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ALPHA-AMINO ACIDS CONTAINING ALPHA, FLUORINATED-ALKYL OR CYCLOALKYL GROUPS

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This invention relates to fluorine-containing organic compounds and, more particularly, to a new class of fluorosubstituted amino acids.

Fluorosubstituted aromatic aminocarboxylic acids have been known heretofore. In these acids such as the fluorophenylalanines and fluorotryptophane, the aromatic nuclei are fluorosubstituted. However, no recorded example of either a fluorosubstituted aliphatic or cycloaliphatic aminocarboxylic acid is known.

An object of the present invention is to provide a new class of fluorine-containing organic compounds. A further object is to provide a new class of fluorosubstituted aliphatic or cycloaliphatic aminocarboxylic acids. A more specific object is to provide new compounds of value in the important insecticide and fungicide field. Other objects will be apparent from the description of the invention given hereinafter.

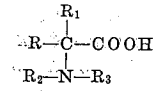
The above objects are accomplished according to the present invention by the preparation of aminocarboxylic acids wherein a carbon alpha to a carboxyl carries an amino group and either a fluorosubstituted aliphatic or cycloaliphatic radical. Because of their ease of synthesis, reactivity, and biological activity, the preferred group of these compounds are the alpha-monoaminomonocarboxylic acids wherein the carbon alpha to the carboxyl carries a fluorosubstituted aliphatic or cycloaliphatic radical, particularly those where the alpha-amino group is primary.

Within the above preferred group of these new compounds are certain compounds that are outstanding because of their high physiological activity, for instance, as curative fungicides and systemic aphicides. These are the fluorosubstituted, saturated straight chain aliphatic alpha-monoaminomonocarboxylic acids wherein the carbon alpha to the carboxyl carries a single hydrogen and the fluorine atoms are located on odd numbered carbons of the carbon chain, especially those acids in which the carbon chain contains an odd number of carbons and the terminal carbon carries a fluorine atom. From the standpoint of ease of synthesis and high physiological activity, such acids having only a single fluorine substituent and that on the terminal carbon of the carbon chain, the alpha-amino group being primary and, preferably, the carbon chain containing not more than 7 carbons, i. e.,

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the straight chain aliphatic radical attached to the carbon alpha to the carboxyl containing not more than 5 carbons, are of great value.

The fluorosubstituted amino acids of this invention have the structural formula



wherein R is a fluorosubstituted aliphatic or cycloaliphatic hydrocarbon radical of no more than 18 carbons and, preferably, no more than 7 carbons; R_1 is H, R, or an aliphatic or cycloaliphatic hydrocarbon radical of no more than 18 carbons and, preferably, no more than 7 carbons; and R_2 and R_3 which can be alike or different, are H or aliphatic or cycloaliphatic hydrocarbon radicals of no more than 18 carbons and, preferably, no more than 7 carbons each. Because of their greater physiological activity, the preferred amino acids of this invention are those of the above type structural formula wherein R is a fluorosubstituted, particularly a monofluorosubstituted, saturated straight chain aliphatic hydrocarbon radical wherein the fluorine substituents are on odd numbered carbons and R_1, R_2, and R_3 are all hydrogen. Because of the readier availability of their intermediates the amino acids of the above type bearing a saturated aliphatic hydrocarbon radical containing an odd number of carbons, but no more than 5, linearly arranged and possessing a single terminal fluorine atom, are especially preferred.

In general, the solubility of these compounds in aqueous solutions can be increased through salt formation involving either the amino or carboxyl groups. When R_2 and R_3 are not hydrogen, quaternary betaine salts may be formed. The activity of these compounds is not limited, however, to the water-soluble forms since the copper salt of delta-fluoronorvaline is also an effective fungicide. These various salts are well recognized in the organic chemical art as close chemical equivalents to the free amino carboxylic acids and are considered part of this invention.

