Attempted Hydrolysis of Leucenol.—One hundred milligrams of leucenol was refluxed with 2 ml. of 47.3% hydrobromic acid for eight and one-half hours. The aqueous solution was evaporated to dryness *in vacuo.* The product dissolved in 5 ml. of absolute ethanol, but after precipitation with ether was no longer soluble in ethanol, m. p. after washing with absolute ethanol, 176–179° (cor.); melting point of a mixture with leucenol hydrobromide, 177.5–179° (cor.).

Anal. Calcd. for $C_8H_{11}O_4N_2Br$: C. 34.42; H, 3.96. Found: C, 34.37; H, 4.09.

No product was obtained which was soluble in absolute ethanol.

One hundred milligrams of leucenol was heated at reflux with 2 ml. of constant-boiling hydriodic acid for thirty-six hours. After removal of the excess acid and water *in vacuo,* the product was taken up in 2 ml. of absolute ethanol and precipitated with ether. The product, insoluble in boiling absolute ethanol, was apparently impure leucenol hydroiodide. No product soluble in ethanol was obtained.

Methylation of Leucenol.—(a) To a suspension of 200 mg. of leucenol in 50 cc. of ether, a large excess of an ether solution of diazomethane was added and the mixture allowed to stand at room temperature for two days. At the end of this time, most of the leucenol had reacted and gone into solution. Upon evaporation of the ether, an oily residue remained which could not be crystallized. Oxidation of the oil by refluxing with 50 cc. of 2% aqueous potassium permanganate for an hour failed to give a product which could be isolated.

(b) One hundred milligrams (1 mole equiv.) of leucenol was suspended in 0.2 ml. of water and an ethereal solution of diazomethane containing about 250 mg. (6 mole equiv.) of diazomethane was added. Nitrogen was evolved and the yellow color was bleached rapidly. Two more additions of 125-mg. portions of diazomethane were necessary before the yellow color persisted for one hour. The entire product was in the aqueous phase which was neutral to litmus. The water was removed *in vacuo* leaving a thick yellow sirup, which could not be induced to crystallize. The product was insoluble in ether and highly soluble in methanol and in water.

The hydrochloride of this product was obtained as a tan solid, soluble in water and in methanol. It was highly hygroscopic and therefore not suitable as a derivative.

The chloroaurate, picrate and picrolonate were prepared, but were not crystalline.

The product gave a pale yellow color with aqueous ferric chloride.

Oxidation with aqueous 1% potassium permanganate (5 atoms of oxygen and 11 atoms of oxygen per estimated mole of product) was carried out at room temperature. Permanganate equivalent to five atoms of oxygen was decolorized almost instantaneously, whereas the larger amount took several hours to react. No ether-soluble product could be isolated from either reaction.

Ultraviolet Absorption Spectrum of Leucenol.—The ultraviolet absorption spectra of leucenol in water and in dilute hydrochloric acid were determined in a Hilger spectroscope.

Summary

1. Leucenol was extracted from *Leucaena glauca benth* by means of 90% ethanol. It was shown to have the same empirical formula $(C_4H_5O_2N)_x$ as that reported by Mascré.

2. The presence of a phenolic group was confirmed by ferric chloride and Folin reagent tests; an α-amino acid by the ninhydrin test; half of the nitrogen as a primary amino group by Van Slyke analysis.

3. A methyl ester dihydrochloride was prepared.

4. Absorption spectra in aqueous and dilute hydrochloric acid resembled the spectra of hydroxypyridines.

5. Leucenol was pyrolyzed and yielded a compound which, by its properties and analyses, appears to be 2,5-dihydroxypyridine. The product forms a diacetate and salts which were characterized.

6. Leucenol was unaffected by long refluxing with hydrobromic or hydriodic acids.

7. Various possible structures for leucenol were discussed. The blue color with Folin reagent which is typical of a β-hydroxypyridine, along with the other available facts, leads to the conclusion that leucenol is probably β-N-(3-hydroxy-6-pyridone)-α-aminopropionic acid, although β-(3-hydroxy-6-pyridoxy)-α-aminopropionic acid is not excluded.

URBANA, ILLINOIS RECEIVED AUGUST 7, 1944

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN COMPANY]

An Improved Synthesis of β-Alanine

BY SAUL R. BUC, JARED H. FORD AND E. C. WISE

A convenient laboratory method for the preparation of substantial quantities of β-alanine was desired since none of the earlier methods[1] appeared suitable.

