[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL]

The Synthesis of α-Methylamino Acids

BY FREDERICK C. UHLE AND LOUIS S. HARRIS

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A general procedure for the synthesis of α-methylamino acids employing the crystalline sodium derivative of dimethyl acetylmethylaminomalonate has been developed. The intermediate dimethyl methylaminomalonate has been prepared by two methods: (1) by esterification of methylaminomalonic acid with methanol and thionyl chloride and (2) by reaction of dimethyl bromomalonate with methylbenzylamine followed by hydrogenolysis in acetic acid solution in the presence of platinum. Condensation of the sodium derivative VII with gramine methiodide, with benzyl chloride and with 4(5)-chloromethylimidazole, followed by hydrolysis of the intermediate alkylation products, has led to the production, respectively, of α-methylamino-β-(3-indole)-propionic acid, N-methyl-DL-phenylalanine, and α-N-methyl-DL-histidine.

α-Methylamino acids have been the subject of interest in a number of biochemical studies relating to the intermediary metabolism and fate of the twenty-odd building blocks of the proteins.[1] Furthermore, they are of concern to the organic chemist as potential intermediates in the synthesis of complex natural products, a significant number of which are characterized by the presence in the molecule of an N-methyl group.

Hitherto, synthetic methylamino acids have been constructed principally by two methods: (1) by the reaction of an α-halogen acid with methylamine,[2] or (2) by the condensation of an aldehyde with creatinine[3] or with N-methylhydantoin,[4] followed by reduction with reagents of the type of sodium amalgam,[3d] ammonium sulfide[5] or red phosphorus–hydriodic acid,[6] and, finally, alkaline cleavage of the cyclic dihydro derivative. A less frequently employed procedure has involved the treatment of an aldehyde cyanohydrin with methylamine,[7] while the device of methylation of amino acid *p*-toluenesulfonates with dimethyl sulfate, followed by vigorous acid hydrolysis, has occasionally been exploited.[8] The generality of these methods, however, is compromised by the frequent inaccessibility or difficulty of preparation of the required halogen acid or carbonyl compound, in the case of complex, or of sensitive structures. Moreover, reduction of the intermediate aldals obtained in the creatinine and methylhydantoin procedures has often proved troublesome and no single reagent has been found to be uniformly satisfactory for the purpose.[9]

Inasmuch as certain α-methylamino acids were desired as intermediates in connection with synthetic work in the field of the ergot alkaloids, some effort was devoted to attempts to develop a general procedure suitable for application with the rather labile indole systems concerned. The route chosen was patterned on the now well established method for the preparation of α-amino acids incorporating the condensation of primary halides, or of reactive quaternary salts with acetaminocyanoacetic or acetaminomalonic esters.[10]

The related methylamino esters required for an appraisal of this approach were secured by two independent pathways as a consequence of study of a number of alternatives. Although diethyl bromomalonate has been transformed in good yield to diethyl dimethylaminomalonate[11] and to diethyl piperidinomalonate,[12] with dimethylamine and with piperidine, respectively, attempts to effect the reaction of methylamine with the bromo ester under a multiformity of experimental conditions led invariably to the isolation of ethyl ethylenetetracarboxylate as the predominant product of the reaction.[13] While bromomalonamide and bromomalonmethylamide readily reacted with methylamine to afford the substituted methylamino amides which were characterized as their salts and as their acyl derivatives, alcoholysis of the amides to yield malonic ester derivatives was not achieved.

Attempts to prepare dimethyl methylaminomalonate by catalytic hydrogenation of a mixture of methyl oxomalonate and methylamine in methanol solution, as well as efforts to methylate[14] with dimethyl sulfate the anil derived from aminomalonic ester, appeared without promise. Treatment of ethyl acetaminocyanoacetate with methyl iodide in acetone solution in the presence of potassium hydroxide[15] led to the production of the DL-

(1) C. G. MacKenzie in "Amino Acid Metabolism," edited by W. D. McElroy and B. Glass, The Johns Hopkins Press, Baltimore, Md., 1955, pp. 684–726; W. G. Gordon and R. W. Jackson, *J. Biol. Chem.*, **110**, 151 (1935); J. B. Fishman and A. White, *ibid.*, **113**, 175 (1936).

