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Amino Acid Analogs. I. Analogs of the Glutamic Acid–Proline Interconversion. II. A New Synthesis of 5-Methylproline

HERMAN GERSHON AND ALFRED SCALA

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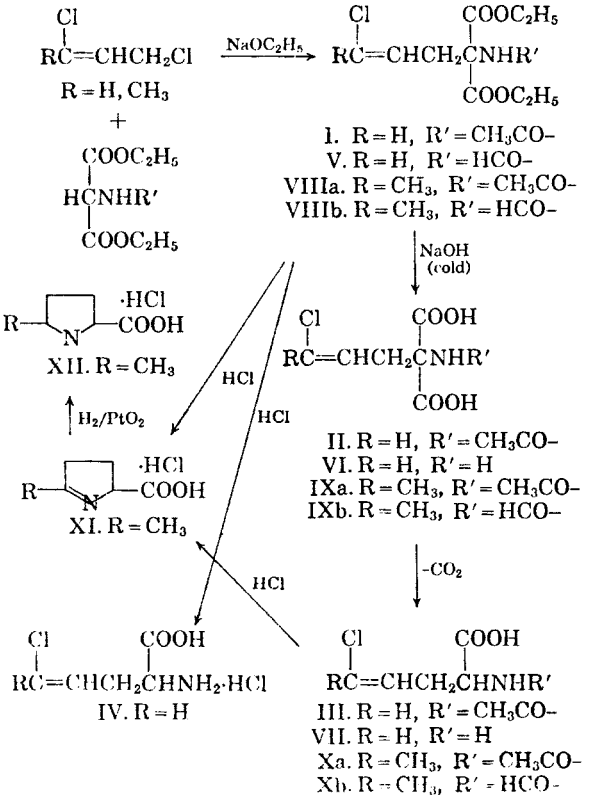
A new synthesis of 5-methylproline was accomplished by acid hydrolysis of ethyl 2-acylamido-2-carbethoxy-5-chloro-4-hexenoate to Δ^1-2-methylpyrroline-5-carboxylic acid followed by hydrogenation.

In a previous paper,[1] the interest in preparing analogs of the metabolities involved in the glutamic acid to proline interconversion was established. When a number of these analogs became available, inhibition studies on *Escherichia coli* auxotrophs were initiated. It was decided that attempts at reversal of inhibition caused by these antimetabolites should include the results to be obtained with Δ^1-pyrroline-5-carboxylic acid, in addition to proline and glutamic acid. The preparation of the pyrroline carboxylic acid was reported by Vogel and Davis[2] and by Strecker.[3] At best, their approach from γ,γ-dicarbethoxy-γ-acetamidobutyraldehyde was tedious, due in part to the difficulty in purifying the intermediate which was a sirup. The product obtained was also of questionable purity.

Vinyl halides can be hydrolyzed with great difficulty, if at all[4]; however, cases are known[5] to make the investigation of the approach to Δ^1-pyrroline-5-carboxylic acid by way of the intermediate, ethyl 2-acetamido-2-carbethoxy-5-chloro-4-pentenoate, followed by hydrolysis, worth while. This intermediate had been previously reported by Albertson.[6] It was crystallizable and, consequently could be more easily purified than γ,γ-dicarbethoxy-γ-acetamidobutyraldehyde. Albertson also reported that on acid hydrolysis, 2-amino-5-chloro-4-pentenoic acid was obtained. It was thought that under more vigorous conditions, hydrolysis of the vinyl chloride might be effected, and cyclization would follow as previously observed.[1-3]

As both 1,3-dichloropropene and 1,3-dichloro-2-butene are readily available, the preparation of four series of compounds was undertaken based on the condensations of ethyl acetamidomalonate and ethyl formamidomalonate with the dichloropropene and the dichlorobutene, respectively.

Scheme I indicates the reaction sequences based on the condensation of the dichloropropene and the dichlorobutene with the acylamidomalonates.



