[CONTRIBUTION NO. 573 FROM THE DEPARTMENT OF CHEMISTRY, INDIANA UNIVERSITY]

Amino Acids. VII. *dl*-β-Aminoadipic Acid; Preparation and Oxidation of 2-, 3- and 4-Acetamidocyclohexanols

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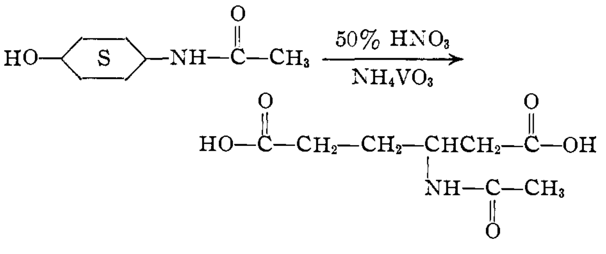
RECEIVED JULY 23, 1952

Improved methods have been developed for the synthesis of the 2-, 3- and 4-acetamidocyclohexanols. β-Aminoadipic acid and β-acetamidoadipic acid have been prepared from the 4-acetamidocyclohexanols. β-Phthalimidoadipic acid has been prepared.

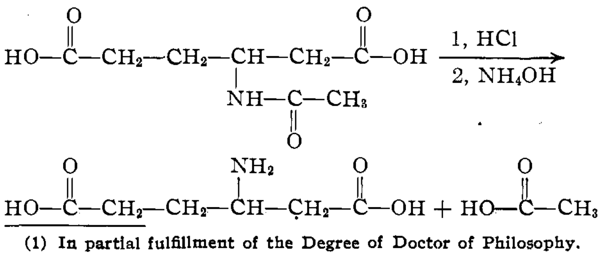
Since Wollaston's[2] discovery of cystine in urinary calculi, considerable interest has centered around the isolation of naturally occurring amino acids from protein hydrolysates or the synthesis of them from readily available chemicals. Numerous other amino substituted acids have been synthesized some of which possess interesting and valuable properties. In view of these facts it was thought that it would be of interest to see if amino acids were obtainable by the oxidation of 2-, 3- and 4-aminocyclohexanols under the proper conditions.

It is well known that adipic acid is readily prepared by the oxidation of cyclohexanol with nitric acid and it was felt that the aminocyclohexanols might also undergo a similar reaction provided, of course, that the amino group was protected against oxidation. This protection may be accomplished by acylating the amino group as shown in an earlier publication.[3] In this instance the acetamidocyclohexanols were prepared by hydrogenating the corresponding acetamidophenols.

A study of the oxidation of *cis*-, *trans* and a *cis–trans* mixture of the 4-acetamidocyclohexanols, with nitric acid, was made and it was found that there is no appreciable difference in the ease of oxidation of these isomers. The concentration of nitric acid (16 *N*) and the temperature (30°) at which oxidation commenced were the same in all cases. β-Acetamidoadipic acid was isolated in 63–77% yields from numerous oxidations.



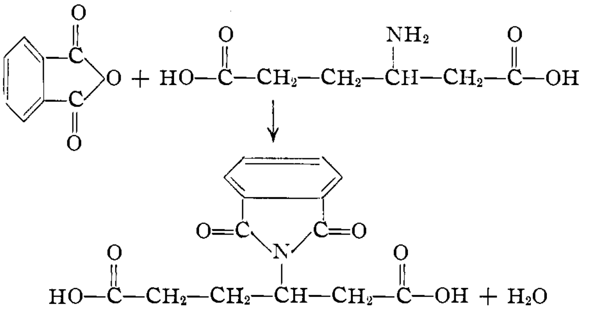
Hydrolysis of the β-acetamidoadipic acid with 18% hydrochloric acid gave yields of as high as 91% of the β-aminoadipic acid hydrochloride. The free amino acid was obtained by removing the HCl with ammonium hydroxide. The average over-all yield of the β-aminoadipic acid from 4-acetamidophenol was 56.4%.



$$HO-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-\underset{\underset{\underset{O}{\|}}{NH-C-CH_3}}{\underset{|}{CH}}-CH_2-\overset{O}{\overset{\|}{C}}-OH \xrightarrow[2,\ NH_4OH]{1,\ HCl}$$

$$HO-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-\overset{NH_2}{\overset{|}{C}H}-CH_2-\overset{O}{\overset{\|}{C}}-OH + HO-\overset{O}{\overset{\|}{C}}-CH_3$$