(2) *Cf.* E. Fischer, *Ber.*, **37**, 3062 (1909); references 28c, 31, 33.

(3) *Cf.* (a) E. Erlenmeyer, *Ann.*, **284**, 49 (1895); (b) B. H. Nicolet and E. D. Campbell, THIS JOURNAL, **50**, 1155 (1928); (c) V. Deulofeu and G. Mendivelzua, *Ber.*, **68**, 783 (1935); (d) V. Deulofeu and T. J. Guerrero, "Organic Syntheses," Coll. Vol. 3, John Wiley and Sons Inc., New York, N. Y., 1955, p. 586.

(4) *Cf.* H. L. Wheeler and C. Hoffman, *Am. Chem. J.*, **45**, 369, 471 (1911); T. B. Johnson and B. H. Nicolet, *ibid.*, **47**, 459 (1912).

(5) W. J. Boyd and W. Robson, *Biochem. J.*, **29**, 546 (1935); reference 28b.

(6) C. R. Harington and G. Barger, *ibid.*, **21**, 169 (1927); J. Lamb and W. Robson, *ibid.*, **25**, 1231 (1931).

(7) *Cf.* J. Fried and D. E. Walz, THIS JOURNAL, **74**, 5471 (1952); M. L. Wolfrom and A. Thompson, *ibid.*, **66**, 1847 (1947).

(8) *Cf.* E. Fischer and W. Lipschitz, *Ber.*, **48**, 360 (1915); W. Cocker and A. Lapworth, *J. Chem. Soc.*, 1894 (1931).

(9) *Cf.* A. H. Cook and S. F. Fox, *ibid.*, 2342 (1949), for comments on the desideratum for a general synthesis of N-alkylamino acids.

(10) H. R. Snyder and C. W. Smith, THIS JOURNAL, **66**, 350 (1944); H. R. Snyder, F. F. Shekleton and C. D. Lewis, *ibid.*, **67**, 310 (1945); N. F. Albertson, S. Archer and C. M. Suter, *ibid.*, **67**, 36 (1945); N. F. Albertson and S. Archer, *ibid.*, **67**, 308 (1945); N. F. Albertson and B. F. Tullar, *ibid.*, **67**, 502 (1945).

(11) E. R. H. Jones and W. Wilson, *J. Chem. Soc.*, 547 (1949).

(12) N. H. Cromwell and A. Hassner, THIS JOURNAL, **77**, 1570 (1955).

(13) The propensity of diethyl bromomalonate to yield ethyl ethylenetetracarboxylate when allowed to react with basic reagents of diverse types serves as the principal method of preparation of the tetraester; *cf.* B. B. Corson and W. L. Benson, "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 273, and references therein.