The compounds of this invention can be prepared by type reactions well known in the art from a wide selection of known fluorosubstituted intermediates. They can be prepared by direct amination with ammonia or the requisite amine

of the corresponding alpha-chloro or bromocarboxylic acids. Alternately, they can be prepared by the Bucherer et al. hydantoin route or the Strecker aminonitrile method from the requisite aldehydes or ketones. The former route is preferred because of higher yields and greater reaction efficiency. Further, the fluorosubstituted amino acids of this invention can be prepared by the condensation of the requisite fluorosubstituted aliphatic or cycloaliphatic bromide or chloride with the sodio derivative of acetamidomalonic ester, phthalimidomalonic ester, or acetamidocyanoacetic ester and subsequent hydrolysis of the intermediate obtained. A still further route involves the condensation of the requisite fluorosubstituted aldehydes or ketones with hydantoin followed by reduction and hydroylsis.

The following examples in which all proportions are by weight unless otherwise stated, illustrate the preparation and certain properties of specific compounds of this invention.

EXAMPLE I

Part A.—Preparation of ethyl acetamido(2-fluoroethyl) malonate

To a solution of 15.8 parts of sodium in about 550 parts of absolute ethyl alcohol was added 149 parts of ethyl acetamidomalonate and 87 parts of 1-bromo-2-fluoropropane (see Hoffmann, J. Org. Chem. 15, 425 (1950)) and the resulting mixture was heated at the reflux for 15 hours. The white, solid precipitate of sodium bromide was removed from the resulting reaction mixture by filtration, the filtrate evaporated to dryness, and the solid residue remaining washed with water. The crude ethyl acetamido(2-fluoroethyl) malonate thereby obtained was recrystallized from warm 2–B ethyl alcohol to give 62 parts in 3 crops of white crystals, melting at 74–76° C.

Anal.—Calc'd for $C_{11}H_{18}NO_5F$: F, 7.22%; N, 5.32%
Found: F, 7.4%; N, 5.25%
7.6%; 5.23%

Part B.—Preparation of DL-gamma-fluoro-alpha-aminobutyric acid

A solution of 10 grams of the above ethyl acetamido-(2-fluoroethyl) malonate in about 60 parts of water containing about 7.5 parts of concentrated sulfuric acid was refluxed for 15 hours. At the end of this time the sulfuric acid was neutralized by adding an equivalent amount of barium hydroxide (about 24.5 parts) in the form of a hot aqueous solution. The resulting precipitate of barium sulfate was removed by filtration and the aqueous filtrate concentrated by evaporation under reduced pressure. Upon the addition of excess 2–B alcohol, there was obtained a precipitate of a mixture of approximately equal parts of gamma-fluoro-alpha-aminobutyric acid and gamma-hydroxy-alpha-aminobutyric acid. The fluoro acid can be separated from the hydroxy acid by fractional crystallization from mixtures of ethanol and water.

EXAMPLE II

Part A.—Preparation of ethyl acetamido(3-fluoropropyl) malonate

To a solution of 23 parts of sodium in about 800 parts of absolute ethyl alcohol was added 217 parts of ethyl acetamidomalonate and 141 parts of 1-bromo-3-fluoropropane (Hoffmann, loc. cit.). The resulting mixture was heated at the reflux for 15 hours and the white precipitate of sodium bromide removed by filtration. Upon evaporation of the filtrate, a white crystalline mass was obtained. After washing with water and recrystallization from 2–B alcohol, there was thus obtained 174 parts (63% yield) of ethyl acetamido(3-fluoropropyl) malonate in 3 crops as white crystals, melting at 76–77° C.

Anal.—Calc'd for $C_{12}H_{20}NO_5F$: F, 6.85%; N, 5.05%
Found: F, 6.7%; N, 5.00%
7.0%; 5.03%

Part B.—Preparation of delta-fluoronorvaline

A mixture of 140 parts of the above ethyl acetamido(3-fluoropropyl) malonate, 325 parts of 48% hydrofluoric acid, and 100 parts of water were charged into a pressure-resistant vessel, the vessel then sealed, and the contents heated for 5 hours at 105–112° C. At the end of this reaction period, the reactor was cooled in an ice-water bath, opened, and solid calcium hydroxide added in portions to bring the pH of the reaction mixture to 3.5 (about 300 parts required). The resulting precipitate of calcium fluoride was removed by filtration and washed with water. The aqueous filtrate was then evaporated to dryness under reduced pressure, and the solid residue thereby obtained extracted with excess 2–B alcohol. Upon recrystallization of the alcohol insoluble residue from an ethanol/water mixture, there was obtained 18.5 parts (27% yield) of delta-fluoronorvaline as resplendent plates melting at 190° C.