In the present investigation we have obtained β-alanine by means of the following reactions:

$$\text{(1)}\quad CH_2{=}CHCN + NH_3 \longrightarrow NH_2CH_2CH_2CN + NH(CH_2CH_2CN)_2$$

$$\text{(2)}\quad NH_2CH_2CH_2CN + 2HCl + 2H_2O \longrightarrow NH_2CH_2CH_2COOH{\cdot}HCl + NH_4Cl$$

$$\text{(3)}\quad NH_2CH_2CH_2COOH{\cdot}HCl \xrightarrow[\text{resin}]{\text{anion exchange}} NH_2CH_2CH_2COOH$$

The first step, addition of ammonia to acrylonitrile, has been described by Hoffmann and Jacobi,[2] and by Whitmore, *et al.*[3] These authors

---

[1] For a summary of the literature prior to 1942 see "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943. After the completion of our experimental work the following patents describing the preparation of β-alanine from acrylonitrile and several of its derivatives by heating with aqueous ammonia at 150–225° were issued: Carlson and Hotchkiss, U. S. Patent 2,335,997; Carlson, U. S. Patent 2,336,067; Kirk, U. S. Patent 2,334,163; Paden and Kirk, U. S. Patent 2,335,605; Dean, U. S. Patent 2,335,653.

[2] Hoffmann and Jacobi, U. S. Patent 1,992,615.

[3] Whitmore, Mosher, Adams, Taylor, Chapin, Weisel and Vanko, THIS JOURNAL, **66**, 725 (1944).

used liquid ammonia and obtained a 12.5% yield of primary amine when the molar ratio of ammonia to acrylonitrile was 1.25 to 1[2] and 22% when the ratio was 8 to 1.[3] Whitmore also mentioned the use of aqueous ammonia but implied that it gave lower yields of primary amine. We have found that aqueous ammonia, under proper conditions, gives yields of primary amine as high as 39%.

A rather extensive study of the reaction was carried out. It was found, as would be predicted on theoretical grounds, that increasing the ratio of ammonia to acrylonitrile favors formation of the primary amine. Temperature is also an exceedingly important factor, higher temperatures favoring formation of primary amine. Results illustrating these effects are given in Table I.

After removal of the ammonia and water *in vacuo*, the residue was distilled *in vacuo*, yielding the primary and secondary amines as easily separable fractions. In no case were we able to isolate the as yet undescribed tertiary amine, *tris*-(cyanoethyl)-amine, by distillation of the small high boiling residues at a pressure of 1 mm.

Whitmore, *et al.*,[3] have reported that β-aminopropionitrile polymerizes with evolution of ammonia on standing. We have observed that this polymerization takes place slowly when the compound is stored in an open container or very rapidly when 1 mole of concentrated hydrochloric acid is added to 4 moles of the nitrile. However, we have found it to be quite stable when obtained anhydrous by vacuum distillation. It boils without decomposition at 185° at atmospheric pressure and samples stored in tightly stoppered bottles for two years at 5° or for several months at room temperature show no evidence of decomposition.

The hydrolysis of β-aminopropionitrile to β-alanine hydrochloride was accomplished in yields of 90–94%. The reaction was found to be extremely sensitive to changes in conditions and procedure. The best results were obtained when the nitrile was added to 2.2 moles of concentrated (37.0–38.5%) hydrochloric acid. The use of more dilute acid or of a larger excess of concentrated acid decreased the yield.

Liberation of β-alanine from its hydrochloride by the use of lead oxide proved to be very tedious and troublesome. Attempts to use aniline or pyridine in methanol or ethanol were unsuccessful. Austin's[4] method using pinene is reported to give only 50% yield. We have found that commercial anion exchange resins such as De-Acidite[5] or Amberlite IR4[6] can be used effectively for this purpose. When an aqueous solution of pure β-alanine hydrochloride is passed through a bed of the resin, the resulting effluent is substantially chloride free. The yield of chloride-free β-alanine is 93% when pure β-alanine hydrochloride is used or 83–88% (based on β-aminopropionitrile) when crude β-alanine hydrochloride is used.

In view of a recent study by Englis and Fiess[7] wherein it was shown that glycine, norleucine and tryptophan were not adsorbed to any great extent by anion exchange resins, it seems quite likely that the method may prove useful for obtaining other amino acids from their anion salts. It will probably be unsuitable for monoaminodicarboxylic acids since Englis and Fiess have shown that glutamic acid is adsorbed.

Experimental

Addition of Ammonia to Acrylonitrile.—Two series of experiments were carried out: (A) with cooling, and (B) under pressure without cooling.

(A) With cooling: To 3900 ml. of concentrated ammonium hydroxide (*ca.* 60 moles) was added 792 ml. (12 moles) of acrylonitrile from a dropping funnel. When the temperature reached 33° ammonia began to boil out of the solution and the flask was surrounded by an ice-bath. The temperature dropped to 30° and the addition was completed at this temperature. The mixture was allowed to stand overnight at room temperature. The water and ammonia were distilled off under reduced pressure and the residue was transferred to a distilling flask and fractionated.