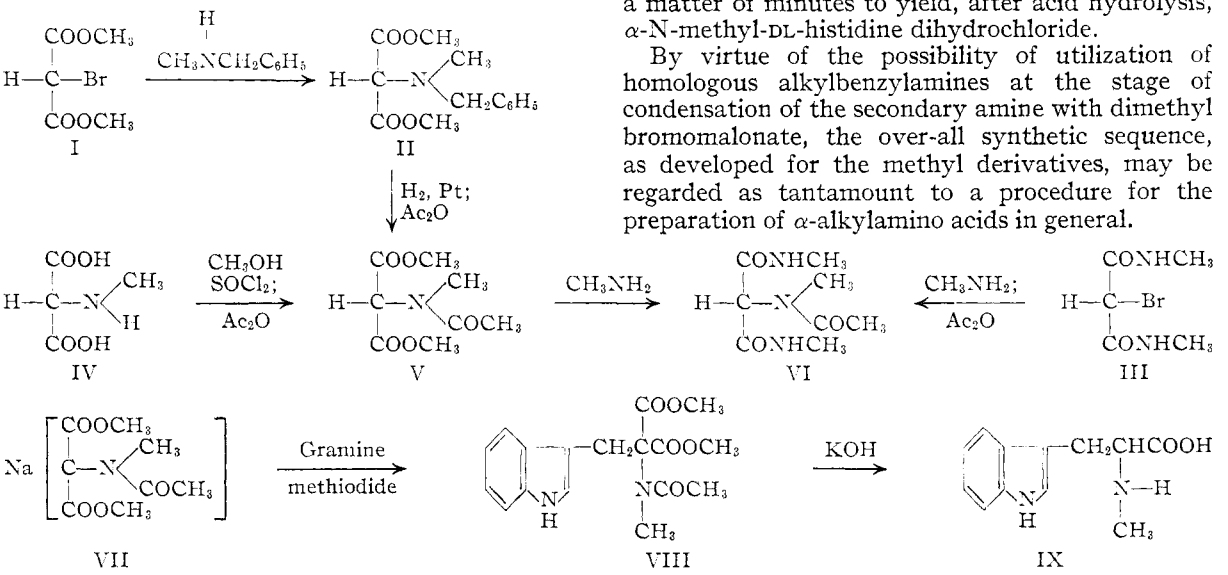
(14) *Cf.* G. S. Walpole, *J. Chem. Soc.*, 941 (1910); S. Kirkwood and L. Marion, THIS JOURNAL, **72**, 2523 (1950).

(15) *Cf.* I. J. Pachter and M. C. Kloetzel, *ibid.*, **74**, 1321 (1952).

alanine precursor, ethyl α-methyl-α-acetaminocyanoacetate.[16]

The preparation of dimethyl acetylmethylaminomalonate (V) was accomplished by two methods. Methylaminomalonic acid (IV), which under esterification conditions of all conventional types investigated yielded sarcosine ester, was transformed with methanol and thionyl chloride[17] at −5° to the dimethyl ester which was isolated as the hydrochloride and which, on treatment with acetic anhydride, afforded the acetyl derivative V. This substance when allowed to react with methylamine in methanol solution yielded the methylamide VI, identical with the product obtained by treatment of bromomalonmethylamide (III) with methylamine and acetic anhydride.

In a second procedure eminently adapted for large scale preparation, dimethyl bromomalonate (I) was allowed to react with methylbenzylamine to afford dimethyl methylbenzylaminomalonate



(II), which, on hydrogenolysis in acetic acid solution in the presence of platinum, followed by acetylation with acetic anhydride, yielded V, identical with the esterification product from methylaminomalonic acid.

The acetylmethylamino ester V, when allowed to react with sodium methoxide in methanol solution, gave a slightly soluble sodium derivative which was demonstrated to be non-hygroscopic, stable and suitable for storage without special precautions. This nicely crystalline sodium derivative proved to be an appropriate reagent for the preparation of α-methylamino acids. Treatment with alkylating agents under conditions imposed by the reactivity of the individual quaternary salt or alkyl halide afforded condensation products which in most cases were not isolated. Hydrolysis with aqueous sodium carbonate[18] gave the acetylmethylamino acid, while vigorous cleavage in acid or in fixed alkali solution yielded the methylamino acid.

Condensation of VII with gramine methiodide in methanol solution afforded dimethyl α-acetylmethylamino-α-skatylmalonate (VIII), alkaline cleavage of which gave rise to α-methylamino-β-(3-indole)-propionic acid, "DL-abrine," IX. When the sodium derivative VII was allowed to react in methanol solution at reflux temperature with benzyl chloride in the presence of a small quantity of sodium iodide, the transformation was observed to be complete after a period of five hours. Sodium carbonate hydrolysis of the total reaction product afforded α-acetylmethylamino-β-phenylpropionic acid, acid cleavage of which gave N-methyl-DL-phenylalanine. Treatment of VII in methanol solution at 0° with the exceedingly reactive 4(5)-chloromethylimidazole led to neutralization within a matter of minutes to yield, after acid hydrolysis, α-N-methyl-DL-histidine dihydrochloride.

By virtue of the possibility of utilization of homologous alkylbenzylamines at the stage of condensation of the secondary amine with dimethyl bromomalonate, the over-all synthetic sequence, as developed for the methyl derivatives, may be regarded as tantamount to a procedure for the preparation of α-alkylamino acids in general.