Anal.—Calc'd for $C_5H_{10}NO_2F$: F, 14.1%; N, 10.4%
Found: F, 14.0%; N, 10.2%
14.2%; 10.1%

Aqueous solutions of delta-fluoronorvaline at concentrations of 0.1 and 0.02% in a regular greenhouse preventive fungicide test were sprayed on bean plants and, 24 hours after spraying the plants, were inoculated with bean rust (*Uromyces appendiculatus*). Control plants which were not sprayed were treated similarly under the same conditions. Seven days after inoculation the sprayed plants exhibited no rust whatever whereas the control plants were heavily covered with rust pustules. The sprayed plants were reinoculated with bean rust and after eight additional days the plants sprayed with the 0.1% delta-fluoronorvaline solution exhibited no rust whatever on either the primary, or new, secondary leaves. The plants sprayed with the less concentrated solution exhibited a small amount of rust on the new, secondary leaves, but none on the primary leaves. These results show the activity of this material as a systemic fungicide and, as applied here in a foliar spray, demonstrate that it is translocated to other parts of the plant and protects new growth. These results also suggest that the delta-fluoronorvaline acts as a curative fungicide killing established infections at least in the earlier stages.

The same plants were again reinoculated and after six additional days the plants sprayed with the less concentrated solution exhibited some rust on the older, secondary leaves, but less than half the amount developing on the control plants and none on the younger, secondary leaves. The plants sprayed with the more concentrated solution exhibited only about 25% (based on the controls) disease on the older secondary leaves and none on the younger secondary leaves. These results show that delta-fluoronorvaline, as applied here in a foliar spray, continues to move, i. e., is translocated in the plant to the younger

portions and provides protection to the new growth. It is to be noted that this protection as described above is effective over a period of 21 days, and presumably longer, even in the face of three inoculations with the disease. The control plants were heavily infected during and at the end of the test.

To demonstrate the efficacy of delta-fluoronorvaline as a curative fungicide, Pinto variety bean plants were inoculated with a spore suspension of bean rust and the plants placed in a humidity chamber to permit infection to develop. Twenty-four and 48 hours after inoculation, duplicate sets of the plants were sprayed with an aqueous 0.2% solution of delta-fluoronorvaline. Nine days after inoculation the treated plants in both sets exhibited no rust whatever; whereas, both sets of unsprayed, inoculated controls were heavily infected. These results demonstrated that delta-fluoronorvaline functions as a curative fungicide. In contrast, under like conditions, plants sprayed and inoculated with 0.2% aqueous solutions of the closely related compound DL-norvaline exhibited 89% and 88% infection based on the control plants, rated as 100%. To further demonstrate the systemic action of delta-fluoronorvaline, the above described sets of plants were reinoculated with bean rust. After seven additional days the delta-fluoronorvaline sprayed plants exhibited a very small amount of rust on the primary leaves, but none on the secondary leaves, with no noticeable plant injury. In contrast, the control plants were heavily infected.

Further demonstrations of the outstanding efficiency of delta-fluoronorvaline as a curative fungicide were obtained by spraying similar sets of Pinto bean test plants with aqueous 0.1% solutions of the compound, 24 and 48 hours after inoculations with bean rust. Complete control of the disease was obtained in both sets. This performance, in so far as known published data reveals, is unique among known fungicides.

In a regular screening test for aphicidal activity delta-fluoronorvaline was found to be a highly effective material for controlling these insects. In particular, when petioles of excised nasturtium leaves infected with aphids were immersed in aqueous solutions of delta-fluoronorvaline even at concentrations as low as 0.01 to 0.05% by weight, the compound was translocated rapidly through the vascular system of the leaf and led to essentially a complete kill of the aphids sucking the plant sap. The high systemic insecticidal activity of delta-fluoronorvaline is also demonstrated in aqueous sprays applied to the intact leaf surface or through the roots. Thus, delta-fluoronorvaline is an extremely effective systemic insecticide when sprayed on the plants or applied to the soil in which the plant is growing. In similar tests closely related DL-norvaline was ineffective.

