and dried *in vacuo* over phosphorus pentoxide at 60° for 8 hr.; yield 1.05 g. (53%); m.p. 178–180°, the melt solidifying and remelting > 260° dec.; λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1—248 (15.5), 274 (23.6), 320 (6.55); pH 7—234 (17.5), 268 (13.2), 338 (12.5); pH 13—232 (17.9), 267 (12.7), 338 (12.6); R_{Ad}: A—1.23; B—0.94 and 1.16; C—1.48; D—2.26.

Anal. Calcd. for $C_8H_{10}ClN_3S$: C, 44.54; H, 4.68; N, 19.49. Found: C, 44.66; H, 4.72; N, 19.47.

(b) **Hydrochloride.**—A well stirred suspension of 1-(2-chloroethyl)-2,3-dihydromidazo[1,2-*c*]pyrimidine-5(1*H*)-thione (IV) (500 mg., 2.33 mmoles) in 20 ml. of chloroform was cooled in an ice bath to 0° and anhydrous hydrogen chloride slowly bubbled through the suspension for 2 hr. The volatiles were removed under reduced pressure to give a thick syrup, which formed a white crystalline residue on repeated *in vacuo* evaporations with additions of ethyl alcohol. The residue was recrystallized from a small volume of ethyl alcohol and dried over phosphorus pentoxide *in vacuo* at 60° for 18 hr.; yield 450 mg. (76%); m.p. 196–198°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1—247 (14.3), 273 (21.9), 320 (6.00); pH 7—233 (16.4), 267 (12.3), 338 (12.0); pH 13—233 (16.4), 267 (11.9), 338 (12.0); EtOH—244 (13.4), 277 (23.4), 329 (5.56); R_{Ad}: A—1.34; B—1.03 and 1.17; C—1.50; D—2.14.

Anal. Calcd. for $C_8H_{10}ClN_3S \cdot HCl$: C, 38.10; H, 4.40; N, 16.67. Found: C, 38.34; H, 4.52; N, 16.60.

The picrate was prepared in ethyl alcohol and recrystallized from methyl alcohol; m.p. 176–178° dec.; λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1—245 (16.0), 274 (15.7), 335 (9.06); pH 7—232 (17.4), 260 (10.9), 344 (14.7); pH 13—232 (17.7),; 260 (10.9), 345 (15.0); R_{Ad}: A—1.47; B—1.22; C—1.59 and 1.94; D—1.49.

Anal. Calcd. for $C_{14}H_{13}ClN_6O_7S$: C, 37.80; H, 2.94; N, 18.90. Found: C, 38.02; H, 3.21; N, 18.59.

Acknowledgment.—The authors are indebted to the members of the Analytical Section of Southern Research Institute who, under the direction of Dr. W. J. Barrett, performed the spectral and microanalytical determinations reported and to Miss Mary Broadaway for the chromatographic work reported.

Methylaminomethylsuccinic Acid

FREDERICK C. UHLE

Department of Pharmacology, Harvard Medical School, Boston 15, Massachusetts

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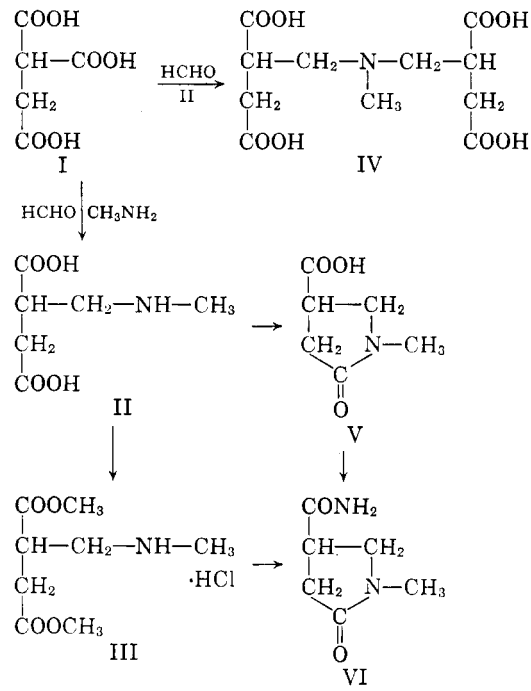
Some years ago the preparation of a methylaminodicarboxylic acid designed as an intermediate for a projected synthesis of lysergic acid was mentioned in a preliminary communication.[1] Experimental details, together with newer results, are given in the present report.

