Ω,Ω,Ω-Trifluoroamino Acids[1a]

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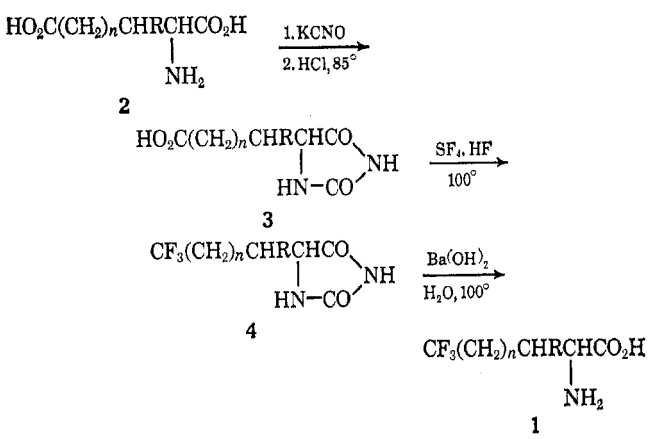
Received October 21, 1969

DL-5,5,5-Trifluoronorvaline and DL-4,4,4-trifluorovaline have been synthesized in three steps from readily available starting materials. In the preparation of these compounds, hydantoin intermediates have been shown to be chemically, but not optically, stable to sulfur tetrafluoride in liquid hydrogen fluoride.

The furtherance of certain laboratory objectives required a supply of DL-5,5,5-trifluoronorvaline (**1**, n = 1, R = H). A search of the literature revealed that this compound had been previously prepared[2] from trifluoroacetaldehyde and ethyl bromoacetate in seven steps and in an overall yield of 6%. For a shorter synthesis involving no shortening or lengthening of the carbon chain, glutamic acid (**2**, n = 1, R = H) appeared to be an ideal starting material. If the α-carboxyl group is protected, the γ-carboxyl group can be treated with sulfur tetrafluoride[3] to yield, after removal of the protecting group, 5,5,5-trifluoronorvaline (**1**, n = 1, R = H). Search for a protective group disclosed[3] esters and to a lesser extent amides. Application of the usual esterification processes to glutamic acid yields γ-hemiesters rather than α-hemiesters. The more circuitous methods by which α-hemiesters of glutamic acid are obtained would greatly decrease the attractiveness of our projected synthesis. A possible way around this difficulty involved use of the hydantoin[4] (**3**, n = 1, R = H), a cyclic imide which incorporated both the α-amino and the proximal carboxyl group. Use of the imide as a protective group would be novel. The projected synthesis is outlined below.



While the hydantoin ring was shown to be chemically stable under the reaction conditions, the product was largely racemized. By independent experiments L-5-hydantoin-β-propionic acid (**3**, n = 1, R = H) has been shown to lose 97% of its optical activity on exposure to anhydrous hydrogen fluoride at 100° for 3 hr and all optical activity on exposure to constant-boiling hydrochloric acid at 108° for 3 hr.

In contrast, Raasch[5] has shown that under similar reaction conditions, noncyclic amino acids retain some of their optical activity. He did not, however, provide an independent measure of or any proof of optical purity. The degree of retention of optical activity in his experiments cannot be stated with assurance, although it would appear to be high. Hydantoins can also racemize in basic media. West[6] has shown that L-5-hydantoin-β-propionic acid (**3**, n = 1, R = H), on treatment with strong base, loses optical activity (20% over a period of 6 hr at reflux in 0.5 *N* sodium hydroxide). L(Enriched)-5-(3′,3′,3′-trifluoropropyl)-hydantoin (**4**, n = 1, R = H) was racemized completely on hydrolysis with saturated barium hydroxide at reflux for 30 hr. Hydrolysis so vigorous as to liberate fluoride ion must be avoided. DL-5,5,5-Trifluoronorvaline (**1**, n = 1, R = H) was obtained in three steps in an overall yield of 50%.

Failure to obtain the physical constants reported by Dakin[4] for L-5-hydantoin-β-propionic acid has led to preparation of the compound optically pure and to improvements in the method for making it thus. Since, however, the end product of this work, 5,5,5-trifluoronorvaline, is racemic, there is no requirement for conservation of optical activity in any of the intermediates. Racemization can occur in each of the three steps and there is no preferred step for its occurrence.

