

Experimental

N-Bis-(2-cyanoethyl)-acetamide.—A solution of 25 g. (0.203 mole) of β,β' -iminodipropionitrile in 30 ml. of chloroform was cooled and rapidly stirred during the addition of 7.85 g. (0.1 mole) of acetyl chloride. A vigorous reaction set in instantly, causing the precipitation of a white solid. After stirring for about one hour, the solid was removed by suction filtration. The solid melted at 147°, the melting point of the hydrochloride of β,β' -iminodipropionitrile, and it was obtained in 95–100% of the theoretical amount. The filtrate was a clear yellow solution, and when hydrogen chloride gas was bubbled through it, more of the hydrochloride formed. In addition, the yellow color was discharged, giving rise to a yellow gum and a water-white solution. The solid and gum were removed by filtration, and the chloroform solvent was evaporated from the clear filtrate. A solid began to crystallize out, and even before the entire product had solidified, it was poured into boiling ethyl acetate. Upon cooling, white plates crystallized slowly; a dried sample of this material melted at 50° (cor.). The yield of product was 82%.

Anal. Calcd. for $C_8H_{11}N_3O$: C, 58.16; H, 6.71; N, 25.44. Found: C, 58.32; H, 6.65; N, 25.37.

β,β' -Iminodipropionitrile Hydrochloride.—Dry hydrogen chloride was passed into a solution of β,β' -iminodipropionitrile in chloroform and a white solid precipitated immediately. The needles were filtered off, washed with chloroform and ethanol, and then dried in a vacuum desiccator. A sample of this solid melted at 147–148°, and recrystallization from methanol did not raise the melting point. A determination of the melting point of a mixture consisting of the pure hydrochloride and a sample of the white solid obtained during the preparation of N-bis-(2-cyanoethyl)-acetamide showed no depression.

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Preparation and Chlorinolysis of α -Mercaptodiethylacetic Acid

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A recent oxidation of thioglycolic acid to chlorosulfonylacetic acid with chlorine¹ suggested the possibility of obtaining α -chlorosulfonyldiethylacetic acid, desired for synthetic purposes, in this way. The action of chlorine on α -mercaptodiethylacetic acid resulted, however, in the formation of dichloro- α -ethylbutyric acid (apparently the α,β -isomer), α -ethylcrotonic acid and sulfuric acid as the only isolable products.² These observations may be helpful in suggesting the nature of products obtained from the chlorine oxidation of other sulfur compounds.

Experimental³

α -Bromodiethylacetic Acid (I).—A modification of the general method of Marvel⁴ was used. A mixture of 288.7 g. of diethylacetic acid, 435 g. of dry bromine and 4.4 ml. of phosphorus trichloride was heated at 70–80° for ten hours. Additional bromine (23 g.) was added and heating continued for six hours. Distillation using a 15-cm. Vigreux column gave 370 g. (76%) of I, b.p. 98.5–103.5° (0.9 mm.); m.p.

(1) J. B. Dickey, U. S. Patent 2,466,396 (1949) [C. A., 43, 4868 (1949)].

(2) Dr. E. Campaigne of Indiana University has informed us that an attempted synthesis of ethyl α -chlorosulfonylisobutyrate by the wet chlorine oxidation of the isothiuronium salt of ethyl α -bromoisobutyrate resulted in the evolution of sulfur dioxide upon working up the product.

(3) Melting points are corrected and boiling points are uncorrected. Most of the analyses are by the Clark Microanalytical Laboratory, Urbana, Ill.

(4) C. S. Marvel, *Org. Syntheses*, 29, 106 (1940).

20–21.5°; n_D^{25} 1.4743; reported⁵ b.p. 130–133° (18 mm.); m.p. 20°; Br found, 40.73 (calcd., 40.97).

I reacts rapidly with two equivalents of 0.1 N sodium hydroxide upon titration in the usual way. Thus, while rapidly fading end-points corresponding to neut. equiv. of 170–192 (calcd. 195) were observed, end-points stable for one-half hour corresponded to neut. equiv. 97.9 (calcd. for I/2 97.5).

