Solid A, recrystallized (ethyl acetate–ethanol) gave 0.65 g., m.p. 207–208°, identical with compound 17.[21]

Solid B, recrystallized (ethyl acetate–hexane) gave 0.37 g., m.p. 140–144° of unproved structure[22] which fits the following empirical formula.

Anal. Calcd. for $C_9H_{16}N_2O_5$: C, 46.6; H, 6.9; N, 12.1. Found: C, 47.2; H, 6.8; N, 12.2.

δ-p-Carbethoxyphenylhydantoamide (Compound 26). A solution of 2.42 g. (0.008 mole) of compound 9 in 30 ml. of methanol was maintained below 35° while saturated with ammonia and stoppered. After 3 days at 20°, 1.6 g. of product separated, m.p. 204–205°. The filtrate on standing gave an additional 0.35 g., m.p. 204–205° (total yield 90%).

N-Benzyl-δ-hydroxyethylhydantoamide. A solution of 3.2 g. (0.016 mole) of compound 1 in 20 ml. of methanol was treated with 1.9 g. (0.018 mole) of benzylamine. After 3 days, 100 ml. of ether was added. On standing, 1.17 g. of crystals was obtained, m.p. 90–95°. The filtrate was evaporated and on solution in 40 ml. of ethyl acetate and seeding yielded 0.8 g. of crystals. Repetition of this process gave 0.32 g. of the above, total 2.29 g. This was dissolved in a mixture of 3 ml. of ethanol and 55 ml. of ethyl acetate. The initial crop of crystals was separated (0.25 g.), m.p. 135–141°, and recrystallized (ethanol–ethyl acetate) to give 0.1 g. of product, m.p. 140–141°.

Anal. Calcd. for $C_{12}H_{17}N_3O_3$: C, 57.4; H, 6.8; N, 16.7. Found: C, 57.4; H, 6.6; N, 17.1.

The filtrate on further standing gave a different solid which recrystallized (ethanol-hexane), m.p. 103.5–104°, proved to be 3-hydroxyethylhydantoin.[23]

Anal. Calcd. for $C_5H_8N_2O_3$: C, 41.7; H, 5.6. Found: C, 41.7; H, 5.4.

δ-Hydroxyethylhydantoamide (Compound 18). A solution of 4.0 g. (0.02 mole) of compound 1 in 20 ml. of methanol was saturated with ammonia. After storage for 3 days at 20° and seeding, 1.65 g. of crude product was obtained. The filtrate on dilution with 200 ml. of ether gave 0.85 g. of crude 3-hydroxyethylhydantoin, m.p. 90–96°.

N-Benzyl-δ-allylhydantoamide (Compound 34). A solution of 3.0 g. (0.016 mole) of compound 2 in 30 ml. of methanol was treated with 1.9 g. (0.018 mole) of benzylamine. After 3 days, upon seeding and cooling at 10° for 4 hr., 0.9 g. of product was obtained, m.p. 186–188°. Concentration of the filtrate and trituration with ethyl acetate gave an additional 0.6 g. of product, m.p. 186–187°; total yield 38%. The ethyl acetate was removed from the filtrate and the residue triturated with hexane gave 1.35 g. (60%) of crystals of 3-allylhydantoin,[24] m.p. 75°; recrystallized (ethyl acetate–hexane) m.p. 78°.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.4; H, 5.8; N, 20.0. Found: C, 50.8; H, 5.8; N, 20.1.

Under similar conditions, employing ammonia and compound 2, *δ-allyl-hydantoamide* (compound 19) was obtained in 47% yield, and *3-allylhydantoin* (m.p. 78°) was obtained in 19% yield.

δ,δ¹-Trimethylenebishydantoamide (Compound 32). A solution of 4.0 g. (0.012 mole) of compound 14 in 45 ml. of methanol was maintained below 30° while saturated with ammonia. After 24 hr., 2.57 g. of crystals were obtained and dissolved in 60 ml. of water, yielding 0.8 g. (24%), m.p. 224–225°. The aqueous filtrate was concentrated to 10 ml. to give 0.85 g. (24%) of crystals, m.p. 180–184°, which analysis indicated to be the hydantoin II, X = H.