The copper salt of delta-fluoronorvaline is also an effective fungicide. It is nearly insoluble in water and may be applied in aqueous suspension or as a dust.

EXAMPLE III

Part A.—Preparation of ethyl acetamido (4-fluorobutyl)-malonate

To a solution of 18.6 parts of sodium, dissolved in about 630 parts of absolute ethyl alcohol, was added 175 parts of ethyl acetamidomalonate and 128 parts of 1-bromo-4-fluorobutane (Hoffmann, loc. cit.). The resulting mixture was heated at the reflux for 15 hours and the precipitated sodium bromide removed by filtration. After removing the alcohol from the resulting filtrate by evaporation, there was obtained a crude syrup of 210 parts (90% of theory) of ethyl acetamido (4-fluorobutyl) malonate.

Part B.—Preparation of epsilon-fluoronorleucine

A reactor was charged with 180 parts of the above crude ethyl acetamido(4-fluorobutyl) malonate and 360 parts of 48% hydrofluoric acid and the reaction mixture heated on a steam bath for 15 hours. The resulting solution was then cooled to room temperature, diluted with 1500 parts of water, and neutralized to pH 6 by the addition of solid calcium hydroxide (about 340–350 parts required). The precipitated calcium fluoride was removed by filtration, washed with water, and the aqueous filtrate then evaporated to dryness. The crude solid epsilon-fluoronorleucine thus obtained was dissolved in excess water and heated with 70 parts of basic copper carbonate to convert it to its sparingly soluble copper salt, which was removed by filtration, washed with water, and subsequently decomposed in aqueous suspension with gaseous hydrogen sulfide. The precipitated copper sulfide was then removed by filtration and the aqueous filtrate evaporated to dryness. Upon recrystallization of the solid residue thereby obtained from ethanol/water mixture, there was obtained 50.6 parts (55% of theory) of epsilon-fluoronorleucine as white crystals, melting at 144° C.

Anal.—Calc'd for $C_6H_{12}NO_2F$: F, 12.7%; N, 9.39%
Found: F, 12.1%; N, 9.14%
9.11%

EXAMPLE IV

Part A.—Preparation of 5-methyl-5-trifluoromethylhydantoin

To a solution of 11.2 parts of 1,1,1-trifluoroacetone in an ice cold mixture of about 24 parts of 2-B alcohol and 20 parts of water in a reaction flask, fitted with a reflux condenser (jacket temperature, 7° C.), was added 23 parts of solid ammonium carbonate and a solution of 5.6 parts of sodium cyanide in 15 parts of water. The reaction solution was heated at 50–60° C. for 1.5 hours and the solvents removed by evaporation under reduced pressure. The resulting residue was taken up in water and the solution neutralized to pH 4 with aqueous 10% hydrochloric acid in a hood to avoid possible fumes of HCN. The solution thereby obtained was then extracted three times with excess diethyl ether. Upon evaporation of the ether extracts to dryness, there was obtained 6.1 parts of crude, crystalline product from which by recrystallization from water, there was obtained 4.2 parts (23% yield) of 5-methyl-5-trifluoromethylhydantoin as white crystals, melting at 137° C.

Anal.—Calc'd for $C_5H_5N_2O_2F_3$: F, 31.3%; N, 15.4%
Found: F, 30.5%; N, 15.4%
29.9%; 15.3%

Part B.—Preparation of alpha-amino-beta, beta, beta-trifluoroisobutyric acid

A mixture of 10 parts of the above 5-methyl-5-trifluoromethylhydantoin and about 38 parts of 60% aqueous sulfuric acid were heated at the reflux for 48 hours. The unreacted sulfuric acid was then removed by treatment with a hot aqueous 10% solution of barium hydroxide until no further precipitate formed. The precipitated barium sulfate was removed by filtration and the

filtrate concentrated to small volume. Excess basic copper carbonate (8 parts) was then added to the concentrate and the resulting mixture heated to form the sparingly soluble copper salt of alpha-amino-beta,beta,beta-trifluoroisobutyric acid. The reaction mixture was then cooled and the insoluble copper salt removed by filtration, washed with cold water, and then suspended in water, and finally decomposed with gaseous hydrogen sulfide. The precipitated copper sulfide was removed by filtration and the aqueous filtrate evaporated to dryness to yield 6.6 parts of crude, solid product. Upon recrystallization from 2-B alcohol, there was obtained 5.0 parts (58% yield) of pure alpha-amino-beta,beta,beta-trifluoroisobutyric acid as white crystals which sublime rapidly at 250–300° C.