Experimental[19]

Methylaminomalonic Acid (IV).[20]—To a well agitated solution of 52.0 g. (0.5 mole) of malonic acid in 500 ml. of acetic acid at 10° was added dropwise 80 g. (0.5 mole) of bromine. The acetic acid was distilled under reduced pressure and the residue was dried to constant weight over potassium hydroxide in a vacuum desiccator. The semi-solid residue was dissolved in methanol and 400 ml. of a 30% solution of methylamine in methanol was added dropwise with external cooling. After the mixture had been maintained at 0° for 2 days, the crystalline deposit was collected by filtration and washed with methanol. The solid material was dissolved in water and treated with an aqueous solution of lead acetate. After 24 hours at 0°, the deposit was collected by filtration, washed with water, resuspended in water and treated with hydrogen sulfide. The lead sulfide was removed by filtration and washed with water. The aqueous filtrate was concentrated under reduced pressure at 30°. The crystalline precipitate was collected by filtration and the filtrate was treated with ethanol to yield an additional

(16) *Cf.* S. Tatsuoka and H. Miyazaki, *J. Pharm. Soc. Japan*, **71**, 716 (1951), who obtained this substance by methylation of ethyl acetaminocyanoacetate with dimethyl sulfate or with methyl *p*-toluenesulfonate, in the presence of sodium ethoxide. Unfortunately, this article, which is not easily accessible, is incorrectly abstracted, though correctly indexed in *C. A.*, **46**, 1978 (1952).

(17) *Cf.* M. Brenner and W. Huber, *Helv. Chim. Acta*, **36**, 1109 (1953).

(18) N. F. Albertson, THIS JOURNAL, **72**, 1396 (1950).

(19) Microanalyses and spectroscopic determinations by Dr. S. M. Nagy and associates of the Massachusetts Institute of Technology, Cambridge, Mass. The melting points were observed on the microhot stage and are corrected.

(20) An adaptation of the procedures of O. Lutz, *Ber.*, **35**, 2549 (1902), and of F. Knoop and H. Oesterlin, *Z. physiol. Chem.*, **170**, 208 (1927).

quantity of product. It was found to be essential to carry out the concentration of the solution shortly after decomposition of the lead salt in order to minimize losses due to decarboxylation; yield 35.0 g. (52%), m.p. 137–142° with ebullition.

Dimethyl Methylbenzylaminomalonate (II).—To a solution of 42.2 g. (0.20 mole) of dimethyl bromomalonate,[21] b.p. 103–104° (19 mm.), in 80 ml. of absolute methanol was added dropwise 48.4 g. (0.40 mole) of methylbenzylamine. The mixture was maintained at reflux temperature for a period of 1 hour, the methanol was distilled under diminished pressure and ether was added to precipitate methylbenzylamine hydrobromide which was collected by filtration. The residue from the ether was distilled under reduced pressure through a 45-cm. vacuum-jacketed Vigreux column; yield 32.0 g. (64%), b.p. 118° (0.3 mm.), *d* 1.122, $n^{24}D$ 1.5037; M_D calcd. 66.05, found 66.28.

Anal. Calcd. for $C_{13}H_{17}NO_4$ (251.28): C, 62.14; H, 6.82; N, 5.58. Found: C, 62.20; H, 6.84; N, 5.71.

Dimethyl Acetylmethylaminomalonate (V). A.—To 24 ml. (0.6 mole) of methanol at −5° was added, dropwise and with stirring, 4.5 ml. (0.06 mole) of thionyl chloride. After the solution had been maintained at −5° for 5 minutes, 3.99 g. (0.03 mole) of methylaminomalonic acid was added in portions and the whole was stirred at −5° for 3 hours. After the solution had been allowed to remain at ordinary temperature for a period of 24 hours, the methanol was distilled under diminished pressure. The residue was dissolved in 3 ml. of water, ether was added and solid potassium bicarbonate was admitted to neutrality. The ether was separated by decantation and the residue was extracted with several successive portions of ether. The combined extracts were dried over magnesium sulfate and the ether was distilled under diminished pressure. The residue was treated at 90° for a period of 15 minutes with 3 ml. of acetic anhydride. The remainder from vacuum distillation of the solvents was crystallized from methylcyclohexane; yield 3.95 g. (65%), m.p. 58–59°.