Anal. Calcd. for $C_9H_{15}N_5O_4$: C, 42.0; H, 5.9. Found: C, 41.5; H, 6.2.

δ,δ¹-Trimethylene(bis-N-benzylhydantoamide). A solution of 3.3 g. (0.01 mole) of compound 14 in 30 ml. of methanol was treated with 4.28 g. (0.04 mole) of benzylamine. After 4 days the formed solid (1.6 g.) was separated, m.p. 160–190°, and recrystallized (dimethylformamide) to give 0.52 g. (12%) of product, m.p. 195–207°.

Anal. Calcd. for $C_{23}H_{30}N_6C_4$: N, 18.5. Found N, 18.1.

Evaporation of the filtrate and trituration with ether gave 1.4 g. of white solid, recrystallized from water to give 0.7 g. (20%) of crystals which analysis indicated to be the hydantoin II, X = $C_6H_5CH_2$—.

Anal. Calcd. for $C_{16}H_{21}N_5O_4$: C, 55.3; H, 6.1; N, 20.2. Found: C, 55.3; H, 5.6; N, 20.3.

Acknowledgment. The authors wish to thank Dr. G. Ungar and his staff for the pharmacological results of the screening of the compounds, and F. Testa for his technical assistance.

YONKERS 1, N. Y.

(21) This may have resulted from the presence of piperazine as an impurity in the *N*-methylpiperazine.

(22) E. Fischer, *Ber.*, **34**, 440 (1901), reports carbonyldiglycindiethyl ester, m.p. 146°, prepared from phosgene and glycine diethyl ester.

(23) A. C. Smith, Jr., and C. C. Unruh, *J. Org. Chem.*, **22**, 442 (1957), report m.p. 98–101°.

(24) Beilstein, XXIV, p. 250, reports m.p. 78°.

[CONTRIBUTION FROM THE PFISTER CHEMICAL WORKS, INC.]

Amino Acid Analogs. I. Analogs of the Glutamic Acid, Proline Interconversion. Part I. ω-Methyl- and ω-Phenylketoglutamic Acids and 5-Methyl- and 5-Phenylprolines

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Some analogs of glutamic acid, Δ′-pyrroline-5-carboxylic acid and proline were synthesized.

The interconversion of glutamic acid and proline in both animal tissues and microorganisms has been reviewed by Stetten[1] and Vogel.[2] This relationship consists essentially of the following series of reversible transformations: glutamic acid ⇌ glutamic-γ-semialdehyde ⇌ Δ′-pyrroline-5-carboxylic

(1) M. R. Stetten, *Amino Acid Metabolism*, W. D. McElroy and H. B. Glass, eds., Johns Hopkins Press, Baltimore, Md., 1955, p. 277.

(2) H. J. Vogel, *Amino Acid Metabolism*, W. D. McElroy and H. B. Glass, eds., Johns Hopkins Press, Baltimore, Md., 1955, p. 335.

acid ⇌ proline. Since this sequence seems to be a major metabolic pathway for both glutamic acid and proline, it was of interest to prepare analogs of these compounds and their respective intermediates in order to determine whether, by this means, metabolic inhibition could be achieved.

It was reported by Ginsburg, Lovett, and Dunn[3] that the strain of tuberculosis bacteria, which infects humans, has on the average 50% more glutamic acid than noninfectious strains. Glutamic acid and proline have also been implicated in cancer[4-7] studies. It is evident that glutamic acid and proline analogs should be of interest in studies of these diseases.