To illustrate the versatility of this method, DL-4,4,4-trifluorovaline (**1**, n = 0, R = CH_3) was prepared starting from DL-*threo*-β-methylaspartic acid (**2**, n = 0, R = CH_3). From nuclear magnetic resonance spectra the *threo* configuration was preserved in synthesis of DL-5-hydantoin-α-propionic acid (**3**, n = 0, R = CH_3). In DL-5-(1′,1′,1′-trifluoro-2′-propyl)hydantoin (**4**, n = 0, R = CH_3) the *threo* to *erythro* ratio was at least 9:1, while in 4,4,4-trifluorovaline (**1**, n = 0, R = CH_3) the ratio had fallen to 3:1; hence epimerization was not serious until the final step. It is not known whether this is the equilibrium ratio. DL-4,4,4-Trifluorovaline (**1**, n = 0, R = CH_3) has been previously prepared[7,8a] by another method. Examination of these preparations by nuclear magnetic resonance shows them to be mixtures of *threo* and *erythro* isomers in the ratio of 2:1.

This consideration also applies to preparations of DL-5,5,5-trifluoroleucine,[8a–f] which are still unknown mixtures of *threo* and *erythro* isomers. Conclusions based on microorganism-feeding experiments, which

(1) (a) A portion of this paper was presented: 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969. (b) To whom inquiries should be addressed.

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employed such unknown mixtures, are not necessarily firm.

Our method promises to be useful in synthesizing other Ω,Ω,Ω-trifluoroamino acids. Aspartic acid (**1**, n = 0, R = H), α-aminoadipic acid (**1**, n = 2, R = H), and levulinic acid are available starting materials.

Experimental Section[9]

L-5-Hydantoin-β-propionic Acid.—By the method of Dakin,[4] L-5-hydantoin-β-propionic acid (**3**, n = 1, R = H), mp 179–181° (last traces melting at 184°), $[\alpha]^{22}D$ −66.8 ± 1.0° (*c* 2, H_2O), was obtained in 64.9% yield. This material was later shown to have an optical purity of 93.6% (the remaining 6.4% was racemic). A second crop, mp 155–160°, $[\alpha]^{22}D$ −25 ± 1° (*c* 2, H_2O), amounted to 24.9%. Dakin's material, mp 179–181°, $[\alpha]D$ −50° (*c* 2, H_2O), 85.5% yield, had an optical purity of 70%.

The following modification of Dakin's method yields a product of higher optical purity. To a slurry of 100 g (0.680 mol) of glutamic acid, mp 205° dec, $[\alpha]^{22}D$ 30.9 ± 1.0° (*c* 1, 6 *N* HCl), purity by phase solubility 100.0%, in 340 ml of water at 80° was added with warming and stirring 36.7 ml of 11.7 *N* sodium hydroxide to bring the pH to 6.0 (5.5 would be slightly better). Addition of 68 g (0.839 mol) of potassium cyanate increased the pH to 7.5. The mixture was stirred and maintained at 85° for 1 hr while 16 ml of concentrated hydrochloric acid was added in portions to maintain the pH at 7.0. During this heating the mixture becomes a solution. Concentrated hydrochloric acid was added to pH 3.5, and then an additional 86 ml was added for a total of 179 ml. The mixture was maintained at 85° for 2 hr, allowed to cool to room temperature, and aged for 18 hr. After filtration, washing with three 35-ml portions of cold water, and drying, the product, mp 182–184°, $[\alpha]^{22}D$ −68.2 ± 1.0° (*c* 2, H_2O), optical purity 96%, amounted to 96.4 g (82.3%).

One recrystallization from water gave an optically pure product, mp 184–186°, $[\alpha]^{22}D$ −71.4 ± 1.0° (*c* 2, H_2O), 68.7% recovery, 56.2% yield. A second recrystallization with 92.0% recovery showed no change in physical properties: mp 185° (DTA); equiv wt, 174 (theory 172.15); $\lambda_{max}^{CH_3OH + base}$ 226 mμ (log ε 3.7); purity by phase solubility 99.5 ± 0.5%; ir (Nujol) 3000–3200, 3300 (NH), 1660–1720, and 1740 (sh) cm^{-1} (C=O).

Anal. Calcd for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.28. Found: C, 42.07; H, 4.62; N, 16.14.

In an autoclave 5.0 g of L-5-hydantoin-β-propionic acid, $[\alpha]^{22}D$ −71.4 ± 1.0° (*c* 2, H_2O), and 10 ml of liquid hydrogen fluoride were maintained at 100° for 3 hr. The mixture was cooled to room temperature, poured into a polyethylene beaker, evaporated in a current of air, and finally dried over solid potassium hydroxide in a plastic desiccator. The recovery of hydantoin, mp 164–167° (lit.[4] mp 167–169°), $[\alpha]^{22}D$ −2.3 ± 1.0° (*c* 2, H_2O), was quantitative and the racemization was 97% complete.