Anal.—Calc'd for $C_4H_6NO_2F_3$: F, 36.3%; N, 8.92%
Found: F, 35.5%; N, 8.87%
35.0%; 8.83%

EXAMPLE V

Part A.—Preparation of 5-(2,2,3,3-tetrafluoro-1-methylcyclobutyl) hydantoin

To a solution of 85 parts of 1-formyl-1-methyl-2,2,3,3-tetrafluorocyclobutane (see Coffman, Barrick, Cramer and Raasch, J. Am. Chem. Soc. 71, 494 (1949)) in about 118 parts of 2-B alcohol and 100 parts of water, was added 114 parts of solid ammonium carbonate followed by a solution of 28 parts of sodium cyanide in 75 parts of water over a period of 20 minutes. The reaction mixture was stirred at 56–61° C. for 2 hours and then evaporated on a steam bath to semi-dryness. The solid obtained was neutralized to pH 4 with aqueous 10% hydrochloric acid in a hood and the white crystalline product removed by filtration and washed with water. Upon recrystallization of the product from 2-B alcohol, there was obtained 59 parts (49% yield) of 5-(2,2,3,3-tetrafluoro-1-methylcyclobutyl) hydantoin as white crystals, melting at 241–243° C.

Anal.—Calc'd for $C_8H_8N_2O_2F_4$: N, 11.7%.
Found: N, 11.1%.

Part B.—Preparation of alpha-amino-2,2,3,3-tetrafluoro-1-methylcyclobutaneacetic acid

A mixture of 50 parts of the above 5-(2,2,3,3-tetrafluoro - 1 - methylcyclobutyl) hydantoin and 200 parts of aqueous 60% sulfuric acid was heated at the reflux for 64 hours. The resulting solution was then diluted to a total volume corresponding to 700 parts of water, the solid removed by filtration, and the pH of the filtrate adjusted to 6.4 with aqueous ammonium hydroxide. On standing, 20 parts of alpha-amino-2,2,3,3-tetrafluoro-1-methylcyclobutaneacetic acid crystallized out and an additional 18.5 parts of the product was obtained on concentrating the aqueous filtrate. The total yield (38.5 parts) represents 68% of theory.

Anal.—Calc'd for $C_7H_9NO_2F_4$:
F, 35.3%; C, 39.1%; H, 4.22%
Found: F, 34.9%; C, 38.9%; H, 4.45%
34.7%; 38.5%; 4.24%

It will be understood the above examples are merely illustrative and that the invention broadly comprises that class of aminocarboxylic acids wherein a carbon alpha to a carboxyl carries an amino group and either a fluorosubstituted aliphatic or cycloaliphatic radical.

Preparation of compounds of the present invention other than those in the examples can be effected by the Strecker type synthesis, or, preferably, the Bucherer et al. modification thereof. Thus, delta,delta,delta-trifluoronorvaline can be prepared from gamma,gamma,gamma-trifluorobutyraldehyde; delta,delta,delta-trifluoro-alpha-(3,3,3-trifluoropropyl) norvaline from 1,1,1,7,7,7-hexafluoro - 4 - heptanone; delta,delta,delta-trifluoro - gamma - trifluoromethylnorvaline from 1,1,1,5,5,5-hexafluoro-2-pentanone; alpha-aminohexafluoroisobutyric acid from hexafluoroacetone; and alpha-amino-beta,beta-difluoroisobutyric acid from 1,1-difluoroacetone. The condensation of a fluorosubstituted aliphatic or cycloaliphatic bromide or chloride with the sodio derivative of the above mentioned type esters, followed by hydrolysis, can be used to prepare delta,delta-difluoronorvaline from 1-bromo-3,3-difluoropropane; gamma-fluoronorvaline from 1-bromo-2 - fluoropropane; alpha-amino-gamma, gamma-difluorobutyric acid from 1-bromo-2,2-difluoroethane; and epsilon,epsilon,epsilon-trifluoronorleucine from 1-bromo-4,4,4-trifluorobutane. The aldehyde condensation with hydantoin route, for example, can be used to prepare epsilon,epsilon,epsilon - trifluoronorleucine from gamma,gamma,gamma-trifluorobutyraldehyde.

