hydrobromide collected. Recrystallization of the hydrobromide from ethanol gave a material, m.p. 222–223°.

Anal. Calcd. for $C_7H_{10}NBr$: Br, 42.49. Found: Br, 42.43 and 42.46.

The ethereal solution was shaken with 150 ml. of 10% aqueous sodium hydroxide solution, separated, and dried over potassium hydroxide. The ether was removed by vacuum, and fractionation of the main material through a Vigreux column under reduced pressure gave: Benzylamine, 21 g., b.p. 62–67°/8–9 mm.; *N*-benzyl-*N*-*n*-octylamine, 220 g., b.p. 140–175°/11–12 mm.; and *N*-benzyl-*N*,*N*-di-*n*-octylamine, 45 g., b.p. 191–213°/10 mm. Separate redistillations through the Vigreux column of the latter two cuts gave the desired products. (See Tables I and II for analyses and physical properties.)

General method for preparing the N-benzyl-N-alkyl-N-n-octylamines. *N*-Benzyl-*N*-*n*-octylamine (21.9 g., 0.1 mole), alkyl halide (0.11 mole), and potassium hydroxide (7.7 g.) were added to a suitable flask and refluxed for 5 hr. The product was then cooled, shaken with 50 ml. of 10% aqueous sodium hydroxide solution, and separated. Fractionation of the colorless oily material through a Vigreux column under reduced pressure gave essentially the desired tertiary amine. The main product collected was then redistilled through the Vigreux column to give the *N*-Benzyl-*N*-alkyl-*N*-*n*-octylamine. (See Tables I and II for analytical data and physical properties.)

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Improved Syntheses of β-Alanine

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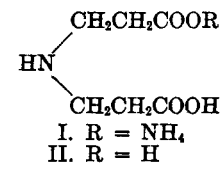
One important group of β-alanine syntheses includes preparative procedures which involve the interaction at elevated temperatures and pressures of aqueous ammonia and acrylonitrile,[1] esters of acrylic acid,[2] or compounds RCH_2CH_2X which can yield acrylonitrile or acrylic acid by a simple, usually base-catalyzed, elimination reaction[3–6], $RCH_2CH_2X \rightarrow RH + CH_2 = CHX$ (X = CN or COOH). These reactions have generally been carried out between 125 and 250°. In each case, the β-alanine was directly isolated by precipitating it from the concentrated reaction products with a solvent in which it is sparingly soluble, *e.g.*, methanol. Where mentioned, the β-alanine thus obtained is claimed to be of high purity.

Preliminary investigations in this laboratory of syntheses of β-alanine by the interaction of aqueous ammonia and either ethyl or methyl acrylate[2] at 125 to 190°, or ethylene cyanohydrin[4] at 180 to 190°, showed, however, that quite impure β-alanine was invariably produced. In some instances, the product contained less than 70% of β-alanine. The prescribed isolation procedures[2,4] were followed in each case.

The impure products were found by titration to contain acidic and basic functions in almost equivalent amounts; moreover, the neutralization equivalents determined were only slightly greater than those calculated for β-alanine. Combined ammonia[7] (in the form of ammonium salts) was, however, present in appreciable quantities. No unsaturated compounds or tertiary amines were detected. These results, together with an analysis specific for the primary amino group,[8] indicated that the major impurity was probably the monoammonium salt of 3,3′-iminodipropionic acid (I).



I. R = NH_4
II. R = H

Pertinently, Ford[9] has pointed out that the monoammonium salt (I) and acid (II) are probable by-products in β-alanine syntheses of the type under discussion. Compounds I and II have solubilities similar to that of β-alanine in water and methanol,[9] the solvents employed for the isolation. Consequently, if these by-products are formed in large enough quantity they will crystallize with the β-alanine. Furthermore, the similarity of solubilities makes purification by fractional crystallization tedious and impractical.