Refluxing 5-hydantoin-β-propionic acid, $[\alpha]^{22}D$ −71.4 ± 1.0° (*c* 2, H_2O), in constant-boiling hydrochloric acid (108°) for 3 hr yielded a product, mp 153–160°, racemic at all wavelengths. One recrystallization from water with 85% recovery yielded racemic material, mp 167–170° (lit.[4] mp 167–169°).

L-5-(3′,3′,3′-Trifluoropropyl)hydantoin and the DL Compound.—To 63.0 g (0.366 mol) of L-5-hydantoin-β-propionic acid (**3**, n = 1, R = H), $[\alpha]^{22}D$ −66.8 ± 1.0° (*c* 2, H_2O), was added 50 ml of anhydrous liquid hydrogen fluoride and 119 g (1.1 mol) of sulfur tetrafluoride. The mixture was heated in a bomb for 3 hr at 100°, cooled to room temperature, vented, and emptied into a polyethylene beaker. The mixture was poured with stirring into a slurry of 150 g of sodium carbonate in 1 l. of water. Care was taken to keep the reaction mixture mildly alkaline. The mixture was extracted with 500-ml and 250-ml portions of ethyl acetate, the extract was filtered through Super-Cel to remove a small amount of black solid, and the filtrate was dried over anhydrous magnesium sulfate. Concentration of dryness yielded 63.9 g (89.0%) of crude product, mp 126–130°, $[\alpha]^{25}D$ −2.7 ± 1.0° (*c* 1, CH_3OH), suitable for the next step.

One recrystallization from methanol and one from acetone–benzene yielded L-5-(3′,3′,3′-trifluoropropyl)hydantoin (1.15% based on the crude product) (**4**, n = 1, R = H) as white clusters of needles, mp 138–141°, ir spectrum consistent with proposed structure, $[\alpha]^{22}D$ −25.8 ± 1.0° (*c* 1, CH_3OH). Another recrystallization from acetone–benzene showed no change in physical properties.

Anal. Calcd for $C_6H_7F_3N_2O_2$: C, 36.74; H, 3.60; N, 14.28; F, 29.06. Found: C, 37.65; H, 3.50; N, 14.21; F, 29.3.

In a similar experiment racemic starting material yielded DL-5-(3′,3′,3′-trifluoropropyl)hydantoin as white scales, mp 136–137°, inactive at all wavelengths (*c* 1, CH_3OH).

Anal. Found: C, 36.72; H, 3.72; N, 14.49; F, 29.3.

Walborsky, *et al.*,[2] prepared the racemic compound by another route but did not characterize it other than to hydrolyze it to DL-5,5,5-trifluoronorvaline.

DL-5,5,5-Trifluoronorvaline.—To 325 ml of water were added 16.0 g (0.0817 mol) of DL- and L-5-(3′,3′,3′-trifluoropropyl)-hydantoin, $[\alpha]^{25}D$ −2.7 ± 1.0° (*c* 1, CH_3OH), and 80 g of barium hydroxide octahydrate. The mixture was refluxed under nitrogen for 30 hr. After cooling to 50°, the mixture was filtered through Super-Cel and the cake was washed with hot water. Gaseous carbon dioxide was passed into the filtrate to precipitate barium ion. The warm mixture was filtered through Super-Cel and the filtrate was brought to pH 6 by dropwise addition of 50% sulfuric acid. The mixture was warmed with 1 g of Nuchar C 1000N, filtered, washed, and concentrated *in vacuo* until the mixture began to deposit crystals. This mixture was warmed at atmospheric pressure to dissolve solid product and set aside to cool slowly overnight. After filtration, washing with water, and drying, DL-5,5,5-trifluoronorvaline (**1**, n = 1, R = H), 6.30 g (45.1%), was obtained as white, electrostatic, crystalline scales, mp 270–272° dec, ir and nmr spectra consistent with proposed structure, inactive at all wavelengths (*c* 1, 6 *N* HCl).

Anal. Calcd for $C_5H_8F_3NO_2$: C, 35.09; H, 4.71; N, 8.18; F, 33.3. Found: C, 35.14; H, 4.94; N, 8.13; F, 32.4.

Concentration of the aqueous mother liquors yielded a second crop, 2.45 g (17.5%), mp 271° dec. The isolated yield in two crops was 62.6%. From glutamic acid the overall yield in three steps was 50.0%.