Carboxysuccinic acid (I) was allowed to react with aqueous methylamine and formaldehyde under Mannich conditions[2] to afford methylaminomethylsuccinic acid (II). Esterification of II with methanolic hydrogen chloride in the presence of 2,2-dimethoxypropane,[3] or with methanol and thionyl chloride,[4] gave 85% of nicely crystalline, nonhydroscopic dimethyl methylaminomethylsuccinate hydrochloride (III). Esterification of II with ethanolic hydrogen chloride furnished the less stable diethyl methylaminomethylsuccinate hydrochloride. The methylamino acid and its dimethyl and diethyl esters were characterized as *N*-p-toluenesulfonyl derivatives.



Brief pyrolysis of II at the melting point, or prolonged boiling of its aqueous solution, gave 1-methyl-5-oxo-3-pyrrolidinecarboxylic acid (V).[5] Treatment of dimethyl methylaminomethylsuccinate hydrochloride (III) with concentrated aqueous ammonia at 0° afforded 1-methyl-5-oxo-3-pyrrolidinecarboxamide (VI). Reaction of diethyl bromomethylsuccinate with ethanolic methylamine provided the ethyl ester of V. Hydrogen chloride ethanolysis of the ethyl ester at reflux temperature opened the pyrrolidone ring to give the diethyl ester hydrochloride of II.

Condensation of methylaminomethylsuccinic acid (II) with carboxysuccinic acid (I) and formaldehyde gave the methylamino tetracarboxylic acid IV. Esterification of IV with methanol and thionyl chloride afforded the tetramethyl ester hydrochloride.

(1) F. C. Uhle, *J. Am. Chem. Soc.*, **73**, 2402 (1951).

(2) C. A. Mannich and E. Ganz, *Ber.*, **55**, 3486 (1922).

(3) For introduction of this excellent general procedure see N. B. Lorette and J. H. Brown, Jr., *J. Org. Chem.*, **24**, 261 (1959).

(4) For other examples of this method see M. Brenner and W. Huber, *Helv. Chim. Acta*, **36**, 1109 (1953); F. C. Uhle and L. S. Harris, *J. Am. Chem. Soc.*, **78**, 381 (1956).

(5) This compound has also been prepared (70%) from itaconic acid with 25% aqueous methylamine at reflux temperature during forty minutes: P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1092 (1956).

Reaction of dimethyl methylaminomethylsuccinate with various heterocyclic α-bromo ketones will be described elsewhere.

Experimental[6]

Methylaminomethylsuccinic Acid (II).—To a solution of 1.62 g. (0.01 mole) of carboxysuccinic acid (I)[7] in 1 ml. of water was added dropwise, with cooling, 1 ml. (0.011 mole) of 11 *N* aqueous methylamine, followed by 0.825 ml. of 37% aqueous formaldehyde (equivalent to 0.33 g. or 0.011 mole of formaldehyde). A brisk evolution of carbon dioxide began within a few minutes. After 2 days at 25°, the solution was heated under reflux for 15 min., cooled, and diluted with 10 ml. of methanol. After 20 hr. at 0°, the precipitate was collected by filtration to give 700 mg. (43%) of prismatic needles; m.p. 110–115°. Recrystallization, accomplished by dissolution in 1 ml. of warm water, followed by dilution with 10 ml. of methanol, gave material melting at 133–137°.