A simple purification procedure for β-alanine made by syntheses based on an acrylate ester or ethylene cyanohydrin has now been found. Refluxing of either diisopropylamine or triethylamine with an aqueous solution of the crude β-alanine converted the impurities into methanol-soluble products but did not affect the β-alanine. Because β-alanine is sparingly soluble in methanol, the amine treatment followed by precipitation with methanol enabled the direct isolation of the amino-acid in a good degree of purity (95 to 98%). One crystallization of this product from water gave β-alanine in a purity of 99.9%.

(1) G. H. Carlson and C. N. Hotchkiss, U. S. Patent 2,377,401 (1945).
(2) S. H. Babcock, Jr., and B. R. Baker, U. S. Patent 2,376,334 (1945).
(3) P. M. Kirk, U. S. Patent 2,334,163 (1943).
(4) P. M. Kirk and J. H. Paden, U. S. Patent 2,364,538 (1944).
(5) J. H. Paden, U. S. Patent 2,414,389 (1947).
(6) P. M. Kirk, U. S. Patent 2,416,630 (1947).
(7) Determined by the method of K. G. Mizuch and A. Y. Savchenko [*Org. Chem. Ind.* (*U.S.S.R.*), **7**, 24 (1940)].
(8) F. E. Critchfield and J. B. Johnson, *Anal. Chem.*, **29**, 1174 (1957).
(9) J. H. Ford, *J. Am. Chem. Soc.*, **67**, 876 (1945).

Prior separation of the crude β-alanine was found to be unnecessary because the amine treatment was equally satisfactory when performed on the concentrated ammonia–acrylate ester or concentrated ammonia–ethylene cyanohydrin reaction products.

The reaction conditions specified in the Experimental Section afforded optimum yields of β-alanine. First-pass yields approached 40%; however, the residues after removal of the β-alanine could be recycled with aqueous ammonia to give further quantities of the amino acid and over-all yields of about 85%.

EXPERIMENTAL

All melting points are uncorrected. β-Alanine purities were calculated from analyses for combined ammonia[7] and for the aliphatic primary amino group.[8]

Preparation of β-alanine from ethyl acrylate and aqueous ammonia. (a) Ethyl acrylate[10] (141.4 g., 153 cc., 1.415 moles), aqueous 28% ammonia (420 cc., 4.4 × 1.415 moles), water (830 cc.), and phenothiazine[11] (0.142 g.) were placed in a 3-l. stainless steel autoclave fitted with a rocking arrangement. The mixture was heated and rocked for 17 hr. at a pressure of 75 p.s.i.g. and an average temperature of 127°.

After being cooled, the reaction product was treated with charcoal (Norit A, 10.0 g.) and evaporated at reduced pressure at below 60° to a volume of 300 cc. Diisopropylamine (156 cc., 112 g.) and phenothiazine[11] (0.1 g.) were added and the mixture refluxed with stirring for 1.5 hr. At the end of this time the amine was distilled as quickly as possible at atmospheric pressure and the residue diluted with distilled water (50 cc.). The solution was treated with charcoal (Norit A, 10.0 g.) and most of the water evaporated therefrom under reduced pressure. Anhydrous methanol (150 cc.) was added to the final sirup and the mixture stirred at room temperature until precipitation of solid was complete (this took about 15 hr.). The solid was collected, washed twice with anhydrous methanol (30 to 35 cc. portions), and dried at 60° under reduced pressure. β-Alanine (43 to 48 g., 34 to 38% yield) was thus secured as colorless crystals, m.p. 194–196° dec.; mixed m.p. with authentic β-alanine, 196–198° dec.; ammonium salts were absent[7] and the purity varied between 96 and 98%.

This slightly impure product was dissolved in a hot aqueous solution previously prepared by saturating water at room temperature with β-alanine (material having a purity of 96 to 98% was suitable). The solution was then cooled to room temperature with gentle stirring and kept at this temperature for 3 hr. to give well-formed crystals of β-alanine (38 to 43 g., 30 to 34% yield), m.p. 199–201° dec.; the purity was 99.9%.