Anal. Calcd. for $C_8H_{13}NO_5$ (203.19): C, 47.29; H, 6.45; N, 6.89. Found: C, 47.23; H, 6.71; N, 6.85.

B.—A solution of 10.0 g. (0.04 mole) of dimethyl methylbenzylaminomalonate (II) in 10 ml. of glacial acetic acid was shaken with hydrogen in the presence of 400 mg. of platinum oxide, prereduced with hydrogen. After 1200 ml. of hydrogen had been absorbed during a period of 10 hours (theory 1020 ml.), the catalyst was removed by filtration, 6.0 ml. of acetic anhydride was added and the solution was concentrated under diminished pressure. The residue was recrystallized from methylcyclohexane; yield 6.5 g. (80%), m.p. and mixed m.p. with Va, 58–59°.

Dimethyl Acetylmethylaminomalonate Sodium (VII).—To a solution of 147 mg. (0.0064 mole) of sodium in 4 ml. of absolute methanol was added 1.3 g. (0.0064 mole) of the ester V. After 5 hours at 0°, the crystalline deposit was collected by filtration and was recrystallized from methanol; yield 1.34 g. (92%), m.p. *ca.* 320°.

Anal. Calcd. for $C_8H_{12}NO_5Na$ (225.19): C, 42.67; H, 5.37; N, 6.22. Found: C, 42.63; H, 5.35; N, 6.05.

Dimethyl Methylaminomalonate Hydrochloride.—An ether solution of the free amino ester was treated with anhydrous hydrogen chloride. The precipitate was collected by filtration and was recrystallized from a mixture of absolute ethanol and ether; m.p. 131–133° with ebullition.

Anal. Calcd. for $C_6H_{11}NO_4 \cdot HCl$ (197.63): C, 36.46; H, 6.12; N, 7.09. Found: C, 36.41; H, 6.21; N, 6.96.

Methylaminomalonmethylamide Hydrobromide.—To a well agitated solution of 150 g. (0.72 mole) of bromomalonmethylamide[22] in 600 ml. of methanol was added 680 ml. (3.75 moles) of a 5.35 *N* ethanolic solution of methylamine. After 3 hours at ordinary temperature the methanol was distilled under diminished pressure and the residue was treated with 126 g. of 48% hydrobromic acid. The solution was concentrated *in vacuo* and the remainder was crystallized from methanol; yield 128 g. (74%), m.p. 197–199°.

Anal. Calcd. for $C_6H_{13}N_3O_2 \cdot HBr$ (240.19): C, 30.01; H, 5.88; N, 17.50. Found: C, 30.29; H, 5.99; N, 17.97.

(21) C. A. Bischoff, *Ber.*, **40**, 3135 (1907).

(22) J. V. Backes, R. W. West and M. A. Whiteley, *J. Chem. Soc.*, 365 (1921).

Acetylmethylaminomalonmethylamide (VI). A.—To a well agitated suspension of 33.0 g. (0.20 mole) of silver acetate in 500 ml. of water was added in small quantities 48.8 g. (0.20 mole) of methylaminomalonmethylamide hydrobromide. The silver bromide was removed by filtration and the filtrate was concentrated to dryness under diminished pressure. The residue was treated at 90° for 15 minutes with 20 ml. of acetic anhydride. The solvents were distilled under diminished pressure and the remainder was recrystallized from isopropyl alcohol; yield 36.0 g. (90%), m.p. 135–136°.

Anal. Calcd. for $C_8H_{15}N_3O_3$ (201.22): C, 47.75; H, 7.51; N, 20.88. Found: C, 47.90; H, 7.58; N, 21.21.

