alpha]^{26}D$ +7.6° (*c* 1.2, acetone).

Anal. Calcd. for $C_{35}H_{34}O_{10}N_4$: C, 62.66; H, 5.11. Found: C, 62.96; H, 5.23.

Methyl α-D-Glucofuranoside (IIIb, R = CH_3).—Reduction of 0.7 g. (3.7 millimoles) of methyl α-D-glucofururonoside as described above gave 0.32 g. of a yellow sirup which crystallized from ethyl acetate yielding 0.24 g. (34%) of methyl α-D-glucofuranoside as rosettes, m.p. 60–62°, $[\alpha]^{25}D$ +110° (*c* 0.5, water); lit.[2a] m.p. 62–63°, $[\alpha]^{20}D$ +118° (*c* 4.5, water)

Ethyl β-D-Glucofuranoside (IIIa, R = C_2H_5).—Reduction of 14.07 g. (0.069 mole) of sirupy ethyl β-D-glucofururonoside as described above for the methyl analog gave 7.3 g. of a sirup which crystallized after drying one week over phosphorus pentoxide. The crystals so obtained were extremely hygroscopic and crystallized with difficulty from ethyl acetate to give the furanoside as prisms, m.p. 61–63°, $[\alpha]^{25}D$ −76° (*c* 1.0, water).

(8) These resins were kindly supplied by Resinous Products Division, Rohm and Haas Co., Philadelphia 5, Pa.

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The Synthesis of Ethyl Adipamate and 2-Keto-6,6-dihydroperfluorohexamethylenimine

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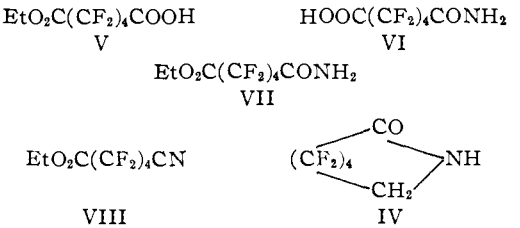
A synthesis of ethyl adipamate (I) could not be found in the literature and since the compound was of interest for comparison with its fluorinated analog, ethyl perfluoroadipamate (VII), methods for its synthesis were investigated. The best method proved to be the reaction of 5-carbethoxyvaleryl chloride (II) in dioxane solution with gaseous ammonia. Under these conditions the acid chloride function of II was preferentially attacked to yield I in 75% yield. However, when the ammonolysis was carried out in aqueous solution, I and adipamide were isolated in approximately equal amounts. This is in conformity with the findings of Day, Gordon and Miller concerning the effect of solvents on the ammonolysis of esters.[1]

Adipamic acid (III) also was used as a starting material for the preparation of I but with less success. Direct esterification of III with ethanol using an acid catalyst and azeotropic distillation of water produced I in only 36% yield. The silver salt of III reacted with ethyl iodide to form I in low yield.

A fluorinated derivative of ε-caprolactam, 2-keto-6,6-dihydroperfluorohexamethylenimine (IV) was prepared for the purpose of studying its polymerization. The compound was synthesized from ethyl perfluoroadipate through the intermediates V, VI, VII and VIII.



Ethyl perfluoroadipate[2] was converted to ethyl hydrogen perfluoroadipate (V) by heating it with perfluoroadipic acid and separating the mixture by fractional distillation. Perfluoroadipamic acid (VI) was obtained from V by ammonolysis. The esterification of VI was accomplished using diazoethane and the ethyl perfluoroadipamate (VII) formed was dehydrated by heating with phosphorus pentoxide. The ethyl 5-cyanoperfluorovalerate thus obtained was catalytically hydrogenated to produce IV.

Ethyl perfluoroadipamate was also prepared in low yield from silver perfluoroadipamate and ethyl iodide. An attempt to obtain VII by the ammonolysis of 5-carbethoxyperfluorovaleryl chloride produced only perfluoroadipamide. This is in contrast to our successful synthesis of ethyl adipamate in this manner from 5-carbethoxyvaleryl chloride. The failure to obtain a preferential reaction of ammonia with the acid chloride function in the case of the fluorinated compound demonstrates the greater reactivity of fluorinated esters.