I had been previously reported[6] but had not been crystallized. The product obtained here was crystallizable and melted at 50–52°. The *cis* and *trans* isomers of V were reported by Shapira and Dittmer[7] and melted at 79–80° and 84–85°, respectively. The mixture of isomers as prepared in this report melted at 58.5–60°. VII was reported[8] to melt at 236°. The *cis* isomer was reported[7] to melt at 226–231°, and the *trans* isomer at 230–234°. The mixture, as prepared here, melted at 204° dec.

The desired hydrolysis of the vinyl chlorides (I and V) to Δ'-pyrroline-5-carboxylic acid was not realized, even under prolonged refluxing with concentrated hydrochloric acid. Instead, 2-amino-5-chloro-4-pentenoic acid hydrochloride, as previously reported.[6-8] was obtained.

(1) H. Gershon and A. Scala, *J. Org. Chem.*, **26**, 2347 (1961).
(2) H. Vogel and B. Davis, *J. Am. Chem. Soc.*, **74**, 109 (1952).
(3) H. J. Strecker, *J. Biol. Chem.*, **235**, 2045 (1960).
(4) E. D. Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941).
(5) J. Anderson, R. M. Stager, Jr., and S. H. McAllister, Brit. Pat. 570,668 (1945).
(6) N. Albertson, *J. Am. Chem. Soc.*, **73**, 452 (1951).
(7) J. Shapira and K. Dittmer, *J. Am. Chem. Soc.*, **82**, 1495 (1960).
(8) J. Fillman and N. Albertson, *J. Am. Chem. Soc.*, **70**, 171 (1948).

TABLE I

AMINOMALONIC ESTERS

$$\begin{array}{l} COOC_2H_5 \\ | \\ RCNHR' \\ \diagdown \\ \quad COOC_2H_5 \end{array}$$

Compd.	R	R′	Yield, %	M.P. (Analytical Sample)	Formula	Calcd., % N	Calcd., % Cl	Found, % N	Found, % Cl
I	$\begin{array}{l} Cl \\ \vert \\ HC{=}CHCH_2{-} \end{array}$	$\begin{array}{l} \vert \\ CH_3C{=}O \end{array}$	80	50–52[a]	$C_{12}H_{18}NO_5Cl$	4.80	12.16	4.60	11.85
V	$\begin{array}{l} Cl \\ \vert \\ HC{=}CHCH_2{-} \end{array}$	$\begin{array}{l} \vert \\ HC{=}O \end{array}$	80	58.5–60	$C_{11}H_{16}NO_5Cl$	5.04	12.77	5.04	12.59
VIIIa	$\begin{array}{l} Cl \\ \vert \\ CH_3C{=}CHCH_2{-} \end{array}$	$\begin{array}{l} \vert \\ CH_3C{=}O \end{array}$	71	72	$C_{13}H_{20}NO_5Cl$	4.58	11.60	4.40	11.88
VIIIb	$\begin{array}{l} Cl \\ \vert \\ CH_3C{=}CHCH_2{-} \end{array}$	$\begin{array}{l} \vert \\ HC{=}O \end{array}$	63	91.5–92	$C_{12}H_{18}NO_5Cl$	4.80	12.16	4.81	11.80

[a] All compounds were crystallized from ether–petroleum ether (b.p. 30–60°) mixtures.

TABLE II

AMINOMALONIC ACIDS

$$\begin{array}{l} COOH \\ | \\ RCNHR' \\ \diagdown \\ \quad COOH \end{array}$$

Compd.	R	R′	Yield, %	M.P. (Analytical Sample)	Formula	Calcd., % N	Calcd., % Cl	Found, % N	Found, % Cl
II	$\begin{array}{l} Cl \\ \vert \\ HC{=}CHCH_2{-} \end{array}$	$\begin{array}{l} \vert \\ CH_3C{=}O \end{array}$	63	114–115 dec.[a]	$C_8H_{10}NO_5Cl$	5.95	15.05	5.94	14.87
VI	$\begin{array}{l} Cl \\ \vert \\ HC{=}CHCH_2{-} \end{array}$	H	93	110–112 dec.	$C_6H_8NO_4Cl$	7.24	18.32	7.41	18.50
IXa	$\begin{array}{l} Cl \\ \vert \\ CH_3C{=}CHCH_2{-} \end{array}$	$\begin{array}{l} \vert \\ CH_3C{=}O \end{array}$	56	133–134 dec.	$C_9H_{12}NO_5Cl$	5.61	14.20	5.32	14.49
IXb	$\begin{array}{l} Cl \\ \vert \\ CH_3C{=}CHCH_2{-} \end{array}$	$\begin{array}{l} \vert \\ HC{=}O \end{array}$	80	116–117 dec.	$C_8H_{10}NO_5Cl$	5.95	15.05	5.88	15.47

