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

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(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).

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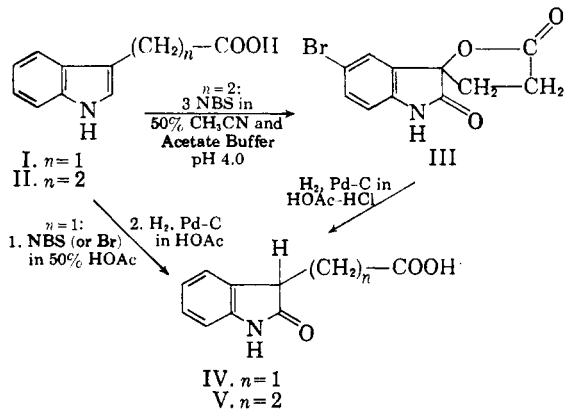

adapted to a direct conversion of indoles to oxindoles without isolation of intermediate (bromo)-dioxindoles. The rapid reaction of *N*-bromosuccinimide with indoles[4,5,6] from a preparative point of view is difficult to arrest at the oxindole stage under the conditions described. Further oxidation at the 3-position and aromatic substitution at the 5-position are invariably observed. The present one-step procedure uses an excess of brominating agent followed by simultaneous hydrogenolytic removal of the benzylic oxygen function of the 3-position and the aromatic bromine substituent in the 5-position of the benzene ring.

The preparation of oxindole-3-propionic acid (V) and of oxindole-3-acetic acid[7] (IV) previously prepared[8,9] only by multistep procedures, proceeds in minimal yields of 50% and better.

EXPERIMENTAL

Oxindole-3-propionic acid (V). To an ice cold solution of 3.0 g. (15.9 mmoles) of indole-3-propionic acid (II) in 100 ml. of 50% acetic acid, 5.65 g. (31.8 mmoles) of *N*-bromosuccinimide was added with constant swirling over a period of 5 min. After 15 min. at room temperature 1 g. of 10% palladium-on-charcoal was added, and the mixture was shaken in a hydrogen atmosphere for 18 hr. The filtered solution was evaporated. Crystallization of the residue from water, after treatment with charcoal, gave 1.60 g. (49%) of oxindole-3-propionic acid, m.p. 165–167° (reported[8] m.p. 169–170°), identical with an authentic sample prepared by hydrogenolysis of the crystalline lactone III.[5]

Oxindole-3-acetic acid (IV). To an ice cold solution of 1.0 g. (5.72 mmoles) of indole-3-acetic acid (I) in 50 ml. of 50% acetic acid was added 4.85 ml. of acetic acid containing 1.83 g. (11.4 mmoles) of bromine. After 1 hr. at room temperature, 500 mg. of 10% palladium-on-charcoal was added, and the mixture was shaken in an atmosphere of hydrogen for 17 hr. The solution was filtered, evaporated to dryness, and 15 ml. of water was added. The mixture was extracted three times with 25-ml. portions of ethyl acetate, and the dried (sodium sulfate) extract was evaporated to dryness. Crystallization of the residue from ether–petroleum ether (b.p. 50–60°) gave 686 mg. (63%) of oxindole-3-acetic acid (IV), m.p. 100–140° (this material probably contains some solvent; *cf.* ref. 9). Recrystallization from acetone-benzene, followed by drying for 45 min. *in vacuo* at 55° gave 536 mg. (49%) of colorless crystals, m.p. 140–142° (reported m.p. 147°, softening at 142°). The compound was further characterized by its smooth acid-catalyzed conversion to 3,4-dihydroquinolone-4-carboxylic acid, m.p. 210–214°.[9]

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Some 6-Bis(2-chloroethyl)aminoalkyladenines[1]

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As it is a widely accepted hypothesis that nitrogen mustard gas [HN-2, bis(2-chloroethyl)methylamine] exerts its carcinostatic (and mutagenic) effects through attack on deoxyribonucleic acid (DNA), it seemed to us of some interest to prepare a variety of HN-2 analogs in which the methyl group was modified by incorporation of purine rings analogous to those naturally incorporated into DNA. To preserve the aliphatic character of the nitrogen mustard group, we did not wish to attach the mustard nitrogen directly to the purine ring system.

We report herein the preparation of two adenine nitrogen mustards, with a mustard group attached to the 6-amino group of adenine through an ethylene and a trimethylene chain. The compounds were extremely hygroscopic and difficult to purify. Against a number of mouse tumors, they showed moderate mustard-like activity. Details of the biological date will be reported elsewhere.

Incidental to the work, a convenient preparation of 4,5-diamino-6-chloropyrimidine has been worked out involving amination of 4,6-dichloro-5-aminopyrimidine.

EXPERIMENTAL

4,5-Diamino-6-chloropyrimidine (II). 4,6-Dichloro-5-aminopyrimidine (5 g., Cyclo Lab., Los Angeles) and 100 ml. of ethanolic ammonia were heated at 150° in a steel bomb for 3 hr. The mixture was evaporated to dryness, and the

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