Attempts to polymerize IV by using sodium or water as catalysts were unsuccessful.

Experimental

5-Carbethoxyvaleryl Chloride (II).—Ethyl hydrogen adipate[3] (168 g., 0.96 mole) and 114 g. (0.6 mole) of thionyl

(1) A. R. Day, M. Gordon and J. G. Miller, THIS JOURNAL, **71**, 1245 (1949).

(2) E. T. McBee, P. A. Wiseman and G. B. Bachman, *Ind. Eng. Chem.*, **39**, 415 (1947).

(3) G. T. Morgan and E. Walton, *J. Chem. Soc.*, 91 (1933).

chloride were heated on a steam-bath for five hours. Unreacted thionyl chloride was removed by further heating at 15 mm. The residual crude acid chloride weighed 175 g.

Ethyl Adipamate (I) from II. By Aqueous Ammonolysis.—Two liters of aqueous ammonia (28%) was cooled to −8° and 175 g. of crude II was added with continuous agitation over a period of 90 minutes, maintaining the temperature at about −7°. The white solid product was separated by filtration and vacuum dried for 1.5 days. There was thus obtained 100 g. of crude product. Part of the crude product was soluble in 95% ethanol and proved to be I. From the alcohol was obtained 34 g. (22%) of I which melted at 77–78° after recrystallization from carbon tetrachloride. The alcohol insoluble portion (30 g.) was identified as adipamide m.p. 220–222°.

By Ammonolysis in Dioxane.—A solution of 38.5 g. of crude 3-carbethoxyvaleryl chloride in 200 ml. of dry dioxane was cooled in an ice-bath and dry ammonia bubbled through the solution for 30 minutes. After removal of the ice-bath the ammonia flow was continued for another 30 minutes. A small amount of I was filtered from the reaction mixture and more was isolated by vacuum evaporation of the solution. By recrystallization from carbon tetrachloride there was obtained 26 g. (75%) of I, m.p. 77–78°.

Anal. Calcd. for $C_8H_{15}NO_3$: N, 8.08. Found: N, 8.09, 8.15, 8.06.

Ethyl Adipamate from Adipamic Acid by Direct Esterification.—Five hundred ml. of absolute ethanol, 38 g. (0.19 mole) of adipamic acid,[4] 150 ml. of benzene and 5 ml. of concentrated sulfuric acid were heated together. A ternary azeotrope of water, ethanol and benzene was distilled from the mixture through a 3-foot packed column and condensed in a Dean–Stark trap. After 8 hours, 15 ml. of the water-rich layer of the azeotrope was collected. On addition of a cold aqueous solution of potassium carbonate (25 g. in 25 ml. of water) to the reaction mixture a strong odor of ammonia was detected and a solid precipitated. The solid was removed by filtration and the filtrate was evaporated under vacuum. The residue was extracted several times with hot carbon tetrachloride and 12 g. (36%) of I was isolated from the cooled solvent.

By the Reaction of Ethyl Iodide with the Silver Salt of III.—In 200 ml. of water 10.0 g. (0.069 mole) of adipamic acid was dissolved and to the solution was added 9.2 g. (0.036 mole) of silver carbonate to form a greyish precipitate of silver adipamate. It was recrystallized from water and then weighed 13 g. In 75 ml. of ethanol 7.4 g. (0.029 mole) of silver adipamate and 4.6 g. (0.029 mole) of ethyl iodide were heated at reflux temperature for 2 hours. A yellow precipitate of silver iodide was filtered from the reaction mixture and the filtrate was evaporated to yield a solid yellow residue. The residue was extracted several times with hot carbon tetrachloride and 1.8 g. (36%) of ethyl adipamate was isolated from the cooled extract. The insoluble residue was adipamic acid.