As mentioned previously, the preferred fluorosubstituted aliphatic alpha-aminocarboxylic acids of this invention, including the metal, e. g., the alkali metal and alkaline metal earth, salts through the carboxylic acid group and the hydrohalic acid salts through the amino group, are outstanding because of their particularly good physiological activity. These compounds are useful as curative fungicides, systemic aphicides, rodent poisons, and the like. These compounds exhibit the important, and thus far not completely understood, property of being translocated in plants; for instance, when applied externally to plant systems, i. e., as a soil spray or a soil additive in concentrations as low as 0.02%, the compounds are absorbed into the plant system, translocated throughout to the stems and leaf systems and render the thus treated plants resistant to fungi and aphids, without causing any noticeable plant injury.

Such properties obviously are of extreme importance since they permit easy pretreatment of soil prior to planting or seeding and render the plants grown in such soils resistant to fungi and aphids, and thus obviate the necessity of constant spraying of the growing plant to prevent such infections. This latter traditional route for protecting growing plants against fungi and aphids is obviously more cumbersome, more time consuming, and less efficient. Using the traditional plant spray technique, constant spraying on a regular schedule must be practiced. Using the preferred amino acids of this invention as pre-treating agents for the soil leads to the production of plants, resistant to these invading organisms with no further treatment.

The fluorosubstituted aliphatic and cycloaliphatic aminocarboxylic acids of this invention are also useful as intermediates in the preparation of low molecular weight synthetic polypeptides which again are of utility as physiologically active compounds and also in the preparation of high molecular weight film- and fiber-forming amino acid polymers, for instance, as obtained through the N-carboanhydride route explained in greater detail in U. S. Patents 2,534,283; 2,572,843; 2,572,844; and 2,592,447.

As many apparently widely different embodiments of this invention may be made without

departing from the spirit and scope thereof, it is to be understood that the invention is not limited to the specific embodiments thereof except as defined in the appended claims.

The invention claimed is:

1. An aminocarboxylic acid wherein a carbon alpha to a carboxyl carries an amino group and a radical from the group consisting of fluoroalkyl and fluorocycloalkyl radicals.

2. An alpha-monoaminomonocarboxylic acid wherein the carbon alpha to the carboxyl carries a fluoroalkyl radical.

3. An alpha-monoaminomonocarboxylic acid as set forth in claim 2 in which the alpha-amino group is primary.

4. An alpha-monoaminomonocarboxylic acid wherein the carbon alpha to the carboxyl carries a single hydrogen and a fluorosubstituted, saturated straight chain alkyl radical in which the fluorine atoms are located on odd numbered carbons of the carbon chain.

5. An alpha-monoaminomonocarboxylic acid as set forth in claim 4 in which the carbon chain contains an odd number of carbons.

6. An alpha-monoaminomonocarboxylic acid as set forth in claim 5, said acid having a single fluorine substituent and that on the terminal carbon of the carbon chain of said acid and the alpha-amino group being primary.

7. An aminocarboxylic acid having the formula



wherein R is a fluorosubstituted, saturated straight chain alkyl radical in which the fluorine atoms are located on odd numbered carbons of the carbon chain.

8. An aminocarboxylic acid as set forth in claim 7 wherein R is a monofluorosubstituted, saturated straight chain alkyl radical containing an odd number of carbons but no more than 5, the terminal carbon carrying the single fluorine atom.

9. An alpha-monoaminomonocarboxylic acid wherein the carbon alpha to the carboxyl carries a fluorocycloalkyl radical.

10. An alpha-monoaminomonocarboxylic acid as set forth in claim 11 in which the alpha-amino group is primary.

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