Although the compound crystallizes exceedingly well, the melting point is not a reliable index of identity or purity, varying considerably from one preparation, and from one crystallization, to the next; samples melting as high as 145–155° have been obtained. A satisfactory infrared spectrum in potassium bromide could not be secured.

Anal. Calcd. for $C_6H_{11}NO_4$ (161.16): C, 44.71; H, 6.88; N, 8.69. Found: C, 44.81; H, 6.91; N, 8.82.

***N*-Methyl-*p*-toluenesulfonamidomethylsuccinic Acid.**—To a solution of 161 mg. (0.001 mole) of methylaminomethylsuccinic acid (II) and 336 mg. (0.006 mole) of potassium hydroxide in 1.5 ml. of water was added 384 mg. (0.002 mole) of finely powdered *p*-toluenesulfonyl chloride. When the mixture had been stirred magnetically for 20 hr. at 25°, the clear solution was diluted with 1 ml. of water and acidified with 1 ml. of 6 *N* aqueous hydrochloric acid. After 20 hr. at 0°, the precipitate was collected by filtration, washed with water, and recrystallized from water to give 220 mg. (70%) of needles; m.p. 141–144°; infrared spectrum: 5.95 (carboxyl), 7.50, 8.65 μ (—SO_2N—).

Anal. Calcd. for $C_{13}H_{17}NSO_6$ (315.35): C, 49.51; H, 5.44; N, 4.44. Found: C, 49.57; H, 5.47; N, 4.51.

Dimethyl Methylaminomethylsuccinate Hydrochloride (III).—(a) To a solution of approximately 3% methanolic hydrogen chloride (prepared by addition of 1 ml. of acetyl chloride to 20 ml. of methanol) was added 322 mg. (0.002 mole) of methylaminomethylsuccinic acid (II) and 832 mg. (0.008 mole) of 2,2-dimethoxypropane. After 45 hr. at 25°, the solution was concentrated under reduced pressure to give a remainder from which 20 ml. of toluene was vacuum distilled. A solution of the residue in a few drops of methanol was diluted with ethyl acetate (in which product is sparingly soluble) to give, after 20 hr. at 0°, 385 mg. (85%) of dense, long needles, m.p. 107–110°. The analytical sample, from methanol–ethyl acetate, melted at 111–113°; the crystals were stable under atmospheric conditions; infrared spectrum: 3.70, 3.75, 3.80, 4.00 (w), 4.25 (w) (substituted ammonium), 5.85 μ (ester), twenty prominent bands in finger print region.

Anal. Calcd. for $C_8H_{16}NO_4Cl$ (225.68): C, 42.57; H, 7.15; N, 6.21. Found: C, 42.38; H, 7.09; N, 6.28.

(b) To 4 ml. of methanol at 0° was added dropwise, with cooling, 715 mg. (0.44 ml.) (0.006 mole) of thionyl chloride; after 1 hr. at 0°, 322 mg. (0.002 mole) of methylaminomethylsuccinic acid (II) was added. After 45 hr. at 0°, followed by 25 hr. at 25°, the solution was concentrated under reduced pressure to give a remainder from which 20 ml. of toluene was vacuum distilled. A solution of the residue in a few drops of methanol was diluted with ethyl acetate to give 360 mg. (80%) of needles, m.p. 96–99°; recrystallization from methanol–ethyl acetate brought the melting point to 111–113°.

Dimethyl *N*-Methyl-*p*-toluenesulfonamidomethylsuccinate.—To a solution of 77 mg. (0.0004 mole) of *p*-toluenesulfonyl chloride in 1 ml. of anhydrous pyridine at 0° was added 68 mg. (0.0003 mole) of dimethyl methylaminomethylsuccinate hydrochloride (III). After 20 hr. at 0°, the mixture was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Recrystallization from a mixture of ethyl acetate and petroleum ether (b.p. 30–60°) gave 55 mg. (53%) of dense, crystalline kernels, m.p. 63–64°. The analytical sample melted at 64–66°; infrared spectrum: 5.80 (ester), 7.50, 8.60 μ (—SO_2N—).