B.—A solution of 406 mg. (0.002 mole) of dimethyl acetylmethyl aminomalonate (V) in 10 ml. (0.01 mole) of a 1 *N* solution of methylamine in methanol was maintained at ordinary temperature for a period of 3 days. The methanol was distilled under diminished pressure and the residue was recrystallized from isopropyl alcohol; yield 370 mg. (92%), m.p. and mixed m.p. with VIa, 135–136°.

Ethyl α-Methyl-α-acetaminocyanoacetate. A.—To a solution of 4.75 g. (0.028 mole) of ethyl acetaminocyanoacetate in 100 ml. of acetone was added 5.6 g. (0.10 mole) of powdered potassium hydroxide. To this mixture at reflux temperature was added a solution of 6.0 g. (0.042 mole) of methyl iodide in 15 ml. of acetone. After 1 minute the solid material was removed by filtration and the filtrate was concentrated under diminished pressure. The residue was recrystallized from ethyl acetate; yield 2.5 g. (50%), m.p. 105–107°.

B.—To a solution of 230 mg. (0.01 mole) of sodium in 10 ml. of absolute ethanol was added 1.56 g. (0.01 mole) of ethyl acetaminocyanoacetate followed by 1.26 g. (0.01 mole) of dimethyl sulfate. The ethanol was distilled under diminished pressure and the residue was extracted with ether. The product from the ether solution was recrystallized from ethyl acetate; yield 1.3 g. (71%), m.p. and mixed m.p. with A, 105–107°.[16]

DL-Alanine Derivatives.—A solution of 500 mg. (0.0027 mole) of ethyl α-methyl-α-acetaminocyanoacetate in 5 ml. of water containing 500 mg. of sodium carbonate was maintained at reflux temperature for a period of 15 hours. The solution was acidified with hydrochloric acid and the solvents were distilled under reduced pressure. The residue was extracted with hot absolute ethanol and the remainder after distillation of the ethanol was recrystallized from ethyl acetate to yield N-acetyl-DL-alanine, m.p. and mixed m.p. with an authentic specimen, 137–138°.[23]

A solution of 500 mg. (0.0027 mole) of the ester in 10 ml. of 6 *N* hydrochloric acid was maintained at reflux temperature for a period of 5 hours. The hydrochloric acid was distilled *in vacuo* and the residue was treated with benzoyl chloride and potassium hydroxide solution to yield, after trituration with petroleum ether of the material precipitated by hydrochloric acid, 440 mg. (85%) of N-benzoyl-DL-alanine which was recrystallized from water; m.p. and mixed m.p. with an authentic sample, 164–165°.[24]

A solution of 500 mg. (0.0027 mole) of ethyl α-methyl-α-acetaminocyanoacetate in 2 ml. of 6 *N* hydrochloric acid was maintained under reflux for a period of 15 hours. The solution was concentrated to dryness under diminished pressure and the residue was transformed to N-*p*-toluenesulfonyl-DL-alanine with *p*-toluenesulfonyl chloride and dilute potassium hydroxide solution; yield 230 mg. (35%), m.p. 137–138°[25]; mixed m.p. with *p*-toluenesulfonylsarcosine (m.p. 150–152°),[26] 110–120°.

Dimethyl α-Acetylmethylamino-α-skatylmalonate (VIII).—A solution of 1.58 g. (0.005 mole) of gramine methiodide[27] and 1.15 g. (0.005 mole) of the sodium derivative of dimethyl acetylmethylaminomalonate (VII) in 10 ml. of methanol was maintained at reflux temperature for a period of 15 hours. An equal quantity of water was added to the cooled solution, the crystalline deposit was collected by filtration and was recrystallized from a mixture of methanol and water; yield 1.08 g. (65%), m.p. 140–141°.

(23) E. Fischer and E. Otto, *Ber.*, **36**, 2115 (1903).

(24) E. Fischer, *ibid.*, **32**, 2451 (1899).

(25) E. McChesney and W. Swann, Jr., THIS JOURNAL, **59**, 1116 (1937).

(26) E. Fischer and M. Bergmann, *Ann.*, **398**, 118 (1913).

(27) T. A. Geissman and A. Armen, THIS JOURNAL, **74**, 3916 (1952).

