United States Patent [19]

Stammer

[11] **Patent Number: 4,954,158**

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[54] **2,3-METHANOPROLINE**

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[73] Assignee: **University of Georgia Research Foundation, Inc.**, Athens, Ga.

[21] Appl. No.: **285,542**

[22] Filed: **Dec. 15, 1988**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 41,642, Apr. 22, 1987, which is a continuation of Ser. No. 879,842, Jun. 26, 1986, which is a continuation of Ser. No. 636,091, Aug. 3, 1984, which is a continuation-in-part of Ser. No. 523,080, Aug. 16, 1983.

[51] **Int. Cl.**[5] **A01N 43/38**; C07D 209/52

[52] **U.S. Cl.** **71/76**; 71/95; 548/452

[58] **Field of Search** 548/452, 455; 71/76, 71/95

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[57] **ABSTRACT**

The present invention is 2,3-methanoproline, derivatives thereof, and biologically active molecules incorporating 2,3-methanoproline. These compounds are useful as inhibitors of ethylene production in plant material, and as synthetic analogs of biologically active molecules.

7 Claims, 2 Drawing Sheets

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fig. 1

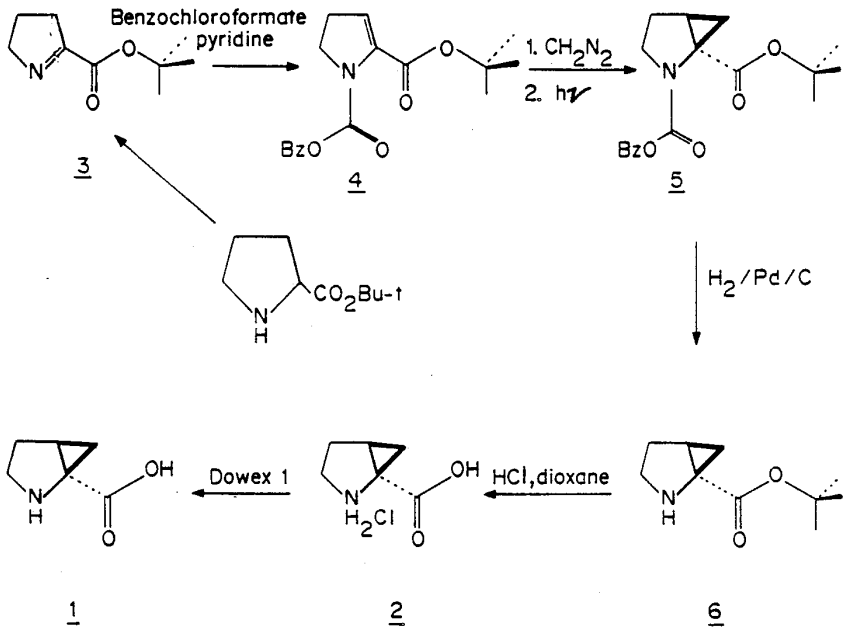
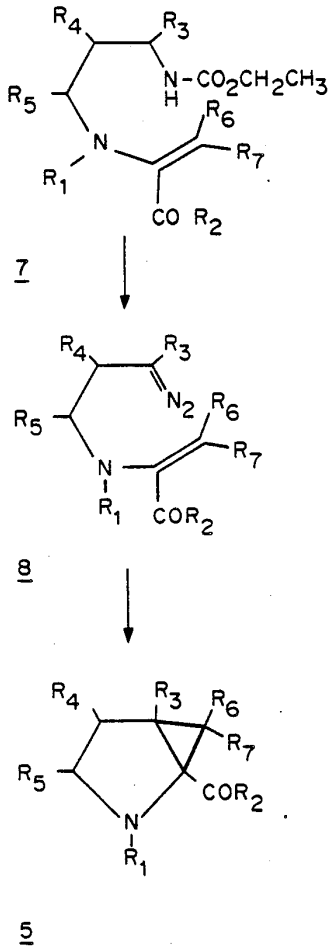


fig. 2



2,3-METHANOPROLINE

This application is a Continuation-in-Part of U.S. Ser. No. 041,642, filed Apr. 22, 1987 by Charles H. Stammer, entitled "The Synthesis of Cyclopropyl Amino Acids and Peptides", which is a Continuation of U.S. Ser. No. 879,842, filed by Charles H. Stammer on June 26, 1986, which is a Continuation of U.S. Ser. No. 636,091, filed by Charles H. Stammer on Aug. 3, 1984, which is a Continuation-in-Part of U.S. Ser. No. 523,080, filed by Charles H. Stammer on Aug. 16, 1983, entitled "The Synthesis of Cyclopropane Amino Acids."

This invention relates to biochemistry, and in particular to new proline derivatives.

BACKGROUND OF THE INVENTION

U.S. Pat. No. 4,629,784 to Stammer describes the synthesis of cyclopropyl amino acids from dehydroalanine, and the synthesis of peptides containing cyclopropyl amino acids. The patent is a continuation of U.S. Ser. No. 523,808, to which this invention claims priority.

Several amino acids containing cyclopropyl rings exist in nature. The simplest cyclopropyl amino acid, 1-aminocyclopropane-1-carboxylic acid (ACC) has been discovered in the fruit of the perry pear and the cowberry. Burroughs, *J. Sci. Food Agric.* 11 14 (1960). It is now known that ACC is a biological precursor to ethylene in plants.