[a] All compounds were crystallized from methanol, below 40°.

TABLE III

AMINO ACIDS

$$\begin{array}{l} RCHCOOH \\ | \\ NHR' \end{array}$$

Compd.	R	R′	Yield, %	M.P. (Analytical Sample)	Formula	Calcd., % N	Calcd., % Cl	Found, % N	Found, % Cl
III	$\begin{array}{l} Cl \\ \vert \\ HC{=}CHCH_2{-} \end{array}$	$\begin{array}{l} \vert \\ CH_3C{=}O \end{array}$	90	126–128[a]	$C_7H_{10}NO_3Cl$	7.31	18.51	7.14	18.29
VII	$\begin{array}{l} Cl \\ \vert \\ HC{=}CHCH_2{-} \end{array}$	H	92	204 dec.[a,c]	$C_5H_8NO_2Cl$	9.37	23.71	8.87	23.67
IV	$\begin{array}{l} Cl \\ \vert \\ HC{=}CHCH_2{-} \end{array}$	H·HCl	69	201–202[b]	$C_5H_9NO_2Cl_2$	7.53	38.12	7.29	37.78
Xa	$\begin{array}{l} Cl \\ \vert \\ CH_2C{=}CHCH_2{-} \end{array}$	$\begin{array}{l} \vert \\ CH_3C{=}O \end{array}$	95	112–113.5[a]	$C_8H_{12}NO_3Cl$	6.81	17.24	6.78	16.81
Xb	$\begin{array}{l} Cl \\ \vert \\ CH_3C{=}CHCH_2{-} \end{array}$	$\begin{array}{l} \vert \\ HC{=}O \end{array}$	95	135–136.5[a]	$C_7H_{10}NO_3Cl$	7.31	18.51	7.22	18.51

[a] Crystallized from water. [b] Crystallized from a methanol-acetone mixture. [c] Lit.[8] m.p. 236°.

XI and XII were previously reported[1,9,10] and prepared by acid hydrolysis of ethyl 2-acetamido-2-carbethoxy-5-oxohexanoate followed by hydrogenation. The melting point of XI was 193.5–195° dec. and showed no depression when mixed with an authentic sample of the compound. XII melted at 190–191° and no depression in melting point was observed when admixed with an authentic sample.

It can be seen that on mild alkaline hydrolysis, V, derived from 1,3-dichloropropane, not only was saponified, but was also deformylated to yield compound VI, 2-amino-(3-chloro-2-propenyl)malonic acid. The corresponding compound, VIIIb, derived from 1,3-dichloro-2-butene, was only saponified under these mild alkaline conditions and not deformulated.

To obtain evidence that the mechanisms of cyclization on acid hydrolysis of VIIIa, VIIIb, Xa, and Xb to XI was preceded by hydrolysis of the vinyl chloride to a methyl ketone, 1,3-dichloro-2-butene and 1,3-dichloropropene were heated under reflux with concentrated hydrochloric acid for several hours. The hydrolyzate from the dichlorobutene showed positive iodoform and 2,4-dinitrophenylhydrazone tests. The corresponding hydrolyzate from the dichloropropene gave a negative carbonyl test with 2,4-dinitrophenylhydrazine. It was thus apparent that hydrolysis of the vinyl chloride groups of VIIIa, VIIIb, Xa, and Xb to methylketo groups preceded cyclization to the pyrroline, XI.