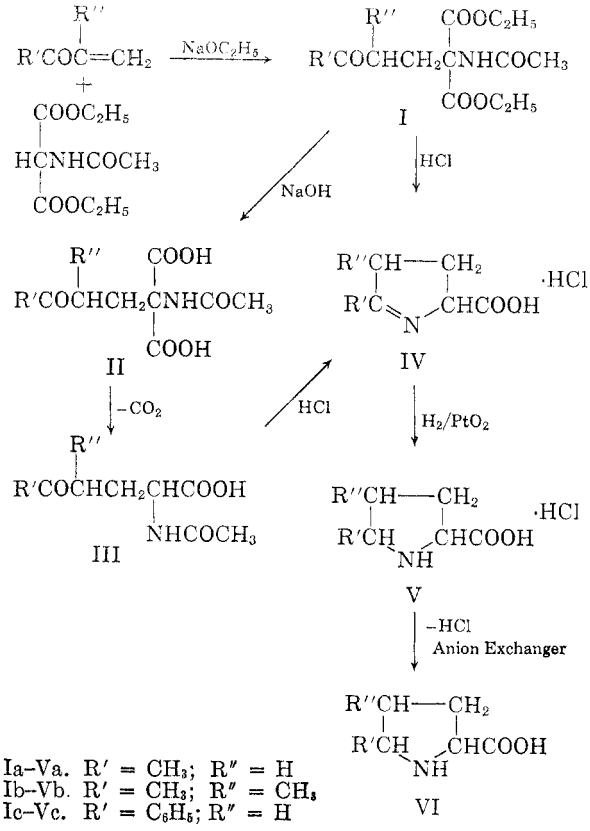
Among the structural alterations which can be employed for forming antimetabolites is the substitution of a methyl or phenyl ketone for a carboxyl group. Several successful antimetabolites have thus been prepared. Woolley,[8] *et al.* found that β-acetylpyridine was a nicotinic acid antagonist. Upon replacing the carboxyl group in pantothenic acid by a phenyl ketone, Woolley[9] and Collyer produced a potent pantothenic acid antagonist. Employing the same structural alteration, Dittmer[10] reported that α-aminolevulinic acid and aspartophenone were aspartic acid antagonists.

The substitution of a methyl group for a hydrogen atom has also led to successful antagonists. Examples of this replacement include α-methylaspartic acid,[11] ethionine,[12] methyltryptophans,[13,14] and many others.

Scheme I indicates the approach to the preparation of the analogs of each of the intermediates of the glutamic acid to proline interconversion.

The synthetic methods with some modifications were modeled after the condensation of acrolein with ethyl acetamidomalonate by Moe and Warner[15] and the hydrolysis and hydrogenation procedures of Vogel and Davis.[16] Methyl vinyl ketone and methyl isopropenyl ketone were condensed with acetamidomalonate according to the conditions of the Michael condensation, and β-bromopropiophenone was condensed with ethyl acetamidomalonate in the presence of sodium ethylate, slightly in excess of one molecular proportion. When the intermediates were hydrolyzed by alkali, malonic acids were obtained which, on decarboxylation, yielded the corresponding acetylated glutamic acid analogs. These analogs, and the ethyl acetamidomalonate condensation products, were acid hydrolyzed to yield 2- and 2,3-substituted Δ′-pyrroline-5-carboxylic acids which, in turn, were hydrogenated over Adams' catalyst at three to four atmospheres of hydrogen to 5- and 4,5-substituted prolines.

Scheme I



Ia–Va. R′ = CH_3; R″ = H
Ib–Vb. R′ = CH_3; R″ = CH_3
Ic–Vc. R′ = C_6H_5; R″ = H

The substituted prolines, Va–c, the pyrroline, IV-b and the methyl ketone, III-b can exist as diastereoisomeric racemates. The stereochemistry of these compounds has not been determined.

After completion of this work, the current literature revealed the preparation of ethyl acetamido-3-oxobutylmalonate by Sanno[17] and its hydrolysis to Δ′-2-methylpyrroline-5-carboxylic acid hydrochloride. The hydrogen of this pyrroline to 5-methylproline hydrochloride was also reported by Sanno[18] *et al.*