Ethyl Hydrogen Perfluoroadipate (V).—Anhydrous perfluoroadipic acid, m.p. 129–133°, weighing 43.5 g. (0.15 mole) and 52 g. (0.15 mole) of ethyl perfluoroadipate[2] were heated at 170° for 3 hours. The reaction mixture was then distilled through a Vigreux column at 15 mm. and two fractions were collected: 26 g. at 110–125°, 39 g. at 125–135°. The low boiling fraction was returned to the residue from the distillation and the mixture was heated at 200° for 5.5 hours. A second distillation was made at 15 mm. and the following fractions were collected: 13 g. at 102–110°, 23 g. at 120–136°. The two high boiling fractions were combined and redistilled at 14 mm. and 46.5 g. (80%) of ethyl hydrogen perfluoroadipate was collected at 123–135°. From the residue, 17 g. of perfluoroadipic acid was recovered.

Anal. Calcd. for $C_8F_8H_6O_4$: F, 47.78; neut. equiv., 318. Found: F, 47.95, 47.66; neut. equiv., 320.

Perfluoroadipamic Acid (VI).—Ammonia gas was passed into a solution of 100 g. of ethyl hydrogen perfluoroadipamate in 400 ml. of dry benzene for 30 minutes. Ammonium perfluoroadipamate which precipitated was separated by filtration. It was then added to a solution of 15 ml. of concentrated sulfuric acid in 100 ml. of water at −5°. The resulting thick paste was stirred for 15 minutes before filtering with suction. The solid thus isolated and its mother liquor were extracted with ether. Evaporation of the dried ether solution gave 70 g. of crude perfluoroadipamic acid. After recrystallization from benzene and alcohol the product melted at 150–151°.

Anal. Calcd. for $C_8F_8H_3NO_3$: neut. equiv., 289; N, 4.85. Found: neut. equiv., 298; N, 4.85, 4.87, 4.89.

Ethyl Perfluoroadipamate (VII). From Silver Perfluoroadipamate and Ethyl Iodide.—To a solution of 2.1 g. (0.0073 mole) of perfluoroadipamic acid in 75 ml. of distilled water, 1.9 g. (0.0069 mole) of silver carbonate was added. The mixture was boiled a few minutes and filtered hot to remove unreacted silver carbonate. Silver perfluoroadipamate was isolated by evaporation under vacuum at room temperature. In this way 2.6 g. (91%) of greyish white solid was obtained. This weight (0.0066 mole) of silver perfluoroadipamate was mixed with 1.4 g. (0.0089 mole) of ethyl iodide in 50 ml. of dry methanol and the mixture was heated with stirring at reflux temperature for 1 hour. On cooling, silver iodide was filtered from the reaction mixture. The solvent was removed from the filtrate by evaporation on a steam-bath. The yellow, sticky residue was then extracted with hot carbon tetrachloride, leaving undissolved perfluoroadipamic acid which melted at 147–151° after recrystallization from benzene and alcohol. A small amount of ethyl perfluoroadipamate precipitated from the cooled solution of carbon tetrachloride, m.p. 41–42°.

From Perfluoroadipamic Acid and Diazoethane.—Diazoethane was prepared by an adaptation of a method for diazomethane.[5] To a solution of 5.9 g. (0.11 mole) of diazoethane in about 300 ml. of ether was added an ether solution of 19 g. (0.066 mole) of crude perfluoroadipamic acid. After standing at room temperature for 20 minutes dilute hydrochloric acid was added to destroy the excess diazoethane. The ether solution was washed once with water, dried over calcium sulfate and the ether removed by distillation to leave a waxy solid. On recrystallization from carbon tetrachloride 18 g. (86.5%) of ethyl perfluoroadipamate was obtained, m.p. 44–45°.

Anal. Calcd. for $C_8F_8H_7NO_3$: F, 47.93; N, 4.42. Found: F, 47.69, 48.12; N, 4.27, 4.37, 4.63.

