U. S. Atomic Energy Commission and Yale University.

The author wishes to take this opportunity to express his appreciation of the interest and advice of Professor Herbert S. Harned.

NEW HAVEN, CONN. RECEIVED[9] FEBRUARY 7, 1951

(9) Original manuscript received November 8, 1950.

[CONTRIBUTION NO. 1537 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

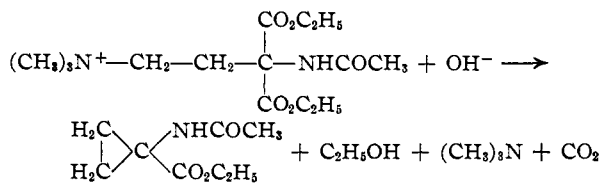
The Synthesis of a Cyclopropane Derivative through Exhaustive Methylation

BY HEINRICH RINDERKNECHT[1] AND CARL NIEMANN[2]

1-Acetamido-1-carbethoxycyclopropane has been prepared by the thermal decomposition of the quaternary base derived from the methiodide of diethyl β-dimethylaminoethylacetamidomalonate. This appears to be the first example of the synthesis of a cyclopropane ring through exhaustive methylation.

In the course of several unsuccessful attempts to prepare α-aminovinylacetic acid, diethyl acetamidomalonate was condensed with β-chloroethyldimethylamine and the resulting diethyl β-dimethylaminoethylacetamidomalonate quaternized with methyl iodide to give the expected γ,γ-dicarbethoxy-γ-acetamidopropyltrimethylammonium iodide. This latter compound upon hydrolysis and decarboxylation with aqueous hydriodic acid gave γ-carboxy-γ-aminopropyltrimethylammonium iodide hydroiodide. The γ,γ-dicarbethoxy-γ-acetamidopropyltrimethylammonium iodide was allowed to react with silver oxide, the aqueous solution of the quaternary base lyophilized, to minimize hydrolytic decomposition, and decomposed to give a distillate which subsequently crystallized. This latter substance, m.p. 79–80°, possessed the empirical formula $C_8H_{13}O_3N$, did not react with hydrogen in the presence of a platinic oxide catalyst, bromine water or aqueous permanganate, and did not give α-aminobutyrolactone hydrochloride upon hydrolysis with hydrochloric acid. Therefore, it was concluded that the product obtained by the thermal decomposition of γ,γ-dicarbethoxy-γ-acetamidopropyltrimethylammonium hydroxide was 1-acetamido-1-carbethoxycyclopropane. The above conclusion was confirmed when it was found that 1-acetamidocyclopropane-1-carboxylic acid and 1-aminocyclopropane-1-carboxylic acid prepared from the decomposition product were identical with the same compounds obtained by an independent synthesis, *i.e.*, from 1,1-dicarbethoxycyclopropane *via* the diamide, dibromoamide and hydantoin.[3]

The conversion of γ,γ-dicarbethoxy-γ-acetamidopropyltrimethylammonium hydroxide to 1-acetamido-1-carbethoxycyclopropane can be described in terms of a typical γ-elimination reaction, *i.e.*



It is of interest to note that ethyl α-benzylisocrotonate was obtained by the thermal decomposition of the methiodide of diethyl β-dimethylaminoethylbenzylmalonate.[4] In this instance it was concluded[4] that elimination of the carbethoxy group is accompanied by a 1:2 shift of one of the β-hydrogen atoms and elimination of trimethylamine. It should be noted that when the thermal decomposition of γ,γ-dicarbethoxy-γ-acetamidopropyltrimethylammonium iodide was attempted the bulk of the material resinified. While it may be argued that the acetamido group favors retention of the hydrogen atoms on the β-carbon atom over that obtaining with the benzyl derivative, the lack of comparable experimental data deprives the argument of much of its force.

1-Aminocyclopropane-1-carboxylic acid was tested in respect to its ability to function as a precursor, or as an antagonist, of methionine and threonine and γ-carboxy-γ-aminopropyltrimethylammonium iodide hydroiodide was evaluated as a methyl donor. All tests were negative.[5]

Experimental[6,7]

Diethyl β-Dimethylaminoethylacetamidomalonate (I) (A).—Diethyl acetamidomalonate (4.4 g.) was added to a solution of 0.46 g. of sodium in 50 ml. of absolute ethanol, the solvent was removed under reduced pressure and was replaced by 75 ml. of dry toluene. To this suspension was added 2.5 g. of redistilled β-chloroethyldimethylamine,[8] the reaction mixture refluxed for 6.5 hours with mechanical stirring, the sodium chloride removed by filtration and the filtrate evaporated to dryness under reduced pressure. The residue was distilled to give 5.15 g. (88%) of I, a yellow oil, b.p. 132–137° (1 mm.), which solidified upon standing. This product was repeatedly recrystallized from a benzene–petroleum ether mixture to give I, m.p. 76–78°. I is freely soluble in water, ethanol, benzene and acetone.