(3) B. Ginsburg, S. L. Lovett, and M. S. Dunn, *Arch. Biochem. Biophys.*, 60, 164 (1956).
(4) S. Kit and J. Awapara, *Cancer Research*, 13, 694 (1953).
(5) F. S. Hammett, *Proc. Soc. Exptl. Biol. Med.*, 45, 601 (1940).
(6) J. M. White, G. Ozawa, G. A. L. Ross, and E. W. McHenry, *Cancer Research*, 14, 508 (1954).
(7) J. R. Beaton, W. J. McGanity, and E. W. McHenry, *Can. Med. Assoc. J.*, 65, 219 (1951).
(8) D. W. Woolley, F. M. Strong, R. J. Madden, and C. A. Elvehjem, *J. Biol. Chem.*, 124, 715 (1938).
(9) D. W. Woolley and M. L. Collyer, *J. Biol. Chem.*, 159, 263 (1945).
(10) K. Dittmer, *Antimetabolites*, R. W. Miner, ed., *Annals N. Y. Acad. Sci.*, 52, 1274 (1950).
(11) E. Roberts and P. F. Hunter, *Proc. Soc. Exptl. Biol. Med.*, 83, 720 (1953).
(12) H. M. Dyer, *J. Biol. Chem.*, 124, 519 (1938).
(13) T. F. Anderson, *Science*, 101, 565 (1945).
(14) P. Fildes and H. M. Rydon, *Brit. J. Exptl. Pathol.*, 28, 211 (1947).
(15) O. A. Moe and D. T. Warner, *J. Am. Chem. Soc.*, 70, 2763 (1948).
(16) H. J. Vogel and B. D. Davis, *J. Am. Chem. Soc.*, 74, 109 (1952).
(17) Y. Sanno, *Yakugaku Zasshi*, 78, 1113 (1958); *Chem. Abstr.*, 53, 5238 (1959).

Seven of these compounds, III-a and b; IV-a, b, and c; and V-a and b were screened for antitubercular activity in mice by Dr. Crowle[19] according to his method, and were found to be ineffective.

All of the malonic acids, glutamic acid analogs, pyrrolines, and prolines were screened by the Cancer Chemotherapy National Service Center against Sarcoma-180, Carcinoma-755, and Leukemia-1210 in mice. The results were generally negative.

Work with proline requiring mutants of *Escherichia coli* is now in progress and will be reported on at a later date.

EXPERIMENTAL

Ethyl 2-acetamido-2-carbethoxy-5-oxohexanoate (I-a). To 200 ml. of absolute ethanol in which 1.25 g. (0.054 g.-atom) of sodium had been dissolved, was added 217 g. (1.0 mole) of ethyl acetamidomalonate. Keeping the temperature below 25°, 90 g. (1.29 moles) of methyl vinyl ketone[20] was added dropwise with agitation. Stirring was continued overnight, and then the sodium ethylate was neutralized with glacial acetic acid and the crystalline product filtered and washed with ether. The yield was 214 g., m.p. 80–85°. The mother liquor was diluted with an equal volume of ether and cooled in the freezer overnight. An additional yield of 47 g. was obtained, m.p. 76–85°. The combined crude yield was 94%. An analytical sample was prepared by recrystallization from water, m.p. 87°, lit.,[17] m.p. 89–90°.

Anal. Calcd. for $C_{13}H_{21}NO_6$: C, 54.36; H, 7.32; N, 4.88. Found: C, 54.89; H, 7.20; N, 4.87.

Ethyl 2-acetamido-2-carbethoxy-4-methyl-5-oxohexanoate (I-b). To 180 ml. of absolute ethanol, in which 1.25 g. (0.054 g.-atom) of sodium had been dissolved, was added 217 g. (1.0 mole) of ethyl acetamidomalonate, and 110 g. (1.29 moles) of methyl isopropenyl ketone[21] was added dropwise with agitation at 12–15°. The mixture was stirred for 4 hr. and let stand overnight. After neutralization of the base with glacial acetic acid, the alcohol was removed under vacuum, and the residue was taken up in 200 ml. of methylene chloride and washed with 100 ml. of water, which was back extracted with methylene chloride. Upon evaporation of the methylene chloride, 282 g. of a sirupy residue remained, which could not be crystallized. The yield was 93% and the product was sufficiently pure for further work.