Anal. Calcd. for $C_{15}H_{21}NSO_6$ (343.40): C, 52.46; H, 6.17; N, 4.08. Found: C, 52.41; H, 5.94; N, 4.22.

Diethyl Methylaminomethylsuccinate Hydrochloride.—To a solution of approximately 6% ethanolic hydrogen chloride (prepared by addition of 2 ml. of acetyl chloride to 20 ml. of absolute ethanol) was added 403 mg. (0.0025 mole) of methylaminomethylsuccinic acid (II). After 20 hr. at 25°, the solution was concentrated under reduced pressure to give a residue from which three successive portions of 10 ml. of benzene were vacuum distilled. The ethanolic hydrogen chloride treatment (20 hr.) and evaporation with benzene were repeated. The residue was recrystallized from ethyl acetate to give 530 mg. (83%) of plates; m.p. 60–70°. The analytical sample, from ethyl acetate, melted at 70–71°; infrared spectrum: 3.65, 4.10 (w) (substituted ammonium), 5.80 μ (ester).

Anal. Calcd. for $C_{10}H_{20}NO_4Cl$ (253.73): C, 47.33; H, 7.95; N, 5.52; Cl, 13.97. Found: C, 47.08; H, 7.90; N, 5.86; Cl, 13.94.

Although the ester hydrochloride crystallizes well from ethyl acetate, the isolated solid is rather hygroscopic and must be stored in a desiccator; extended exposure to humid atmosphere leads to liquefaction and decomposition.

The compound was also prepared from ethyl 1-methyl-5-oxo-3-pyrrolidinecarboxylate with ethanolic hydrogen chloride at reflux temperature[8]; the reaction was worked up as was the esterification of II.

Diethyl *N*-Methyl-*p*-toluenesulfonamidomethylsuccinate.—To a solution of 77 mg. (0.0004 mole) of *p*-toluenesulfyl chloride in 1 ml. of anhydrous pyridine at 0° was added 51 mg. (0.0002 mole) of diethyl methylaminomethylsuccinate hydrochloride. After 2 days at 0°, the solution was diluted with water to give a precipitate which was collected by filtration, washed with water, dried, and recrystallized from a mixture of ethyl acetate and petroleum ether (b.p. 30–60°) to give 65 mg. (87%) of dense, crystalline kernels; m.p. 51–52°; infrared spectrum: 5.80 (ester), 7.50, 8.60 μ (—SO_2N—).

Anal. Calcd. for $C_{17}H_{25}NO_6S$ (371.45): C, 54.97; H, 6.78; N, 3.77. Found: C, 54.61; H, 6.69; N, 4.02.

1-Methyl-5-oxo-3-pyrrolidinecarboxylic Acid (V).—(a) Pyrolysis of methylaminomethylsuccinic acid (II) at the melting point during 5 min., followed by recrystallization from ethyl acetate, gave 70% of dense crystals; m.p. 155–156°[5]; infrared spectrum: 5.85 (carboxyl), 6.15 μ (cyclic tertiary amide).

Anal. Calcd. for $C_6H_9NO_3$ (143.14): C, 50.34; H, 6.34; N, 9.79. Found: C, 50.27; H, 6.26; N, 9.79.

(b) A solution of 161 mg. (0.001 mole) of methylaminomethylsuccinic acid (II) in 3 ml. of water was heated under

(6) Melting points were observed on a calibrated micro hot stage. Microanalyses were performed by Dr. S. M. Nagy, Massachusetts Institute of Technology, Cambridge, Massachusetts. Infrared spectra, in potassium bromide, were recorded with a Perkin-Elmer spectrophotometer, Model 137; only those maxima of significance in interpretation are noted.

(7) C. A. Bischoff, *Ann.*, **214**, 40 (1882).