Anal. Found: C, 34.66; H, 4.69; N, 8.06; F, 34.1.

Walborsky, *et al.*,[2] obtained the compound and characterized it by analysis, paper chromatography, and melting point (258° dec). They report 30% yield overall for the conversion of 4,4,4-trifluorobutyraldehyde into DL-5,5,5-trifluoronorvaline *via* the hydantoin.

DL-*threo*-5-Hydantoin-α-propionic Acid.—By the method of Dakin,[4] DL-*threo*-5-hydantoin-α-propionic acid (**3**, n = 0, R = CH_3), mp 206–208°, ir and nmr spectra consistent with proposed structure, was prepared from DL-*threo*-β-methylaspartic acid (**2**, n = 0, R = CH_3), in 60% yield. The ir and nmr spectra of starting material were compared with those of a sample of DL-*erythro*-β-methylaspartic acid.[10]

Anal. Calcd for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.28; O, 37.17. Found: C, 41.98; H, 4.56; N, 15.98; O, 37.1.

DL-*threo*-5-(1′,1′,1′-Trifluoro-2′-propyl)hydantoin.—By the method previously described, DL-*threo*-5-(1′,1′,1′-trifluoro-2′-propyl)hydantoin (**4**, n = 0, R = CH_3), mp 211.5–213°, was obtained in 32% yield. The ir spectrum was consistent with the proposed structure and the nmr spectrum was consistent but suggested at least a 9:1 mixture of *threo* and *erythro* isomers, respectively.

Anal. Calcd for $C_6H_7F_3N_2O_2$: C, 36.74; H, 3.60; N, 14.28; F, 29.06. Found: C, 37.19; H, 3.56; N, 14.08; F, 26.9.

DL-4,4,4-Trifluorovaline.—To 162 ml of water in a stainless steel flask were added 8.0 g (0.0408 mol) of DL-*threo*-5-(1′,1′,1′-trifluoro-2′-propyl)hydantoin (**4**, n = 0, R = CH_3) and 40 g of barium hydroxide octahydrate. The mixture was refluxed under nitrogen for 22 hr. Without cooling the mixture was filtered and the cake was washed with hot water. The combined filtrates were titrated to pH 5 with dilute sulfuric acid and filtered through Super-Cel. The filtrate was concentrated at or below room temperature *in vacuo* until the first precipitate appeared. The mixture was chilled overnight in the refrigerator at 5° to yield 0.1 g of DL-N-carbamyl-4,4,4-trifluorovaline, mp 196° dec, ir spectrum consistent with the proposed structure and nmr spectrum consistent but suggesting a 3:1 mixture of *threo* and *erythro* isomers, respectively.

Anal. Calcd for $C_6H_9F_3N_2O_3$: C, 33.68; H, 4.24; N, 13.08; F, 26.68. Found: C, 33.88; H, 4.12; N, 13.00; F, 25.67.

(9) Melting points were taken with total immersion thermometers and are uncorrected. Rotations were measured on a Zeiss polarimeter, while nmr spectra were obtained on a Varian 60-MHz spectrometer.

(10) Kindly supplied by Professor H. A. Barker.

After removal of the hydantoic acid by-product, the filtrate was concentrated to a slurry, diluted with methanol, and filtered to yield 2.45 g (26.8%) of 4,4,4-trifluorovaline (1, n = 0, R = CH_3), mp 252° dec, ir spectrum consistent with the proposed structure and nmr spectrum consistent but suggesting a 3:1 mixture of *threo* and *erythro* isomers, respectively.

Anal. Calcd for $C_5H_8F_3NO_2$: C, 35.06; H, 4.70; N, 8.18; F, 33.3. Found: C, 35.02; H, 4.75; N, 7.92; F, 34.4.

A sample of DL-4,4,4-trifluorovaline,[11] mp 248° dec, prepared by Loncrini and Walborsky,[7] was by nmr spectrum a 2:1 mixture of *threo* and *erythro* isomers, respectively. Another sample,[12] mp 239° dec, prepared by Lazar and Sheppard,[8a] was by nmr spectrum the same 2:1 mixture. The above-reported decomposition points were verified in our laboratory. The position of the α-H doublet center is pH dependent, but the relative chemical shift, *threo* to *erythro*, is τ 0.22, while that for the methyl doublet, *threo* to *erythro*, is τ −0.17. The infrared spectra of these two samples, despite the difference in decomposition point, were identical and differed only slightly in relative intensities between 650 and 950 cm^{-1} from that of the 3:1 mixture of *threo* and *erythro* isomers.