Tables I–III summarize the pertinent data on the malonic esters, malonic acids, and amino acids, respectively.

EXPERIMENTAL[11]

Ethyl 2-acetamido-2-carbethoxy-5-chloro-4-hexenoate (VIIIa). In 750 ml. of absolute ethanol were dissolved 17.25 g. (0.75 g.-atom) of sodium and 163 g (0.75 mole) of ethyl acetamidomalonate. The solution was heated to boiling and a solution of 94 g. (0.75 mole) of 1,3-dichloro-2-butene[12] in 100 ml. of absolute ethanol was added dropwise. After heating under reflux for about 18 hr., the sodium chloride was removed by filtration, washed with isopropyl alcohol, and the combined filtrates were evaporated to dryness under reduced pressure. The residue was dissolved in 250 ml. of methylene chloride and the resulting solution was washed twice with water which was back extracted with methylene chloride. The combined methylene chloride solutions were evaporated under vacuum on a water bath. The sirupy residue was dissolved in 250 ml. of isopropyl alcohol and placed in a refrigerator overnight. A yield of 162 g. (71%) of product was obtained which melted at 66–70°. An analytical sample (m.p. 72°) was prepared by crystallization from an ether–petroleum ether (b.p. 30–60°) mixture.

Acetamido(3-chloro-2-butenyl)malonic acid (IXa). To a solution of 14 g. (0.35 mole) of sodium hydroxide in 140 ml. of water cooled to 10°, was added 42.8 g. (0.14 mole) of ethyl 2-acetamido-2-carbethoxy-5-chloro-4-hexenoate (VIIIa). The mixture was allowed to stand at room temperature overnight. The solution was treated with decolorizing carbon and passed through a column of Amberlite IR-120 (H^+) to remove the alkali. The eluate was again decolorized with charcoal and evaporated in a flash evaporator below 40° The yield of malonic acid was 19.6 g., 56%, m.p. 130–132° dec. An analytical sample which was prepared by crystallization from methanol below 40°, decomposed at 133–134°.

2-Acetamido-5-chloro-4-hexenoic acid (Xa). A solution was made in water of 15.0 g. (0.06 mole) of the malonic acid, (IXa) and boiled for 1 hr. until cessation of gas evolution. The hot solution was decolorized with charcoal and cooled overnight in the refrigerator. A yield of 2.7 g. of white crystals was obtained, m.p. 112–113.5°. The mother liquid was evaporated to a small volume and, on cooling, an additional 9.1 g. of product was recovered. For analysis, the product was crystallized from water and melted at 112–113.5°.

Δ'-2-Methylpyrroline-5-carboxylic acid hydrochloride (XI). Ten and one-tenth grams (0.033 mole) of ethyl 2-acetamido-2-carbethoxy-5-chloro-4-hexenoate (VIIIa) was heated under reflux with 100 ml. of concd. hydrochloric acid overnight. The product was isolated as previously described.[1] The yield of product was 2.5 g. (46%), m.p. 193.5–195° dec., lit. m.p.[1,9] 189–190° dec. and 193° dec. A mixed melting point with an authentic sample showed no depression.

Anal. Calcd. for $C_6H_{10}NO_2Cl$: N, 8.56. Found: N, 8.49.

5-Methylproline hydrochloride (XII). The pyrroline (XI) was hydrogenated at 3 atm. as previously reported.[1] The yield of product was nearly quantitative, m.p. 190–191°, lit. m.p.,[1,10] 191–192°, 186–187°, respectively. No depression was observed in a mixed melting point with an authentic sample.

RIDGEFIELD, N. J.

(9) Y. Sanno, *Yakugaku Zasshi*, **78**, 1113 (1958); *Chem. Abstr.*, **53**, 5238 (1959).

(10) S. Tatsuoka, K. Tanaka, Y. Ueno, and Y. Sanno, Japan Pat. 9977 (158), Nov. 19; *Chem. Abstr.*, **54**, 5696 (1960).

(11) All melting points are uncorrected, and the procedures are general.

(12) Purchased from Eastman Organic Chemicals, Rochester 3, N. Y.