(8) *Cf.* the ethanolysis of 5-oxo-2-pyrrolidinecarboxylic acid with ethanolic hydrogen chloride under reflux to give diethyl glutamate hydrochloride: R. B. Angier, C. W. Waller, B. L. Hutchings, J. H. Boothe, J. H. Mowat, J. Semb, and Y. SubbaRow, *J. Am. Chem. Soc.*, **72**, 74 (1950).

reflux for 15 hr.[9] The solution was concentrated under reduced pressure to give a residue (freely soluble in absolute ethanol) which was recrystallized from ethyl acetate to afford 105 mg. (74%); m.p. 145–155°.

Ethyl 1-methyl-5-oxo-3-pyrrolidinecarboxylate was prepared by vacuum distillation (after filtration of methylamine hydrobromide) of the product from treatment of diethyl bromomethylsuccinate[10] with 3 equivalents of 3.5 *N* ethanolic methylamine at 0°; b.p. 167–168°/20.5 mm.[11]; d_{20}^{20} 1.1170; $n^{25}D$ 1.4620; M_D calcd.: 42.43; M_D found: 42.13.

Anal. Calcd. for $C_8H_{13}NO_3$ (171.18): C, 56.12; H, 7.65. Found: C, 56.10; H, 7.55.

1-Methyl-5-oxo-3-pyrrolidinecarboxamide (VI).—To 5 ml. of concentrated aqueous ammonia at 0° was added 113 mg. (0.0005 mole) of dimethyl methylaminomethylsuccinate hydrochloride (III). After 20 hr. at 0°, the solution was concentrated under diminished pressure to give a residue which was triturated with chloroform to discard 22 mg. of insoluble ammonium chloride. The chloroform filtrate was concentrated under reduced pressure to give a residue which was recrystallized from a mixture of methanol and ethyl acetate to afford 60 mg. (85%) of plates; m.p. 140–142°[12]; infrared spectrum: 5.95, 6.05, 6.15, 6.65 μ (amide bands).

Anal. Calcd. for $C_6H_{10}N_2O_2$ (142.16): C, 50.69; H, 7.09; N, 19.71. Found: C, 50.97; H, 7.21; N, 19.88.

Methyliminodi(methylsuccinic) Acid (IV).—To a solution of 483 mg. (0.003 mole) of methylaminomethylsuccinic acid (II) and 486 mg. (0.003 mole) of carboxysuccinic acid (I) in 1 ml. of water was added 0.25 ml. of 37% aqueous formaldehyde (equivalent to 100 mg. or 0.0033 mole of formaldehyde); a brisk evolution of carbon dioxide commenced within a few minutes. A precipitate, which began to form within 1 hr., had completely pervaded the solution after 2 hr. The mixture was kept at 25° for 2 days, diluted with 2 ml. of water, and heated to dissolve the product. After 20 hr. at 25°, followed by 2 days at 0°, the precipitate was collected by filtration and recrystallized from water to afford 255 mg. (29%) of plates; m.p. 180–183°; infrared spectrum: 5.80, 5.85 μ (carboxyl).

Anal. Calcd. for $C_{11}H_{17}NO_8$ (291.26): C, 45.36; H, 5.89; N, 4.81. Found: C, 45.33; H, 5.92; N, 4.85.

Tetramethyl Methyliminodi(methylsuccinate) Hydrochloride.—To 2.5 ml. of methanol at 0° was added dropwise, with cooling, 357 mg. (0.22 ml.) (0.003 mole) of thionyl chloride; after 1 hr. at 0°, 146 mg. (0.0005 mole) of methyliminodi(methylsuccinic) acid (IV) was added. After 2 days at 0°, followed by 2 days at 25°, the solution was concentrated under diminished pressure to give a remainder from which 20 ml. of toluene was vacuum distilled. Two recrystallizations of the residue from ethyl acetate gave 165 mg. (86%) of needles; m.p. 117–121°; infrared spectrum: 4.20, 4.30 (substituted ammonium), 5.80 μ (ester).