(11) Kindly supplied by Dr. D. F. Loncrini. In a personal communication he states that the melting point in ref 8a should be corrected to the one given above.

(12) Kindly supplied by Dr. J. Lazar.

Registry No.—**1** (n = 1, R = H), 23809-57-6; **1** (n = 0, R = Me) (*threo*), 23809-58-7; **1** (n = 0, R = Me) (*erythro*), 23796-83-0; **3** (n = 1, R = H), 17027-50-8; **3** (n = 0, R = Me), 23809-60-1; **4** (n = 1, R = H), 23809-61-2; **4** (n = 0, R = Me), 23809-62-3; DL-5-(3′,3′,3′-trifluoropropyl)hydantoin, 23809-63-4; DL-*threo*-N-carbamyl-4,4,4-trifluorovaline, 23809-64-5; DL-*erythro*-N-carbamyl-4,4,4-trifluorovaline, 23809-65-6.

Acknowledgment.—The authors are indebted to Dr. J. M. Chemerda and Dr. J. van de Kamp for encouragement and valued advice, to Mr. R. N. Boos and associates for microanalytical data, and to Mr. R. W. Walker and Dr. B. H. Arison for instrumental assistance.

Synthesis and Application in Peptide Chemistry of Amino Acids Possessing an Optically Active Selenohomocysteine Skeleton[1a-c]

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Received October 6, 1969

The general and convenient method developed earlier in these laboratories to replace the O-tosyl moiety by selenium nucleophiles has been extended to O-tosylated homoserine derivatives and has resulted in the preparation of L-selenomethionine (**17**), L-selenoethionine (**20**), Se-benzyl-L-selenohomocysteine (**10**), and L-(+)-selenocystathionine (**23**). The specific optical rotations of **10**, **17**, and **20** were found to be higher than reported earlier for these compounds. The use of the derivatives of the foregoing selenium-containing amino acids in the synthesis of peptides was demonstrated in the case of Se-benzyl-L-selenohomocysteine. During decarbobenzoxylation of N-carbobenzoxy-L-selenomethionine and N-carbobenzoxy-L-selenoethionine with hydrogen bromide, the attack by the benzyl bromide on the selenium, which results in the displacement of the methyl or ethyl group, was prevented by the addition of the highly nucleophilic β-mercaptoethanol.

With the displacement of the O-tosyl moiety by selenium nucleophiles we introduced a general and convenient method for the preparation of selenocysteine and selenocystine derivatives which bear readily and selectively removable protecting groups[2-4] and which therefore fulfill all the prerequisites for incorporation into peptides—even those of more complex structures.[5-7] This method should also provide a versatile pathway for the synthesis of derivatives of selenohomocysteine and of amino acids possessing a selenohomocysteine skeleton as long as appropriately protected O-tosyl homoserine derivatives can be secured.

In our initial experiments we attempted to apply a synthetic route which had been successful for the conversion of L-serine into L-selenocysteine, *i.e.*, the use of O-tosylated N-carbobenzoxy-L-serine esterified with benzhydrol.[2] However, when DL-homoserine was carbobenzoxylated according to Flavin and Slaughter[8] and then allowed to react with diphenyldiazomethane,[9] the sole product was the γ-lactone of DL-N-carbobenzoxyhomoserine.[10] This result was not quite unexpected in view of the extensive lactone formation encountered when amino acids possessing a free γ-hydroxyl function are prepared, derivatized, or employed for peptide synthesis.[8,11-15] In fact, the ready formation of the γ-lactone is the basis for the selective, nonenzymatic cleavage of the peptide chain at amino acid residues which are convertible into γ-hydroxyamino acid resi-

(1) (a) This work was supported by U. S. Public Health Service Grants AM-11580 and AM-10080 and by the U. S. Atomic Energy Commission. One of us (J. R.) was a recipient of a Career Scientist Award from the New York Health Research Council (I-541). (b) Part of this work was presented before The First American Peptide Symposium, Yale University, New Haven, Conn., Aug 1968. (c) The following abbreviations have been used: Z, carbobenzoxy; Tos, *p*-toluenesulfonyl; Bzl, benzyl; DPM, diphenylmethyl; BZLN, *p*-nitrobenzyl; AcOH, acetic acid; DMF, dimethylformamide; TosBZLN, *p*-nitrobenzyl *p*-toluenesulfonate; MeOH, methanol. (d) To whom correspondence should be addressed: Department of Physiology, Mount Sinai School of Medicine of The City University of New York, 10 East 102nd St., New York, N. Y. 10029.

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