(b) The same quantities of reactants as were employed for the foregoing preparation were heated 8 hr. at 190° under an average pressure of 280 p.s.i.g.

After being cooled, the mixture was treated with charcoal (Norit A, 10.0 g.) and evaporated at reduced pressure at below 60° to a volume of 300 cc. The solution was treated once more with charcoal (Norit A, 10.0 g.) then evaporated to a sirup under reduced pressure. Anhydrous methanol (200 cc.) was added and the mixture stirred at room temperature until precipitation of solid was complete. The precipitate was collected, washed twice with methanol (50-cc. portions), and dried at 60° under reduced pressure. The product consisted of colorless crystals (58.5 g.), m.p. 133–147°, which contained 1.68% of combined ammonia and 75% of β-alanine.

This crude β-alanine (15.0 g.) was dissolved in distilled water (100 cc.). Diisopropylamine (56 cc., 40.2 g.) was added and the mixture refluxed with stirring for 1.5 hr. The excess of amine was distilled under reduced pressure, the residue dissolved in water (20 cc.), and the solution treated with charcoal (3.5 g.). Evaporation of most of the water from the filtrate under reduced pressure left a nearly colorless sirup. Anhydrous methanol (50 cc.) was added and the mixture stirred at room temperature for 16 hr. The precipitate was collected, washed twice with methanol (10 cc. portions), and dried at 60° under reduced pressure to give β-alanine (8.8 g.), m.p. 196–198° dec., which had a purity of 97%.

Preparation of β-alanine from ethylene cyanohydrin and aqueous ammonia. Ethylene cyanohydrin (68.0 cc., 71.1 g., 1 mole), aqueous 28% ammonia (345.0 cc., 5.0 moles), and water (501 cc.) were introduced into a 3-l. stainless steel autoclave equipped with a rocking device. The mixture was heated and rocked for 8 hr. at 190° under an average pressure of 285 p.s.i.g.

After being cooled, the reaction product was treated with charcoal (10.0 g.) and evaporated to low bulk at reduced pressure at below 60°. The residual sirup was stirred with anhydrous methanol (106 cc.) for 16 hr. at room temperature. The precipitated solid was collected, washed twice with anhydrous methanol (20-cc. portions), and dried at 60° under reduced pressure. A faintly pink solid (45.8 g.), m.p. 114–144°, was obtained; it contained 1.96% of combined ammonia and 78.1% of β-alanine.

The foregoing crude β-alanine (15.0 g.) was treated with diisopropylamine (56 cc., 40.2 g.) as described in the preceding experiment to give β-alanine (9.0 g.), m.p. 192–195° dec., in a purity of 95%.

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(10) An equivalent quantity of methyl acrylate gave substantially the same yield of β-alanine.

(11) To inhibit polymerization.

A Simple Method for the Preparation of Oxindoleacetic and Propionic Acids from the Parent Indoles

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The known methods for the conversion of indoles into oxindoles involving oxidation with peracetic[1] or persulfuric[2] acids or hydrolysis of parent disulfides[3] leave much to be desired from a preparative point of view.

The smooth hydrogenolysis of the lactone III of 5-bromodioxindole-3-propionic acid, obtained by the action of *N*-bromosuccinimide on indole-3-propionic acid (II), to oxindole-3-propionic acid (V),[4] has now been

(1) B. Witkop, *Ann.*, **558**, 98 (1947).

(2) C. E. Dalgliesh and W. Kelley, *J. Chem. Soc.*, 3726 (1958).

(3) T. Wieland *et al.*, *Ann.*, **587**, 146 (1954); **592**, 69 (1955); K. Freter, J. Axelrod, and B. Witkop, *J. Am. Chem. Soc.*, **79**, 3191 (1957).

(4) A. Patchornik, W. B. Lawson, and B. Witkop, *J. Am. Chem. Soc.*, **80**, 4748 (1959); W. B. Lawson, A. Patchornik, and B. Witkop, *J. Am. Chem. Soc.*, **82**, 5918 (1960).