Anal. Calcd. for $C_{15}H_{26}NO_8Cl$ (383.83): C, 46.93; H, 6.83; N, 3.65. Found: C, 47.15; H, 6.80; N, 3.57.

Acknowledgment.—The author is indebted to Louis S. Harris for preparative assistance in the early work; to the National Institute of Mental Health (M-2029) and the National Heart Institute (H-2205), National Institutes of Health, United States Public Health Service; and to the Eugene Higgins Trust for financial support.

(9) Cyclization proceeded to a lesser extent during short periods of reflux as shown by incomplete solubility of the reaction residue in absolute ethanol; *cf.* the conversion of aqueous glutamic acid to 5-oxo-2-pyrrolidinecarboxylic acid: J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, J. Wiley & Sons, Inc., New York, N. Y., 1961, pp. 1934–1937.

(10) R. Anschütz and F. Reuter, *Ann.*, **254**, 144 (1889). In the older literature, bromomethylsuccinic acid was known as "itabrompyrotartaric acid."

(11) *Cf.* the preparation from diethyl itaconate with methylamine: Y. H. Wu and R. F. Feldkamp, *J. Org. Chem.*, **26**, 1519 (1961).

(12) *Cf.* the preparation from dimethyl itaconate with one equivalent of methanolic methylamine followed by excess methanolic ammonia: H. C. Scarborough, J. L. Minielli, B. C. Lawes, W. G. Lobeck, Jr., J. R. Corrigan, and Y. H. Wu, *ibid.*, **26**, 4955 (1961).

Acyl Derivatives of 3,4-Dihydro-4-oxobenzo-1,2,3-triazine

M. S. GIBSON AND A. W. MURRAY

Chemistry Department, Faculty of Technology, The University, Manchester 1, England

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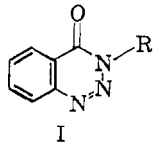
Heller[1] has reported the preparation of an acetyl and a benzoyl derivative of 3,4-dihydro-4-oxobenzo-1,2,3-triazine (I, R = H) by reaction of the sodium or silver salt with the appropriate acid chloride. These compounds were formulated as lactam (*i.e.* *N*-acyl) derivatives rather than lactim (*O*-acyl) derivatives since (i) methylation under similar conditions had been shown to give the *N*-methyl derivative (I, R=Me), and (ii) ethoxycarbonylation had given an ethoxycarbonyl derivative which was degraded by hot hydrochloric acid to (II); the latter compound contains nitrogen linked to two carbonyl groups, thus implying formula (I, R = COOEt) for the ethoxycarbonyl derivative, assuming that no lactim–lactam isomerisation occurs under the influence of acid.



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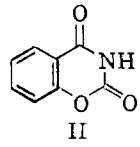

II

In two recent reviews of triazine chemistry,[2,3] the possibility that these compounds are *O*-acyl derivatives has been revived, and, without further evidence, the lactim formulation has actually been adopted for purposes of tabulation.

However, the infrared spectra of both the acetyl and the benzoyl derivative show two absorption bands due to carbonyl in the 1750–1650-cm.$^{-1}$ region. In this respect, these compounds resemble the *N*-acylisocarbostyrils, but differ from, *e.g.*, 2-benzoyloxypyridine and 4-acetoxyisoquinoline which show only one such band (at 1740 cm.$^{-1}$).[4] The ultraviolet absorption spectrum of the acetyl derivative is similar to that of the parent compound, though shifted to shorter wave length;

(1) G. Heller, *J. prakt. Chem.*, (2) **111**, 1 (1925).

(2) J. G. Erickson, "The Chemistry of Heterocyclic Compounds," Vol. 10, A. Weissberger, ed., Interscience Publishers, Inc., New York, N. Y., 1956, p. 17.

(3) J. P. Horwitz, "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, ed., J. Wiley & Sons, Inc., New York, N. Y., 1961, p. 787.

(4) M. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1956).