(B).—To a solution of 1.56 g. of potassium in 250 ml. of *t*-butanol was added 8.68 g. of diethyl acetamidomalonate and then an ethereal solution of β-chloroethyldimethylamine prepared from 11.5 g. of the hydrochloride. The remainder of the procedure was identical with that given above with the exception that it was found necessary to dissolve the crude product in dry ether and to filter the turbid solution prior to distillation. The yield of I was 8.0 g. (70%).

Anal. Calcd. for $C_{13}H_{24}O_5N_2$ (288): C, 54.2; H, 8.4; N, 9.7. Found: C, 54.2; H, 8.4; N, 9.6.

γ,γ-Dicarbethoxy-γ-acetamidopropyltrimethylammonium Iodide (II).—Methyl iodide (4.0 g.) was added to 6.9 g. of I in 50 ml. of acetone and after standing at room tempera-

(1) Research Associate, Ciag. Co., Schaffhausen, Switzerland.

(2) To whom inquiries regarding this article should be sent.

(3) C. K. Ingold, S. Sako and J. F. Thorpe, *J. Chem. Soc.*, 1177 (1922).

(4) C. K. Ingold and M. A. T. Rogers, *ibid.*, 722 (1935).

(5) We are indebted to Drs. N. H. Horowitz and J. W. Dubnoff for this information.

(6) Microanalyses by Dr. A. Elek.

(7) All melting points are corrected.

(8) We are indebted to the Ciba Laboratories of Summit, N. Y., for the hydrochloride of this substance.

ture for 12 hours the crystalline methiodide was recovered and recrystallized from acetone. A further quantity of II was obtained from the mother liquors. The total yield of II was 7.95 g. (77%), m.p. 154–155° (dec.).

Anal. Calcd. for $C_{14}H_{27}O_5N_2I$ (430): C, 39.1; H, 6.3; N, 6.5. Found: C, 39.1; H, 6.4; N, 6.4.

γ-Carboxy-γ-aminopropyltrimethylammonium Iodide Hydroiodide (III).—II (2.7 g.) was refluxed with 20 ml. of 27% aqueous hydriodic acid for 2.5 hours and the excess hydriodic acid removed by distillation under reduced pressure and subsequent repeated distillations with water. The crystalline material thus obtained was recrystallized from aqueous hydriodic acid, sp. gr. 1.70, to give 2.0 g. (77%) of III, m.p. 211–212° (dec.).

Anal. Calcd. for $C_7H_{18}O_2N_2I_2$ (416): N, 6.7. Found: N, 7.0.

III was relatively unstable and was therefore characterized as the dipicrate, m.p. 208–209° (dec.).

Anal. Calcd. for $C_{19}H_{22}O_{16}N_8$ (618): C, 36.9; H, 3.6; N, 18.1. Found: C, 36.8; H, 3.5; N, 18.2.

1-Acetamido-1-carbethoxycyclopropane (IV).—To 2.0 g. of silver nitrate in 15 ml. of carbon dioxide-free water was added 2.0 ml. of a filtered 50% aqueous solution of sodium hydroxide, the resulting precipitate washed 6 times with carbon dioxide-free water and then added to 4.1 g. of II in 15 ml. of water. The reaction mixture was shaken for one-half hour, filtered, the clear filtrate lyophilized, and the residue transferred, with the aid of a small amount of ethanol, to a small distilling flask. The solvent was removed by distillation *in vacuo* and the quaternary base heated slowly to a bath temperature of 170–195° at a pressure of 1–2 mm. A thick yellow oil distilled at 110–115° (1–2 mm.) and crystallized upon cooling to give 0.75 g. (33%) of IV. This product was repeatedly recrystallized from a mixture of benzene and petroleum ether to give IV, m.p. 79–80°.

Anal. Calcd. for $C_8H_{13}O_3N$ (171): C, 56.1; H, 7.7; N, 8.2. Found: C, 56.2; H, 7.6; N, 8.1.

1-Acetamidocyclopropanecarboxylic Acid (V) (A).—An equimolar quantity of 0.163 *N* aqueous sodium hydroxide was added during a period of three-quarters of an hour to 0.2 g. of IV in 5 ml. of boiling water. An amount of aqueous hydrochloric acid equivalent to the amount of sodium hydroxide used was added and the reaction mixture evaporated to dryness under reduced pressure. The residue was dried *in vacuo* over phosphorus pentoxide and then extracted three times with anhydrous ether. The ethereal extract was evaporated to dryness and the residue recrystallized from ethyl acetate to give 0.1 g. (60%) of V, m.p. 158–159°.