1	To 75° (21 mm.)	20 ml.	Mostly water
2	75–140° (21 mm.)	221 g.	Primary amine
3	140° (20 mm.) to 164° (2 mm.)	450 g.	Secondary amine
4	Residue	41 g.	

Fraction 2 was redistilled and yielded 201.3 g. (23%) of β-aminopropionitrile boiling at 38–40° (2 mm.); at 16 mm. the boiling point was 79–81°.

(B) Without cooling, under pressure.—To 1625 ml. of concentrated ammonium hydroxide (*ca.* 25 moles) in a 2-liter round-bottomed Pyrex flask was added 332.5 ml. (5.0 moles) of acrylonitrile. A rubber stopper was wired securely in place, the flask was shaken vigorously for a few seconds. After standing overnight,[8] the reaction mixture was worked up as in Part A. The yields of crude products were: primary amine, 120.5 g. (34.4%); secondary amine 180 g. (58.5%). Redistillation of the crude primary amine yielded 113.5 g. (32.4%) of pure product.

The reaction was also carried out on a larger scale in an iron vessel with a pressure gage using 14.7 liters of ammonium hydroxide (*ca.* 210 moles) and 3712 g. (70.0 moles) of acrylonitrile. The temperatures of the ammonium hydroxide and the acrylonitrile were 29° and 48°, respectively, before mixing. The vessel was rocked to agitate the contents. The temperature began to rise in two to three minutes and reached a maximum of 71° in sixteen minutes. The maximum pressure was 26 lb./sq. in. (gage). The yield of crude primary amine was 1738.5 g. (35.5%).

Hydrolysis of β-Aminopropionitrile.—Four hundred and fifty-six grams (6.50 moles) of β-aminopropionitrile was added to 1100 ml. (*ca.* 13.2 moles) of concentrated hydrochloric acid with efficient stirring and external cooling. The rate of addition was such that the temperature did not exceed 40°. The resulting solution was heated rapidly to 95°. From this point the temperature rose slowly to 117° with no external heating and boiled under reflux for a few minutes. When the temperature dropped to 100°, 150 ml. of concentrated hydrochloric acid was added, the mixture was heated for 18 hours at 90–95° and evaporated to dryness *in vacuo*. The last traces of water were removed in a vacuum desiccator or, more conveniently, by codistillation with xylene *in vacuo*.

Isolation of β-Alanine Hydrochloride.—The following method is used only when pure β-alanine hydrochloride is

---

[4] Austin, U. S. Patent 2,316,215.

[5] Tiger and Sussman, *Ind. Eng. Chem.*, **35**, 189 (1943).

[6] Myers, *ibid.*, **35**, 861 (1943).

[7] Englis and Fiess, *ibid.*, **36**, 609 (1944).

[8] Flasks were stored where explosions would do no damage, but in our six experiments no flasks were lost.

TABLE I

RESULTS OBTAINED BY MIXING ACRYLONITRILE WITH CONCENTRATED AMMONIUM HYDROXIDE AT ROOM TEMPERATURE

Moles ammonia[a]	Moles acrylonitrile	Molar ratio ammonia: acrylonitrile	Percent. yields, based on acrylonitrile		
			Primary amine	Secondary amine	Total
		A. With Cooling[b]			
28.0	1.4	20	39	39	78
28.5	1.9	15	36	40	76
50	5.0	10	35.6	53	88.6
150	20.0	7.5	32.6	54.5	87.1
118[c]	15.8	7.5	30	57	87
31.9[d]	4.25	7.5	26	66	92
60	12.0	5.0	23.0	58.6	81.6
20.7[c]	4.13	5.0	19	..	..
1.0	0.5	2.0	9	67.6	76.6
1.1	2.0	0.55	None	87.2	87.2
1	2.0	0.5	None	85	85
		B. Without Cooling, Under Pressure			
22.5	3	7.5	38.3	53.2	91.5
25	5	5	34.4	58.5	92.7
24	6	4	35.5	57.8	93.3
21	7	3	33.2	61	94.2
6	3	2	24.6	68.6	93.2

[a] C. P. 28–30% ammonium hydroxide used. [b] Temperature allowed to reach 33° before cooling the flask with ice water. [c] 22% ammonium hydroxide used. [d] 46% ammonium hydroxide used. Reaction completed below 10°.

desired. It gives a very good separation of β-alanine hydrochloride from ammonium chloride, but is not as convenient to use for the isolation of β-alanine as the method which employs ethanol.