Attempted Preparation from 5-Carbethoxyperfluorovaleryl Chloride.—Ethyl hydrogen perfluoroadipate weighing 31 g. (0.10 mole) and 21 g. (0.10 mole) of phosphorus pentachloride were combined and the mixture was distilled. Phosphorus oxychloride was removed from the reaction mixture at 30–43° at 20 mm. and the acid chloride was collected at 72–78° at 18 mm. The crude 5-carbethoxyperfluorovaleryl chloride weighed 20 g. (59%).

The acid chloride was dissolved in 50 ml. of anhydrous dioxane and the solution was cooled in an ice–salt mixture for 15 minutes. Ammonia gas was bubbled into the solution for 40 minutes. By filtration 17 g. of perfluoroadipamide was obtained from the reaction mixture and by evaporation of the solvent an additional 2 g. was isolated. It melted at 239–239.5[2] after recrystallization from water.

Ethyl 5-Cyanoperfluorovalerate (VIII).—Ethyl perfluoroadipamate weighing 22 g. (0.05 mole) and 22 g. of phosphorus pentoxide (0.16 mole) were intimately mixed and heated to 230°, at which temperature liquid began to distil. In this way 9.5 g. (64%) of crude 5-cyanoperfluorovalerate was collected. On redistillation 7 g. of material was collected at 145–146°. The following physical constants were determined for the compound: d^{20}_4, 1.4403; $n^{20}D$, 1.3279.

Anal. Calcd. for $C_8F_8H_5NO_2$: F, 50.81; N, 4.68. Found: F, 51.10, 50.65; N, 4.60, 4.72.

2-Keto-6,6-dihydroperfluorohexamethylenimine (IV).—The apparatus used for the hydrogenation of ethyl 5-cyanoperfluorovalerate was an American Instrument Company type rocking microhydrogenator, the bomb of which had a total volume of 120 ml. The platinum oxide catalyst was prepared according to the method of Frampton, Edward and Henze.[6] The method for hydrogenation is an adaptation of that of Weygand.[7]

To the bomb of the hydrogenator was added 50 ml. of glacial acetic acid, 5 g. (0.017 mole) of ethyl 5-cyanoperfluorovalerate, 1 ml. of concentrated sulfuric acid and 0.4 g.

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(6) V. Frampton, J. Edward and H. Henze, THIS JOURNAL, **73**, 4432 (1951).

(7) F. Weygand, *Ber.*, **74**, 256 (1941).

of platinum oxide catalyst. The bomb was sealed and filled with hydrogen to a pressure of 650 p.s.i. and agitated by rocking for 1.5 hours. By that time pressure had dropped to 420 p.s.i. The reaction mixture was removed from the bomb, filtered and the filtrate was then distilled at a maximum temperature of 45° at 9 mm. to remove glacial acetic acid. The residual oil was poured onto 10 g. of ice where it solidified. To it 7 ml. of 50% potassium hydroxide solution was added drop by drop until the solution was basic to litmus. The doughy solid formed was separated from the aqueous solution and an oil was pressed from it. The oil weighed 1.7 g. and solidified to a light tan solid on standing. After recrystallizing twice from carbon tetrachloride, the solid was proved to be 2-keto-6,6-dihydroperfluorohexamethylenimine, m.p. 100–101°.

Anal. Calcd. for $C_6F_8H_3NO$: mol. wt., 257; N, 5.45. Found: mol. wt. (Signer method),[8] 263; N, 5.22, 5.17, 5.47.

Attempted Polymerization of 2-Keto-6,6-dihydroperfluorohexamethylenimine.[9] Sodium Catalyst.—Two-tenths gram of 2-keto-6,6-dihydroperfluorohexamethylenimine and 1 mg. of sodium were sealed in a glass tube after flushing six times with nitrogen. The tube was heated in an oil-bath at 60–124° for 30 minutes and then placed in a furnace at 250° for 1.5 hours. When the hot tube was removed from the furnace and tilted on its side, a white solid froze on its walls and a black residue was left at the bottom. The white solid was unchanged starting material, m.p. 100–101°.