The phthalyl derivative of β-aminoadipic acid was prepared[4] according to the equation



All of the attempts to oxidize the 2- and the 3-acetamidocyclohexanols, under the same conditions as were used for the oxidation of the 4-isomers, failed. In the case of the 2-acetamidocyclohexanols the oxidation, as evidenced by the appearance of oxides of nitrogen, did not take place below 70° whereas, the 3-acetamidocyclohexanols began to oxidize at 40°. However, the oxidation in these cases apparently proceeded farther than it did with the 4-acetamidocyclohexanols since all attempts to isolate a pure solid from either of the reaction mixtures met with little success. Alkaline as well as acid permanganate solutions were tried in place of the nitric acid, but the results were the same. As in the case of the 4-acetamidocyclohexanols, there appeared to be no difference in the ease of oxidation of the *trans* and a *cis–trans* mixture of the 2-acetamidocyclohexanols.

Experimental

***cis–trans*-4-Acetamidocyclohexanol.**—One hundred grams (0.63 mole) of 4-acetamidophenol melting at 165–167° (Eastman Kodak Co.) was placed in a high pressure bomb to which was added 250 ml. of absolute alcohol and 5 g. of Raney nickel. Hydrogen was added to the mixture until the pressure reached 1000 lb. The mixture was then heated to 180° and maintained at that temperature for 1.75 hours at which time the absorption of hydrogen ceased. Hydrogenation started at 165°. After cooling to room temperature the solution was filtered and the alcohol completely removed at 35 mm. pressure and 50–60°. The residue was melted and poured into a mortar where it was stirred until it solidified. The *cis–trans* mixture so produced melted at 100–103° (cor.). Several experiments gave 96–99% yields. The purity of the mixture was determined by analysis.

Anal. Calcd. for $C_8H_{15}O_2N$: N, 8.94. Found: N, 8.81.

***trans* - 4 - Acetamidocyclohexanol.**—The aforementioned *cis–trans* mixture was fractionally crystallized from acetone

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[1] In partial fulfillment of the Degree of Doctor of Philosophy.

[2] W. H. Wollaston, *Ann. chim.*, **76**, 21 (1810).

[3] J. H. Billman and E. E. Parker, THIS JOURNAL, **66**, 538 (1944).

[4] J. H. Billman and W. F. Harting, *ibid.*, **70**, 1473 (1948).

as recommended by Hartmann.[5] Ethyl ether, dioxane, petroleum ether, ethanol and benzene were also tried as solvents, but they were no better than acetone. After nine fractional crystallizations of 95 g. of the *cis–trans* mixture from acetone, 30 g. of the *trans* isomer was obtained melting at 165–167°. Thirty-five grams of a product melting between 115–120° was isolated which contained mainly the *cis* isomer. Hartmann reported the *cis* form as melting at 135°. However further recrystallization of our product from acetone failed to give a product melting at 135°. An analysis of the low melting isomer was performed.

Anal. Calcd. for $C_8H_{15}O_2N$: N, 8.94. Found: N, 8.81.

β-Acetamidoadipic Acid.—One hundred grams (0.637 mole) of *cis,trans*-4-acetamidocyclohexanol was placed in an electrically heated dropping funnel containing 100 ml. of water heated to 75°. This funnel was attached to a 1-liter three-neck flask fitted with a mechanical stirrer and a thermometer and containing 200 ml. of 16 *N* nitric acid and 0.15 g. of ammonium metavanadate.

The aqueous solution of the *cis–trans* mixture was allowed to drop slowly into the well-stirred nitric acid solution. The rate of addition was such that the temperature of the reaction mixture was maintained between 30 and 40° (it is important to keep the temperature of the reaction mixture as low as possible, so long as oxidation occurs, in order to obtain high yields). When two-thirds of the solution had been added the temperature of the reaction mixture was raised to 60° and maintained at that temperature until all the 4-acetaminocyclohexanol had been added to the nitric acid solution. After the addition of all the 4-acetaminocyclohexanol the reaction mixture was permitted to cool while it was stirred. When no more oxides of nitrogen were visibly detectable the stirring was stopped.