Anal. Calcd. for $C_6H_9O_3N$ (143): C, 50.3; H, 6.3; N, 9.8. Found: C, 50.3; H, 6.3; N, 9.9.

(B).—To a solution of 0.5 g. of the hydrochloride of 1-aminocyclopropanecarboxylic acid[3] (VI) in 3 ml. of dry pyridine was added, at 0°, 1 ml. of acetic anhydride. After 60 hours the excess reagents were removed under reduced pressure, the residue extracted with ethyl acetate, and the extract concentrated to give V, m.p. 156–159° undepressed upon addition of V prepared as described above from IV.

1-Aminocyclopropanecarboxylic Acid Hydrochloride (VII).—V prepared from IV was refluxed for 5 hours with 2 *N* hydrochloric acid, the excess acid and solvent removed by distillation *in vacuo*, the residue dried over phosphorus pentoxide, and then dissolved in hot absolute ethanol. The addition of dry ether to the cold ethanol solution gave VII, m.p. 223–224° with decomposition both before and after recrystallization from acetic acid. When VII prepared as described above was mixed with an authentic sample of the hydrochloride[3] no depression of the decomposition point was observed.

PASADENA 4, CALIFORNIA RECEIVED MARCH 26, 1951

[CONTRIBUTION NO. 1546 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

The Synthesis of D- and L-*threo*- and D- and L-*erythro*-α-Amino-β-hydroxy-*n*-caproic Acid[1]

BY ROBERT T. ADAMS[2] AND CARL NIEMANN

The four isomeric α-amino-β-hydroxy-*n*-caproic acids have been prepared from 2-hexenoic acid, and the configuration of each of these compounds has been determined.

In continuation of our studies on the 1,2,3-contiguously substituted dihydroxyamino-*n*-hexanes[3] the four isomeric α-amino-β-hydroxy-*n*-caproic acids have been prepared as starting materials for the synthesis of the isomeric 1,3-dihydroxy-2-amino-*n*-hexanes. The mixture of diastereoisomeric α-amino-β-methoxy-*n*-caproic acids, obtained as before from 2-hexenoic acid,[4,5] was benzoylated and the reaction product fractionally crystallized to give not only DL-*threo*-α-benzamido-β-methoxy-*n*-caproic acid (I) and DL-*erythro*-α-benzamido-β-hydroxy-*n*-caproic acid (II) but also (III).[6] The over-all yields of the three racemic acids, based upon 2-hexenoic acid were: I, 3.3%; II, 22.1%; and III, 1.7%. It is likely that III was formed from the corresponding α-amino-β-hydroxy acid since no special precautions were taken to exclude moisture from the methanolic solution of mercuric acetate used in the reaction with 2-hexenoic acid.[4,5]

The above three DL-acids were resolved *via* a papain-catalyzed conversion of the D-*threo* and L-*erythro* components to the corresponding *p*-toluides, the L-*threo* and D-*erythro* components being recovered unchanged.[7,8] The properties of the six resolution products, *i.e.*, D-*threo*-α-benzamido-β-methoxy-*p*-*n*-caprotoluide (IV), L-*threo*-α-benzamido-β-methoxy-*n*-caproic acid (V), L-*erythro*-α-benzamido-β-methoxy-*p*-*n*-caprotoluide (VI), D-*erythro*-α-benzamido-β-methoxy-*n*-caproic acid (VII), L-*erythro*-α-benzamido-β-hydroxy-*p*-*n*-caprotoluide (VIII), and D-*erythro*-α-benzamido-β-hydroxy-*n*-caproic acid (IX), are summarized in Table I. The isomeric α-amino-β-hydroxy-*n*-caproic acids, *i.e.*, D-*threo* (X), L-*threo* (XI), D-*erythro* (XII) and L-*erythro* (XIII), were obtained from the correspond-

(1) The prefixes *threo* and *erythro* define the relative configuration about the two asymmetric carbon atoms bearing the amino and hydroxyl groups; the letters D and L relate the configuration about the asymmetric carbon atom bearing the hydroxyl group with the configuration about the asymmetric carbon atom present in D- or L-glyceric aldehyde.

(2) United States Rubber Company Fellow, 1948–1949; now at California Research Corporation, Richmond, California.

(3) C. Niemann, A. A. Benson and J. F. Mead, *J. Org. Chem.*, **8**, 397 (1943).

(4) C. Niemann and C. T. Redemann, THIS JOURNAL, **68**, 1932 (1946).

(5) H. D. West and H. E. Carter, *Org. Syntheses*, **20**, 101 (1940).

(6) The configurations of these acids, and of other intermediates to be described, were assigned on the basis of arguments given later in this communication.

(7) E. L. Bennett and C. Niemann, THIS JOURNAL, **72**, 1798 (1950).

(8) W. H. Schuller and C. Niemann, *ibid.*, **73**, 1644 (1951).