Coronatine, which induces phytotoxic lesions on the leaves of Italian rye-grass and hypertrophic growth of potato tuber tissue, is the amide of coronafacic acid with coronamic acid (1-amino-1-carboxy-2-ethyl-cyclopropane). Coronatine has been synthesized by various groups in whole or part. Shiraishi, Ichihara, and Sakamura, "Facile Stereoselective Synthesis of (±)-Allocornonamic Acids", *Agric. Biol. Chem.* 41 (12), 2497 (1977) describe the stereoselective synthesis and optical resolution of (±)-Allocoronamic Acid. See also Shiraishi, Konoma, Sato, Ichihara, Sakamura, Nishiyama, and Sakai, "The Structure-Activity Relationships in Coronatine Analogs and Amino Compounds Derived From (+)-Coronafacic Acid", *Agric. Biol. Chem.* 43 (8), 1753 (1979); Ichihara, Shiraishi, Sakamura, Tet Letters No. 3, 269 (1977) and *Tet Letters No.* 4, 365 (1979); Suzuki, Gooch, and Stammer, "A New Synthesis of Racemic Coronamic Acid and Other Cyclopropyl Amino Acids", *Tet Letters* 24 (36), 3839 (1983); Jung and Hudspeth, "Total Synthesis of (±)-Coronafacic Acid: Use of an Ionic Oxy-Cope Rearrangements on Aromatic Substrates in Synthesis", *J. Am. Chem. S.* 102:7, 2463 (1980).

Shiraishi, et al., in "The Structure-Activity Relationships in Coronatine Analogs and Amino Compounds Derived From (+)-Coronafacic Acid", *Agric. Biol. Chem.* 43 (8), 1753 (1979), describe the synthesis of several coronatine analogs, and the effect of varying the substituents of coronatine on the hypertrophy responsive of potato tubers. Shiraishi, et al. conclude that the presence of the carboxyl group and the configuration at the α-carbon atom in the amino acid are closely related to the activity of the peptide. However, the cyclopropane ring in coronatine was found to have no effect on the biological activity, as indicated by the comparison of the biological activity of 1-N-coronafacoylaminocyclopropane-L-isoleucine and N-coronafacoyl-D-isoleucine.

Cyclopropylphenylalanine and its derivatives have also been synthesized and studied. King, Riordan, Holt, and Stammer, in an article entitled "Synthesis of Racemic (E)- and (Z)-1-Amino-2-Phenylcyclopropane Carboxylic Acid, (E)- and (Z)-(Cyclopropylphenylalanine)", *J. Org. Chem.* 47, 3270 (1982), describe the synthesis of both E and Z isomers of D-L-cyclopropylphenylalanine. See also Stephen Wayne King, 1981 University of Georgia Ph.D Thesis. Kimura and Stammer, in "Resolution and Deblocking of Racemic N-(Benzyloxycarbonyl) Cyclopropylphenylalanine", *J. Org. Chem.* 48, 2440 (1983), report the isolation of the E-diastereomer of cyclopropylphenylalanine from a racemic mixture of Z and E. See also Suzuki, Kumar, and Stammer, "Use of a New Protecting Group in an Attempted Synthesis of Cyclopropyl Dihydroxyphenylalanine", *J. Org. Chem.* 48, 4769 (1983).

Additional examples of naturally occurring cyclopropyl amino acids include the diastereomers of α-(2-carboxy-cyclopropyl)-glycine cyclopropyl)-glycine and cis-3,4-methano-L-proline isolated from *Aesculus parviflora* and *Bliqhia saoida.* Fowden, et al., Phytochemistry, 8, 437 (1969).

Fujimoto, Irreverre, Karle, Karle, and Whitkop, in "Synthesis and X-Ray Analysis of Cis-3,4-Methanoline-L-Proline, The New Natural Amino Acid from Horse Chestnuts, and Its Trans Isomer", *J. Am. Chem. Soc.* 93:14, 3471 (1971), describe the synthesis of cis- and trans-3,4-methano-L-proline. Fujimoto, et al. established by x-ray crystallography that the bicyclic system approaches a boat conformation both in the cis and the trans configuration. They determined that the boat conformation of cis-3,4-methanoline-L-proline is associated with the compound's effect as a powerful competitor for proline in the permease system. 2-Piperidine-carboxylic acid (D-pipecolinic acid), which has a chair conformation, is inactive in these systems.

The nitrogen atom in proline is part of a rigid saturated five membered ring. Since little rotation about the N(proline)-C_{60} peptide bond is possible when proline is incorporated into a peptide chain, proline imparts rigidity to peptides. It would be of chemical and pharmaceutical interest to prepare a cyclopropyl derivative of proline in which the cyclopropane ring is connected to the α-carbon of this sterically unique amino acid.

Proline is a key amino acid in many peptide hormones due to its significant effect on the conformation of the molecule. Examples of proline containing peptides include angiotensinogen, angiotensin I, angiotensin II, saralasin, capoten, vasotec, lysinopril, bradykinin, thyrotropin releasing factor, tuftsin, and melanocyte inhibiting factor.

Angiotensinogen (alternatively called renin substrate and hypertensinogen) is the twelve amino acid peptide: Asp-Arg-Val-Tyr-Ileu-His-Pro-His-Leu-Val-Tyr. Angiotensinogen plays a part in hypertension, the elevation of systolic and/or diastolic blood pressure. Angiotensinogen is cleaved at the Leu-Val bond by renin, a blood protein, to form angiotensin I (AI). AI is an inactive peptide which is cleaved at the Phe-His bond by angiotensinase (or angiotensin converting enzyme (ACE)) to form angiotensin II (AII). ACE is found in the lung, kidney and brain. The octapeptide AII differs among animal species only in the amino acid residue in position 5, where Val is sometimes found in place of Ile. Angiotensin II is a potent vasoconstrictor which also stimulates the release of aldosterone, an adrenocortical steriod.

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