Ethyl 2-acetamido-4-benzoyl-2-carbethoxybutyrate (I-c). In 840 ml. of absolute ethanol was dissolved 23.4 g. (1.02 g.-atoms) of sodium and 217 g. (1.0 mole) of ethyl acetamidomalonate was added. To the clear solution was added, dropwise with agitation, 213 g. (1.0 mole) of β-bromopropiophenone, prepared according to Foreman and McElvain.[22] The mixture was agitated and kept under reflux overnight. On cooling, the sodium bromide was filtered off and washed with alcohol. The combined filtrates were evaporated under vacuum and the residue was taken up in methylene chloride, washed with water, and the methylene chloride evaporated. The residue was dissolved in isopropyl alcohol, cooled in the freezer, and the crystals were collected and washed with ether. The yield was 261 g., 75%, m.p. 110–112°. An analytical sample was prepared from 50% aqueous isopropyl alcohol, m.p. 113–114°.

Anal. Calcd. for $C_{18}H_{23}NO_6$: C, 61.89; H, 6.59; N, 4.01. Found: C, 61.55; H, 6.45; N, 3.92.

Acetamido (3-oxobutyl)malonic acid (II-a). To a solution of 20 g. (0.5 mole) of sodium hydroxide in 200 ml. of water was added 57.4 g. (0.2 mole) of ethyl 2-acetamido-2-carbethoxy-5-oxohexanoate. The mixture was allowed to stand 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 decolorized with charcoal and evaporated under vacuum below 40°. The crude yield was 17.7 g. of product, 60% m.p. 92–95° dec. An analytical sample was prepared from isopropyl alcohol, keeping the temperature below 50°, m.p. 97–98° dec.

Anal. Calcd. for $C_9H_{13}NO_6$: C, 46.75; H, 5.63; N, 6.06. Found: C, 46.97; H, 5.51; N, 5.66.

DL-*2-Acetamido-5-oxohexanoic acid* (III-a). A solution was made of 46.2 g. (0.2 mole) of the malonic acid in water and boiled for 1 hr. till gas evolution ceased. The solution was decolorized with charcoal and evaporated to dryness under vacuum. The sirupy residue was taken up in 150 ml. of isopropyl alcohol, decolorized with charcoal, and 20 ml. of ether was added. After cooling to −20° with occasional stirring, the solution was allowed to remain in the freezer 1–2 days. A crude product weighing 35.5 g. (95% yield) was obtained, m.p. 96–98°. An analytical sample was prepared by recrystallization from 2:1 methanol-ether, m.p. 102–103°.

Anal. Calcd. for $C_8H_{13}NO_4$: C, 51.34; H, 6.95; N, 7.49. Found: C, 51.69; H, 7.15; N, 7.48.

Acetamido(2-methyl-3-oxobutyl)malonic acid (II-b). The procedure was the same as for the previous malonic acid. The yield was 54% and the product decomposed at 100–102°. An analytical sample was prepared from isopropyl alcohol, which melted with gas evolution at 106°.

Anal. Calcd. for $C_{10}H_{15}NO_6$: C, 48.98; H, 6.12; N, 5.71. Found: C, 49.12; H, 6.01; N, 5.46.

2-Acetamido-4-methyl-5-oxohexanoic acid (III-b). The procedure was the same as for the previous hexanoic acid, and the yield was 92%. The product melted at 118–122°. An analytical sample was prepared from isopropyl alcohol, m.p. 128–129°.

Anal. Calcd. for $C_9H_{15}NO_4$: C, 53.73; H, 7.46; N, 6.97. Found: C, 53.57; H, 7.60; N, 7.11.

Acetamido(2-benzoylethyl)malonic acid (IV-c). To a solution of 20 g. (0.5 mole) of sodium hydroxide in 400 ml. of 50% ethanol was added 69.8 g. (0.2 mole) of ethyl 2-acetamido-4-benzoyl-2-carbethoxybutyrate. On standing overnight, the sodium salt of the malonic acid crystallized. The product was brought into solution by the addition of 1000 ml. of water, decolorized with charcoal, and acidified with concentrated hydrochloric acid. The malonic acid was filtered off, washed free of chloride, and dried at 50°, m.p. 189–192° with gas evolution. The crude yield was 55.7 g. 95%. An analytical sample was prepared by recrystallization from isopropyl alcohol, m.p. 192–193° dec.

Anal. Calcd. for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.12; N, 4.78. Found: C, 57.31; H, 4.31; N, 4.48.