This neutralization of I with two equivalents of alkali was found to involve both elimination and substitution reactions. Addition of 4.1 g. of sodium hydroxide in 23 ml. of water to 10 g. of I with cooling, followed by acidification and extraction gave solid and oil which were separated. Short-path distillation of the solid gave 0.5 g. (8%) of α -hydroxydiethylacetic acid, m.p. 78–79.5° (reported⁶ 80°); neut. equiv., 133 (calcd., 132). Short-path distillation of the oil gave 0.83 g. (14%) of the liquid form of α -ethylcrotonic acid (II), n_D^{25} 1.4441; neut. equiv., 112 (calcd., 114); this form of II upon heating with hydrobromic acid⁷ gave the solid form, m.p. 39.5–40° (reported⁸ 41–42°).

In order to substantiate the α -position of bromine in the presumed I, a portion of the bromo acid was converted with silver oxide in water to α -hydroxydiethylacetic acid, m.p. 78°.

α -(Ethylxantho)-diethylacetic Acid (III).—III was prepared using a procedure based on one of Billmann.⁹ A solution of 600 g. of potassium ethyl xanthate¹⁰ in 950 ml. of water containing 347 g. of I was allowed to stand for two days. Oil which separated was removed with ether and the aqueous layer was treated with 360 ml. of 30% hydrochloric acid. An ether extract of the oily product on partial evaporation and chilling gave 192.0 g. (46%) of III as white crystals, m.p. 108–112° (uncor.), which after recrystallization from aqueous ethanol had a constant m.p. of 114.5–115°.

Anal. Calcd. for $C_9H_{16}O_3S_2$: C, 45.74; H, 6.82; S, 27.13; neut. equiv., 236. Found: C, 46.07; H, 6.67; S, 27.04; neut. equiv., 236.

α -Mercaptodiethylacetic Acid (IV).¹¹—III was converted to IV by a method similar to one of Billmann.⁹ A flask completely filled with 192 g. of III, 332 ml. of 25% ammonium hydroxide and 638 ml. of absolute alcohol, was allowed to stand closed for four days. The mixture was then heated at the reflux temperature for three hours, after which excess alcohol and ammonia were removed by distillation. The residue was adjusted with concentrated ammonium hydroxide to about pH 10, extracted with ether, and then brought to about pH 3 with concentrated hydrochloric acid (137 ml.). An ether extract of the resulting oil was dried over anhydrous sodium sulfate, and the IV obtained therefrom was purified by distillation; yield 56.9 g. (47%), b.p. 85–118° (1 mm.). Redistillation gave IV having b.p. 113–117° (5 mm.); m.p. 26–28.5°; n_D^{25} 1.4768; d_4^{25} 1.0718; M_D calcd. 39.14, found 39.06.

Anal. Calcd. for $C_8H_{12}O_2S$: C, 48.62; H, 8.16; S, 21.63; neut. equiv., 148. Found: C, 48.55; H, 8.04; S, 21.44; neut. equiv., 148.

Chlorinolysis of IV.—Chlorine gas was passed through a solution of 10 g. of IV in 10 ml. of water and 25 ml. of acetic acid cooled to -15° . The temperature rose initially to 15° but could soon be maintained at -15° during one hour of chlorination; 16.4 g. of chlorine was absorbed. After addition of ice-water, a benzene extract was dried and concentrated with gentle heating under reduced pressure to an oil from which 0.7 g. (6%) of a dichloro- α -ethylbutyric acid slowly separated, m.p. 99–103.5°. Recrystallization from petroleum ether–benzene (5:1) gave the pure dichloro acid, m.p. 111–112°, an aqueous solution of which was strongly acidic.

(5) K. W. Rosenmund, *Ber.*, 42, 4472 (1909). Cf. M. S. Newman, *This Journal*, 57, 732 (1935).

(6) F. Tiemann and L. Friedländer, *Ber.*, 14, 1974 (1881).

(7) E. Blaise and P. Bagard, *Ann. chim. phys.* [8] 11, 120–131 (1907).

(8) K. von Auwers, *Ann.*, 432, 76 (1923).

(9) E. Billmann, *ibid.*, 343, 128 (1906).