Water as a Catalyst.—One-tenth gram of 2-keto-6,6-dihydroperfluorohexamethylenimine and 0.01 ml. of water were sealed in a glass tube after flushing five times with nitrogen. The tube was heated for three hours at 200°. It was then removed, cooled, opened and connected to a two-way stopcock which allowed access to a vacuum line or to a tank of nitrogen. After flushing the tube with nitrogen it was heated at 140–150° for one hour. Then the tube was evacuated with a water pump and the heating continued. This caused all but a very small amount of dark material to sublime from the bottom of the tube and to condense on the cooler portion of the tube walls. The heating was then discontinued. The solid which sublimed to the walls of the tube was unchanged starting material, m.p. 100–101°.

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The Reaction of Nitrous Acid with γ-Glutamyl Peptides

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The determination of amino nitrogen by the method of Van Slyke[2] gives satisfactory values with most α-amino acids and polypeptides, but high values have been observed with glycine and cystine.[2] Austin[3] has shown that in the case of glycine this anomaly is due to a complex series of reactions which ultimately lead to the formation of N_2O in addition to N_2.

Unusually high values have also been reported for glutathione, glutamine, and the γ-methyl and γ-ethyl amides of glutamic acid. Glutathione[4,5] yielded approximately 66% and the three amides[6,7] approximately 90% of their total nitrogen. These compounds all contain free α-amino and carboxyl groups and a γ-amide linkage. In a study of the action of nitrous acid upon a number of amides (including asparagine) Plimmer[8] showed that under the usual conditions of the Van Slyke procedure the amide group is inert, though it reacts in the presence of strong mineral acid. Lichtenstein[7] suggested that the α-amino group was first replaced by OH, that the resulting γ-hydroxy acid amide underwent ring-closure to yield a lactone with liberation of NH_3 or alkyl amine and that the latter

TABLE I

VAN SLYKE AMINO NITROGEN DETERMINATIONS[a]

Compound[b]	Equivalents of amino N per mole of compound — Reaction time, minutes — 3	10	30	60
H·Glu·OH (L)	1.0	1.0	1.0	1.0
H·Glu·Ala·OH (LL)	1.0	1.0	1.0	
Z·Glu·OBz (LL)	0.0	0.0		
H·Ala-Glu·OH (LLL)	1.0		1.0	1.0
H·Glu·OH (L)	1.7	1.8	1.9	
Glutathione	2.1	2.3	2.6	
S-Acetylglutathione	2.0	2.2		
H·Glu·OH (LL)	2.0	2.0	2.0	
H·Glu·OH (LL)	2.6	2.7	2.8	
H·Glu·OH (LLL)	2.6	2.8	2.8	
H·Glu·OH (LL)	1.9	2.0	2.0	
H·Glu·OH (L)	1.0	1.0	1.0	
H·Glu·OBz·HCl (L)	0.8	1.0	1.0	
H·Glu·Ala·OH [LL / L]	1.2	1.3	1.3	1.3
H·Glu-Ala·OH (LD)			1.4	
H·Glu-Ala·OH (LL)	1.1		1.1	1.2

[a] Temperature 22–26°. [b] The following abbreviations and symbols are used (*cf.* ref. 11); Z, carbobenzyloxy, $C_6H_5CH_2OCO$; Bz, $C_6H_5CH_2$; Ala, $NHCH(CH_3)CO$, C_3H_5ON; Glu, $NHCH(CH_2CH_2COOH)CO$, $C_5H_7O_3N$; peptide linkage indicated by dash, -; configuration follows compound in parentheses. When the γ-carboxyl group of glutamic acid is substituted, the substituent in the γ-position is indicated below the line: Glu; otherwise, a free γ-COOH group is implied, *e.g.*, α-L-glutamyl-D-glutamic acid: H·Glu-Glu·OH (LD); N-carbobenzyloxy-D-alanyl-α-benzyl γ-L-glutamyl-L-alanine; Z·Ala-Glu·OBz (DLL). [c] The stereoisomers gave almost identical amino N values (*cf.* ref. 9, 11).

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