Commercial 99% isopropanol was added to the dry residue from the hydrolysis using 1.7 liters per mole of β-aminopropionitrile. The mixture was boiled under reflux with mechanical stirring until the lumps disintegrated. The ammonium chloride was filtered off and washed with hot 99% isopropanol. The filtrate, on standing overnight in a refrigerator, deposited 79% of the theoretical amount of β-alanine hydrochloride. By concentrating the filtrate to one fourth of its original volume and cooling, an additional 13% was obtained. One recrystallization from 99% isopropanol gives an analytically pure product; m. p. 121–122° (uncor.).[9]

Anal. Calcd. for $C_3H_8NO_2Cl$: N, 11.16; Cl, 28.54. Found[10]: N, 11.43; Cl, 28.58, 28.44.

Isolation of β-Alanine.—To the dry residue obtained from the hydrolysis of 6.5 moles of β-aminopropionitrile was added 3.8 liters of S.D. 3A alcohol.[11] The mixture was warmed to 50–60° and stirred mechanically until the lumps had disintegrated. After standing overnight at 20–25° the mixture was filtered. The ammonium chloride thus removed amounted to 82–86% of the theoretical amount. The remainder was removed during the subsequent purification.

The alcoholic filtrate was diluted with 5 liters of distilled water, the alcohol distilled off, and the residual aqueous solution heated two hours at 90–95° to hydrolyze any esters that may have formed. After cooling to room temperature the solution was diluted to a volume of 12 liters with distilled water and passed through a bed of commercial anion exchange resin (De-Acidite)[12] containing 5.3 liters of resin (backwashed and drained volume) at the rate of 8–10 liters per hour. The solution of β-alanine hydrochloride was followed by 12 liters of distilled water. The effluent[13] and washings were evaporated to dryness under reduced pressure, and the residue dried to constant weight. The resulting solid was ground to a fine powder and washed thoroughly with 3A alcohol[11] to remove the color imparted by the resin.[14] The alcohol-washed product was dissolved in hot water and treated with a small amount of decolorizing carbon. The resulting solution was concentrated on the steam-bath to 60–62% solids using an air jet. It was then cooled rapidly with stirring and diluted slowly with 2.5 liters of 3A alcohol. After standing overnight the resulting white crystals were filtered and washed with 3A alcohol. The yield of chloride-free product was 470–500 g. (82–86%) based on β-aminopropionitrile. An additional 30–35 g. containing chlorides was recovered from the filtrate.

Summary

1. A study has been made of the addition of ammonia to acrylonitrile in aqueous solution. Yields of β-aminopropionitrile as high as 39% have been obtained.

2. The hydrolysis of β-aminopropionitrile to β-alanine hydrochloride is described.

3. A method for converting β-alanine hydrochloride into β-alanine by means of anion exchange resins is described.

4. The stability of β-aminopropionitrile has been found to be greater than that reported by previous investigators.

KALAMAZOO, MICH. RECEIVED SEPTEMBER 28, 1944

---

[9] Lengfeld and Stieglitz, *Am. Chem. J.*, **15**, 507 (1893), reported a melting point of 122.5°.

[10] Analyses by Messrs. Harold Emerson and William A. Struck of these laboratories.

[11] Specially denatured alcohol No. 3A has the following approximate composition: 90% ethanol, 5% methanol, 5% water.

[12] De-Acidite (The Permutit Company, New York, N. Y.) and Amberlite IR-4 (Röhm and Haas, Philadelphia, Pa.) were both found to give satisfactory results. The resin was contained in a 6-foot length of 3-inch Pyrex pipe. A larger diameter pipe would have been more convenient. The saturation capacity of the resin bed was determined by passing an excess of 0.5 *N* hydrochloric acid through it and titrating the effluent. Both of the resins were found to have saturation capacities of about 1.2 moles of hydrochloric acid per liter of resin (backwashed and drained volume). With De-Acidite an amount of β-alanine hydrochloride equivalent to 90% of the saturation capacity of the resin could be passed through the column with only traces of chloride ion appearing in the effluent. The corresponding value for the Amberlite IR-4 was found to be approximately 70%. Both resins were regenerated with 4% sodium carbonate solution. It is essential that the resins be saturated with hydrochloric acid and regenerated two or three times before using them on β-alanine hydrochloride. Otherwise the amount of color imparted to the effluent is so great that it is very difficult to remove. Allowing the β-alanine solution to stand overnight in contact with the resin was also found to cause excessive coloring.

[13] The *p*H of the effluent, instead of approximating 6.9, the isoelectric point of β-alanine, was 8.1–8.2 when Amberlite IR-4 was used, and 8.7–8.8 with De-Acidite.

[14] De-Acidite imparts a green color; Amberlite IR-4, an orange brown.