(10) Prepared by Frey's procedure as given by C. Bruchhold, *Eng. Mining J.*, 125, 338 (1928).

(11) The preparation of IV by another method was reported by E. Clemmensen and A. H. C. Heitman, *Am. Chem. J.*, 40, 298 (1908); no physical constants were given.

Anal. Calcd. for $C_8H_{10}O_2Cl_2$: C, 38.94; H, 5.45; Cl, 38.32; neut. equiv., 185. Found: C, 39.01; H, 5.18; Cl, 37.99; neut. equiv., 186.

This acid is presumed to be α,β -dichloro- α -ethylbutyric acid (V), since heating a dioxane solution under reflux with zinc dust gave the solid form of II, m.p. 38.5–41°.

A similar experiment in which chlorination was effected at -3° gave 7.6 g. of oil, which after four distillations from a modified Claisen flask gave 1.45 g. (19%) of II; b.p. 91.5–94° (3 mm.); n_D^{20} 1.4451 (*cf.* above); b.p. reported² 107–108° (10 mm.); rapid decolorization of aqueous potassium permanganate and bromine in carbon tetrachloride (with hydrogen bromide evolution). The identity of the presumed II was confirmed by conversion as described above to the stable form, m.p. 38–40.5°, and by formation of the β -naphthylamide, m.p. 92–95° (reported² 96°).

Concentration of the benzene-extracted aqueous layer from another chlorination gave a hygroscopic viscous liquid which was strongly acidic (neut. equiv. 98) and gave a heavy precipitate with barium chloride but none with silver nitrate; it apparently consisted in large part of sulfuric acid. Neutralization with sodium hydroxide followed by evaporation and recrystallization of the resulting solid gave sodium sulfate; Na, 31.6 (calcd. 32.4).

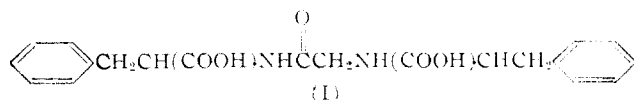
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N,N'-(Oxoethylene)-bis-(DL- β -phenylalanine)

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In the course of the preparation of N-bromoacetyl-DL- β -phenylalanine by the conventional Schotten-Baumann reaction between DL- β -phenylalanine and bromoacetyl bromide there was isolated in addition to the desired product a substance insoluble in dilute mineral acid, ethyl acetate or acetone. The same material could be obtained in somewhat larger yield if only one-half molar amounts of bromoacetyl bromide were used. This fact, together with the analyses for carbon, hydrogen and nitrogen, indicated that the substance was N,N'-(oxoethylene)-bis-(DL- β -phenylalanine) (I).



That this was the correct formulation was shown in two ways. First, the compound was also prepared by the condensation of N-bromoacetyl-DL- β -phenylalanine methyl ester with DL- β -phenylalanine ethyl ester, followed by basic hydrolysis and acidification. Second, (I) was hydrolyzed with concentrated hydrochloric acid to DL- β -phenylalanine and DL- β -phenylalanine-N-acetic acid.¹ The latter compound was isolated from the hydrolysate and identified by its analysis and by conversion to the known hydrochloride.² The presence of β -phenylalanine in the hydrolysate was shown by paper chromatography utilizing an alcohol-water solvent (77% alcohol). No ninhydrin reacting materials other than the two substances mentioned were observed in the developed chromatogram.

The author is indebted to Dr. H. A. Sober of this Laboratory for the chromatographic analysis.

(1) D. A. Hahn and A. Litzinger, *This Journal*, **54**, 4665 (1932).

(2) D. A. Hahn and M. M. Rudicott, *ibid.*, **60**, 1040 (1938).

Experimental³

N-Bromoacetyl-DL- β -phenylalanine Methyl Ester.—To a 10% excess of diazomethane⁴ in 200 ml. of ether there was added in small portions 21.5 g. of N-bromoacetyl-DL- β -phenylalanine.⁵ After one-half hour the excess diazomethane was destroyed with dilute hydrochloric acid following which the ethereal solution was washed with sodium bicarbonate solution and saturated sodium chloride. After drying over sodium sulfate the ether was concentrated and petroleum ether (b.p. 35–70°) was added. There was thus obtained 18.0 g. (80%) of ester, m.p. 80–82°. The melting point was not changed by recrystallization from the same solvents.