The reaction mixture was transferred to a 1-liter flask and concentrated to 100 ml. at 35 mm. pressure and at a temperature of less than 50° (at higher temperatures further oxidation occurs). Seven hundred and fifty milliliters of ether was added to the mixture. After one hour the precipitate was removed and air-dried. (When the solution was concentrated below 50 ml. an explosion occurred.) The crude product weighed 109.5 g. (85% yield) and melted at 100–105°. Recrystallization from water and air-drying gave a product melting at 94–96° which when dried at 110° for six hours yielded 93.4 g. of β-acetamidoadipic acid melting at 141–142° (cor.).

Anal. Calcd. for $C_8H_{13}O_5N$: N, 6.90; neut. equiv., 101.5. Found: N, 7.08; neut. equiv., 102.

β-Acetamidoadipic Acid Hydrates.—When the β-acetamidoadipic acid (m.p. 141–142°) was recrystallized from water and air-dried the product melted at 90–110°. A neutral equivalent determination of this product gave a value of 224. This compares favorably with value of 221 for the molecular weight of β-acetamidoadipic acid monohydrate. This latter compound when dried at 100° for three hours melted at 138–139° (cor.) and gave a molecular weight value of 212 which would correspond to the molecular weight of the half hydrate of β-acetamidoadipic acid which has a molecular weight of 212.

β-Aminoadipic Acid.—A mixture of 100 g. of β-acetamidoadipic acid and 1200 ml. of 18% hydrochloric acid was refluxed for 18 hours. The solution was then concentrated to a heavy slurry at 35 mm. pressure. One hundred ml. of water was added and the solution evaporated as before. This latter step was repeated three more times in order to remove the excess of hydrochloric acid. The theoretical amount of ammonium hydroxide was added to remove the hydrochloric acid from the amino acid. The solution was allowed to stand overnight at room temperature and then filtered. Concentration of the filtrate yielded additional amino acid. The total yield of β-aminoadipic acid was 69.3 g. (81%) which melted at 189–190.5° (cor.).

Anal. Calcd. for $C_6H_{11}O_4N$: N, 8.70. Found: N, 8.95.

β-Phthalimidoadipic Acid.—In a test-tube was placed a mixture of 0.75 g. of β-aminoadipic acid and 0.8 g. of phthalic anhydride. The reaction was carried out and the product purified as previously described.[4] The β-phthalimidoadipic acid was dried at 118° and melted at 166–167° (cor.).

Anal. Calcd. for $C_{14}H_{13}O_6N$: N, 4.81; neut. equiv., 145.5. Found: N, 4.78; neut. equiv., 146.

The *cis–trans*-2-Acetamidocyclohexanols.—One hundred grams (0.663 mole) of 2-acetamidophenol (m.p. 198–200°) was dissolved in 95% ethanol and refluxed for several hours with 10 g. of Raney nickel in order to remove any poisons that may be present. Fresh Raney nickel was added and the hydrogen pressure raised to 1000 lb. at room temperature. Hydrogenation occurred at 200° and required 100 minutes to complete the reaction. The crude solid was recrystallized from acetone and yielded 64 g. of the *cis–trans*-2-acetamidocyclohexanols melting at 120–130°.

Anal. Calcd. for $C_8H_9O_2N$: N, 8.91. Found: N, 8.71.

***trans*-2-Acetamidocyclohexanol.**—This compound was obtained by the method of Hartmann.[5] However, our product melted at 142–145° (cor.) whereas Hartmann reports 146°.

***cis–trans*-3-Acetamidocyclohexanols.**—One hundred grams of 3-acetamidophenol, 200 ml. of absolute alcohol and 10 g. of Raney nickel were placed in a high pressure hydrogenation bomb. A pressure of 1000 lb. of hydrogen, at room temperature, was used. Hydrogenation began at 178° and required 100 minutes for completion. The product was worked up in the same way as the 4-acetamidocyclohexanols. A total yield of 95 g. (91%) of the *cis–trans*-3-acetamidocyclohexanols melting at 95–98° was obtained.

Anal. Calcd. for $C_8H_9O_2N$: N, 8.91. Found: N, 9.17.

Hartmann[5] reports isolating only the *cis* isomer, melting at 120°, from the hydrogenation of 3-acetamidophenol.

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(5) M. Hartmann, H. Ensslin and L. Panizzo, U. S. Patent 2,152,960 (1939).