DL-*2-Acetamido-4-benzoylbutyric acid* (III-C). The decarboxylation of acetamido(2-benzoylethyl)malonic acid was carried out by boiling 58.6 g. (0.2 mole) in 1000 ml. of water for 2 hr. The mixture was cooled in the refrigerator overnight, filtered, and washed with water. The yield of crude product was 38.5 g., 77%, m.p. 195–196°. An analytical sample was prepared from isopropyl alcohol, m.p. 195–196°.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.65; H, 6.02; N, 5.62. Found: C, 62.95; H, 6.07; N, 5.48.

Δ′-*2-Methylpyrroline-5-carboxylic acid hydrochloride* (IV-a). Eighty-six and one-tenth grams (0.3 mole) of ethyl-2-acetamido-2-carbethoxy-5-oxohexanoate was heated under reflux with 500 ml. of concd. hydrochloric acid overnight. The excess acid was removed under vacuum in a flash evaporator. The residue was taken up in water, decolorized with

(18) S. Tatsuoka, K. Tanaka, Y. Ueno, and Y. Sanno, Japan. 9977 (1958), Nov. 19; *Chem. Abstr.*, **54**, 5696 (1960).

(19) A. J. Crowle, *Tubercle*, **39**, 41 (1958).

(20) Methyl vinyl ketone was purchased from Charles Pfizer and Co., Inc., Brooklyn, N. Y.

(21) Methyl isopropenyl ketone was generously supplied by Celanese Corporation of America, New York 16, N. Y.

(22) E. L. Foreman and S. M. McElvain, *J. Am. Chem. Soc.*, **62**, 1435 (1940).

charcoal, and evaporated to dryness in the evaporator. The product was taken up in 150 ml. of methanol and cooled for several days in the freezer. The crystals were filtered, washed with acetone and dried, yielding 29.8 g. of crude material, 61%, m.p. 186–189° dec. An analytical sample was prepared from 1:1 methanol ether, m.p. 189–190° dec., lit.,[17] m.p. 193° dec.

Anal. Calcd. for $C_6H_{10}ClNO_2$: C, 44.17; H, 6.12: N, 8.56. Found: C, 43.97; H, 6.29; N, 8.49.

5-Methylproline hydrochloride (V-a). A solution of 16.4 g. (0.1 mole) of Δ′-2-methylpyrroline-5-carboxylic acid hydrochloride in 150 ml. of methanol was made and 50 mg. of platinum oxide was added. The mixture was hydrogenated in the Parr hydrogenator under 3 atm. of pressure for 0.5 hr., at which time the theoretical uptake of hydrogen was completed. The catalyst was filtered off and the solvent evaporated under a stream of air. A quantitative yield of 5-methylproline hydrochloride was obtained, m.p. 184–188°. An analytical sample was obtained from methanol, m.p. 191–192°, lit.,[19] m.p. 186–187°.

Anal. Calcd. for $C_6H_{12}ClNO_2$: C, 43.50; H, 7.25; N, 8.46. Found: C, 43.66; H, 7.27; N, 8.50.

5-Methylproline (VI-a). The free amino acid was obtained from the hydrochloride by passing an aqueous solution through a column of Amberlite IR-45 in the acetate cycle. The effluent was taken to dryness under vacuum and the residue was recrystallized from isopropyl alcohol, m.p. 188–189°.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.81; H, 8.53; N, 10.85. Found: C, 56.22; H, 8.72; N, 10.60.

Δ′-2,3-Dimethylpyrroline-5-carboxylic acid hydrochloride (IV-b). The title compound was prepared from ethyl 2-acetamido-2-carbethoxy-4-methyl-5-oxohexanoate in the same manner as Δ′-2-methylpyrroline-5-carboxylic acid hydrochloride. The yield was 61%, m.p. 148–150°. An analytical sample was prepared from methanol mixed with ether, m.p. 153–154°.

Anal. Calcd. for $C_7H_{12}ClNO_2$: C, 47.32; H, 6.76; N, 7.89. Found: C, 47.45; H, 6.78; N, 8.01.