*Anal.*⁶ Calcd. for $C_{12}H_{14}O_3NBr$: C, 48.0; H, 4.7; N, 4.7; Br, 26.6. Found: C, 48.0; H, 4.9; N, 4.8; Br, 26.6.

N,N'-(Oxoethylene)-bis-(DL- β -phenylalanine) (I).
Method (A).—In a 500-ml. three neck round-bottomed flask, cooled by an ice-bath and equipped with a stirrer and two addition funnels there was placed 33 g. of DL- β -phenylalanine and 100 ml. of 2 N sodium hydroxide. To the stirred solution, kept below 5° there was added dropwise from one funnel 20 g. of bromoacetyl bromide and from the other funnel 2 N sodium hydroxide was added at such a rate as to just keep the solution alkaline. After the addition was complete the ice-bath was removed and the reaction mixture stirred for three hours.

At the end of this period acetic acid (50 ml.) was added and the resulting precipitate collected by filtration. This was taken up in sodium bicarbonate solution and again precipitated with acetic acid to give 15 g. of material m.p. 210–215° dec. After two more precipitations from bicarbonate by the addition of acetic acid followed by washing of the precipitate with ethanol and ether, there was obtained 9.5 g. (26%) of N,N'-(oxoethylene)-bis-(DL- β -phenylalanine), m.p. 224–227° dec.

*Anal.*⁶ Calcd. for $C_{20}H_{22}O_6N_2$: C, 64.8; H, 5.9; N, 7.6. Found: C, 64.8; H, 6.2; N, 7.6.

Method B.—Eleven and one-half grams of DL- β -phenylalanine ethyl ester hydrochloride was treated with a slight excess of alkali and the free ester was extracted into 150 ml. of ether. To this ethereal solution there was added a solution of 7.5 g. of N-bromoacetyl-DL- β -phenylalanine methyl ester in 150 ml. of ether. Seventy-five ml. of ethyl acetate was then added and most of the ether was removed by boiling, following which the mixture was allowed to stand overnight.

The solvent was removed in a stream of air and the residue triturated with ether. The solid amine hydrobromide was collected by filtration and the ether removed from the filtrate *in vacuo* following which the oily residue was dissolved in 50 ml. of ethanol and treated overnight at room temperature with 2.5 g. of sodium hydroxide in 50 ml. of water. The acid was precipitated by the addition of acetic acid to give 5.9 g. of material, m.p. 200–220° dec.

After one precipitation by dilute hydrochloric acid and one by acetic acid from sodium bicarbonate solution, 4.2 g. (45%) of N,N'-(oxoethylene)-bis-(DL- β -phenylalanine), m.p. 224–227° was obtained. A mixed melting point with I from A showed no depression.

Hydrolysis of N,N'-(Oxoethylene)-bis-(DL- β -phenylalanine).—One and eight-tenths grams of I (from A) was refluxed for 6 hr. in 50 ml. of concentrated hydrochloric acid following which the solution was taken to dryness *in vacuo*. Most of the hydrochloric acid was removed by taking the residue up in 50-ml. portions of water and evaporating to dryness *in vacuo* three times. After the third evaporation the residue was taken up in 10 ml. of water and treated with excess aniline to remove bound hydrogen chloride. An equal volume of alcohol was added and the solution placed in the refrigerator overnight. Filtration gave 1.5 g. of crystals, m.p. 195° (dec.). Two recrystallizations from water gave 0.1 g. of DL- β -phenylalanine-N-acetic acid, m.p. 233–236° dec. (lit.² 225–226°).

Anal. Calcd. for $C_{11}H_{13}O_4N$: C, 59.2; H, 5.8; N, 6.3. Found: C, 59.2, 58.9; H, 5.9, 5.8; N, 6.0, 6.0.

(3) All melting points are corrected.

(4) "Organic Syntheses," Coll. Vol. II, J. Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(5) B. Abderhalden and F. Schweitzer, *Fermentforschung*, **11**, 224 (1930).

(6) Analyses by R. J. Koegel and staff of this Laboratory.