Anal. Calcd. for $C_{17}H_{20}N_2O_5$ (332.25): C, 61.43; H, 6.07; N, 8.43. Found: C, 61.69; H, 6.30; N, 8.49.

α-Methylamino-β-(3-indole)-propionic Acid (IX).—To a solution of 0.40 g. of potassium hydroxide in 2 ml. of water was added 332 mg. (0.001 mole) of the dimethyl ester VIII and the mixture maintained at reflux temperature for a period of 50 hours. The cold solution was acidified with hydrochloric acid and clarified by filtration. The filtrate was neutralized with sodium acetate and the solution was concentrated to dryness under diminished pressure. One milliliter of water was added, and after 15 hours at 0°, the crystalline deposit was collected by filtration and was recrystallized from 1 ml. of water; yield 165 mg. (75%), m.p. 231–233°.[28]

Anal. Calcd. for $C_{12}H_{14}N_2O_2$ (218.25): C, 66.03; H, 6.47; N, 12.84. Found: C, 64.66; H, 6.49; N, 12.47.

The infrared spectrum was identical with that displayed by a specimen of naturally occurring L-abrine.

The hydantion was prepared with potassium cyanate and was crystallized from water; m.p. 213–214°.[28b]

The picrate was prepared in aqueous solution and was recrystallized from a mixture of ethyl acetate and petroleum ether; m.p. 173–175°.[29]

α-Acetylmethylamino-β-phenylpropionic Acid.—A solution of 450 mg. (0.002 mole) of the sodium derivative VII, 253 mg. (0.002 mole) of benzyl chloride and 10 mg. of sodium iodide in 3 ml. of absolute methanol was maintained at reflux temperature for a period of 5 hours. The methanol was distilled under reduced pressure and the residue was treated with a solution of 500 mg. of sodium carbonate in 5 ml. of water. After 15 hours at reflux temperature, the solution was clarified by filtration and was acidified with hydrochloric acid; yield 170 mg. (34%), m.p. 146–147°.[30]

(28) Each investigator who has reported experience with this substance has observed a different melting point: (a) W. G. Gordon and R. W. Jackson, *J. Biol. Chem.*, **110**, 154 (1935), 297°; (b) E. J. Miller and W. Robson, *J. Chem. Soc.*, 1910 (1938), 245°; (c) F. F. Blicke and P. E. Norris, THIS JOURNAL, **76**, 3213 (1954), 272–275°. The compound is considerably more soluble in water and is more difficult to recrystallize and to obtain in anhydrous state than is the naturally occurring L-enantiomorph which melts in the neighborhood of 295°, N. Ghatak and R. Kaul, *J. Indian Chem. Soc.*, **9**, 383 (1932); T. Hoshino, *Ann.*, **520**, 31 (1935).

(29) This picrate generally deposits from aqueous solution as yellow-orange needles which melt initially at *ca.* 110–120°. If temperature elevation is continued, resolidification occurs with final melting at 173–175°.

(30) V. du Vigneaud and C. E. Meyer, *J. Biol. Chem.*, **99**, 143 (1932).

Anal. Calcd. for $C_{12}H_{15}NO_3$ (221.25): C, 65.14; H, 6.83; N, 6.33. Found: C, 65.29; H, 6.87; N, 6.25.

N-Methyl-DL-phenylalanine.—A solution of 90 mg. (0.0004 mole) of α-acetylmethylamino-β-phenylpropionic acid, derived from the above experiment, in 2 ml. of 6 *N* hydrochloric acid solution was maintained at reflux temperature for a period of 15 hours. The solution was concentrated under reduced pressure, the residue was dissolved in a small quantity of water and was neutralized with sodium acetate. The crystalline deposit was collected by filtration and was recrystallized from water; yield 65 mg. (90%), m.p. 252–254°.[31]

Anal. Calcd. for $C_{10}H_{13}NO_2$ (179.12): C, 67.04; H, 7.31; N, 7.82. Found: C, 66.89; H, 7.10; N, 7.84.