4,5-Dimethylproline hydrochloride (V-b). This compound was prepared by hydrogenation in the same manner as 5-methylproline hydrochloride. The yield was quantitative, m.p. 128–130°. An analytical sample was prepared from methanol, m.p. 131.5–133.0°.

Anal. Calcd. for $C_7H_{14}ClNO_2$: C, 46.92; H, 8.35; N, 7.80. Found: C, 46.52; H, 8.30; N, 7.90.

4,5-Dimethylproline (VI-b). The method of preparation was the same as for 5-methylproline. An analytical sample was prepared from isopropyl alcohol, m.p. 196.5–197.5°.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.74; H, 9.09; N, 9.79. Found: C, 58.36; H, 8.86; N, 9.33.

Δ′-2-Phenylpyrroline-5-carboxylic acid hydrochloride (IV-c). The title compound was prepared from ethyl 2-acetamido-4-benzoyl-2-carbethoxybutyrate by the same method as Δ′-2-methylpyrroline-5-carboxylic acid hydrochloride. The yield was 55%, m.p. 169–173°. An analytical sample was prepared from a 1:2 methanol-ether mixture, m.p. 172–173°.

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.76; N, 6.29. Found: C, 58.43; H, 5.50; N, 6.20.

5-Phenylproline hydrochloride (V-c). The method of preparation was the same as for 5-methylproline hydrochloride; however, the product crystallized only once after standing in the freezer for 2 years. It could not be recrystallized. The yield was 62% and the product was analyzed without further purification, m.p. 115–117°.

Anal. Calcd. for $C_{11}H_{14}ClNO_2$: C, 58.02; H, 6.15; N, 6.15. Found: C, 58.38; H, 6.37; N, 6.17.

5-Phenylproline (VI-c). The method of preparation was the same as for 5-methylproline. An analytical sample was prepared from isopropyl alcohol, m.p. 213–214°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.10; H, 6.81; N, 7.33. Found: C, 69.57; H, 7.28; N, 7.23.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, TENNESSEE EASTMAN CO., DIVISION OF EASTMAN KODAK CO.]

Addition of 2-Aminopyridines to Methyl Propiolate

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The reaction of 2-aminopyridine with methyl propiolate gave not only the expected 2H-pyrido[1,2-a]pyrimidin-2-one, but also a noncyclic adduct of one mole of the aminopyridine and two moles of ester, methyl 2-(2-methoxycarbonylvinylimino)-1(2H)-pyridineacrylate. The various methyl-2-aminopyridines reacted similarly to form methyl-2H-pyrido[1,2-a]-pyrimidin-2-ones. Unexpectedly, 6-methyl-2-aminopyridine gave only this type of product. The other methyl-2-aminopyridines gave, in addition, homologs of the 1:2 adduct above noted. A 1:1 adduct, a methyl 2-imino-3(or 4)-methyl-1(2H)-pyridineacrylate, could also be obtained in the reaction with 3-methyl-2-aminopyridine and 4-methyl-2-aminopyridine

The addition of amines to α,β-acetylenic esters has been reported to give β-amino-α,β-ethylenic esters.[1] The addition of 2-aminopyridines to an α,β-acetylenic ester has not been reported. However, this amine adds to methyl acrylate to give not only a noncyclic product derived from the amino tautomer[2] but also a cyclic product derived from the imino tautomer of the aminopyridine.[2,3] It appeared of interest to investigate the effect of the 2-aminopyridine tautomerism on its addition to an α,β-acetylenic ester such as methyl propiolate.

By analogy with the reported reaction with methyl acrylate, the addition of 2-aminopyridine to methyl propiolate might be expected to give two products, methyl 2-(2-pyridylamino)acrylate (I. R = H) and 2H-pyrido[1,2-a]pyrimidin-2-one (II. R = H).

Compounds having both types of structures are known. The acid produced by hydrolysis of I, 2-(2-pyridylamino)acrylic acid, can be prepared by hydrolysis of diethyl (2-pyridylaminomethylene)

(1) C. Moureu and I. Lazennec, *Bull. Soc. Chim.*, **35**, 1190 (1906).

(2) R. Adams and I. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952).

(3) G. R. Lappin, *J. Org. Chem.*, **23**, 1358 (1958).