α-N-Methyl-DL-histidine Dihydrochloride.—To a solution of 450 mg. (0.002 mole) of the sodium derivative VII in 5 ml. of methanol containing 46 mg. (0.002 mole) of sodium was added at 0° 306 mg. (0.002 mole) of 4(5)-chloromethylimidazole hydrochloride.[32] After 1 hour at 0° the methanol was distilled under diminished pressure, 2 ml. of 6 *N* hydrochloric acid was added and the solution was maintained at reflux temperature for a period of 15 hours. The hydrochloric acid was distilled under reduced pressure, the residue was dissolved in water, was neutralized with sodium acetate and was treated at 90° with 900 mg. of picric acid. The precipitate which weighed 1.2 g. and which melted at 121–127° was recrystallized from water; yield 820 mg. (65%), m.p. 121–131°.[33] The picrate was treated with benzene and dilute hydrochloric acid and the acid extract was washed with several successive quantities of benzene. The hydrochloric acid solution was concentrated under diminished pressure to yield 180 mg. of the crystalline dihydrochloride which was recrystallized from a small quantity of dilute hydrochloric acid; m.p. 130–135°.[33]

Anal. Calcd. for $C_7H_{11}N_3O_2 \cdot 2HCl \cdot {}^1/_2H_2O$ (251.10): C, 33.48; H, 5.62; N, 16.74. Found: C, 33.40; H, 5.66; N, 17.09.

Acknowledgment.—These studies were assisted by a grant from the National Science Foundation.

(31) E. Friedman and S. Gutmann, *Biochem. Z.*, **27**, 491 (1910).

(32) F. L. Pyman, *J. Chem. Soc.*, 668 (1911); J. R. Totter and W. J. Darby, "Organic Syntheses," Coll. Vol. 3, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 460.

(33) R. G. Fargher and F. L. Pyman, *J. Chem. Soc.*, 734 (1921). V. Deulofeu and A. E. A. Mitta, *J. Org. Chem.*, **14**, 915 (1949).

BOSTON 15, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Some 3-Substituted Rhodanines

BY FRANCES C. BROWN, CHARLES K. BRADSHER, ELIZABETH C. MORGAN, MARVIN TETENBAUM AND PELHAM WILDER, JR.

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Forty-four 3-phenyl-, 3-benzyl- and related rhodanine derivatives have been synthesized from the corresponding amines and tested for fungitoxic and bacteriotoxic activity. In the 3-phenylrhodanine series, the fungitoxic activity toward *A. niger* is noteworthy, and the bacteriotoxic activity negligible, while the reverse is true of the 3-benzylrhodanines.

In view of the mildew-preventing activity exhibited by some 5-substituted rhodanine derivatives,[1] it seemed advisable to investigate the effect of variations in other portions of the rhodanine molecule on toxicity toward fungi and bacteria. Rhodanine[2] (I) and its derivatives retaining hydrogen attached to the nitrogen atom have been patented as fungicides while the compounds containing a hydrocarbon residue attached to the nitrogen atom[3] were patented as pesticides, with mention being made of their usefulness as fungicides. The improvement in insecticidal activity of 3-methylrhodanine over rhodanine is evident from the data in the Ciba patent, but the relation between the structure of the hydrocarbon residue and the activity of the molecule as a whole was not reported.

The fungicidal activity of 3-phenyl-2,4-thiazoli-

(1) F. C. Brown and C. K. Bradsher, *Nature*, **168**, 171 (1951), F. C. Brown, C. K. Bradsher and E. N. Lawton, *Ind. Eng. Chem.*, **45**, 1027 (1953); F. C. Brown, C. K. Bradsher and S. M. Bond, *ibid.*, **45**, 1030 (1953); F. C. Brown, C. K. Bradsher, S. M. Bond and R. J. Grantham, *ibid.*, **46**, 1508 (1954); C. K. Bradsher, F. C. Brown and R. J. Grantham, THIS JOURNAL, **76**, 114 (1954).

(2) E. Alvord, (to Grasselli Chemical Co.), U. S. Patent 1,962,109 (June 5, 1934).

(3) CIBA, A. G. Swiss Patent 242,300 (Oct. 1, 1946).