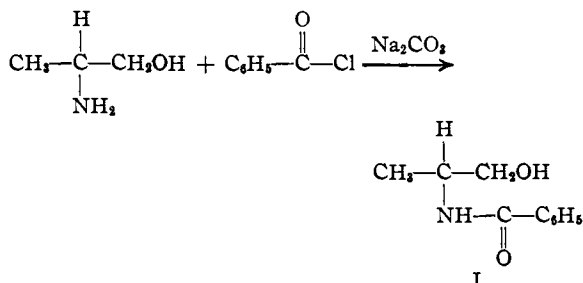# Amino Acids. II. Alanine

BY JOHN H. BILLMAN AND EARL E. PARKER[1]

In a recent publication[2] it was shown that glycine could be prepared from ethanolamine by the oxidation of its phthalimide derivative followed by the removal of the phthalyl group. In an attempt to apply this method to the synthesis of alanine from 2-amino-1-propanol some difficulty was encountered in forming the phthalyl derivative.
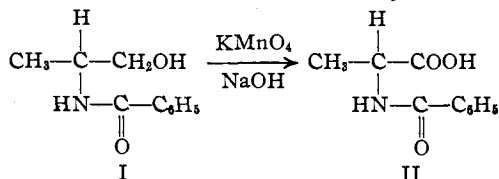
The possibility of forming other derivatives in which only one of the hydrogens of the amino group was replaced by an acyl radical was then investigated, and it was found that the benzoyl group was most desirable since substitution readily took place and the group was removed easily from the oxidation product.

A number of methods were tried for preparing 2-benzoylamino-1-propanol (I) and it was found that the most satisfactory procedure was to use a suspension of sodium carbonate in benzene followed by the addition of benzoyl chloride.

$$CH_3-\underset{\underset{NH_2}{|}}{\overset{\overset{H}{|}}{C}}-CH_2OH + C_6H_5-\overset{\overset{O}{\|}}{C}-Cl \xrightarrow{Na_2CO_3}$$

$$CH_3-\underset{\underset{NH-\overset{\|}{C}-C_6H_5}{|}}{\overset{\overset{H}{|}}{C}}-CH_2OH$$
$$\underset{O}{\overset{}{}}$$
I

This procedure gave a 90–91% yield of crude 2-benzoylamino-1-propanol which gives only slightly lower yields on oxidation than the pure compound obtained by repeated recrystallization from acetone. Since the purification is accompanied by considerable loss, it is advisable to use the impure material for the oxidation.

It was found that alkaline potassium permanganate was the most desirable reagent for the oxidation of the 2-benzoylamino-1-propanol (I) to benzoylalanine (II). When acidified potassium dichromate was tried, as in the preparation of glycine, the yields were unsatisfactory.

$$CH_3-\underset{HN-\overset{\|}{C}-C_6H_5}{\overset{\overset{H}{|}}{C}}-CH_2OH \xrightarrow[NaOH]{KMnO_4} CH_3-\underset{HN-\overset{\|}{C}-C_6H_5}{\overset{\overset{H}{|}}{C}}-COOH$$
$$\qquad\quad O \qquad\qquad\qquad\qquad O$$
$$\qquad\quad I \qquad\qquad\qquad\qquad\quad II$$

Pure benzoylalanine was obtained with little difficulty from the above crude product. However, since the principal impurity is benzoic acid,

more of which is formed in the next step, purification is not advisable.

Hydrolysis of the crude benzoylalanine with hydrochloric acid and isolation of the alanine according to the method of Pacsu and Mullen[3] gave a 70–71% yield of pure alanine.

Acknowledgment.—The authors wish to thank Eli Lilly and Company for assistance in this work.

Experimental

2-Benzoylamino-1-propanol.—In a liter 3-necked flask equipped with an efficient stirrer, a dropping funnel, and a thermometer supported by a notched cork, were placed 50 g. of anhydrous sodium carbonate, 15.5 g. (0.1 mole + 0.5 g.) of 2-amino-1-propanol and 500 cc. of dry benzene. The stirrer was started and the mixture cooled to 10° by means of an ice water-bath. At this point, 28.1 g. (0.1 mole) of benzoyl chloride in 100 cc. of benzene was added drop by drop at such a rate that the temperature did not rise above 10°. (About thirty minutes were required for the addition.) Stirring was continued for six hours longer. At the end of four hours the bath was removed and the mixture was allowed to come slowly to room temperature. The thermometer was then replaced with a condenser and the mixture refluxed until there was no odor of benzoyl chloride. The hot mixture was then filtered. The solid residue was extracted twice with 100 cc. of boiling benzene. The combined filtrates were concentrated to 400 cc. and chilled. The crystals were filtered off and washed with cold benzene. A small second crop was obtained by concentrating the filtrate to about 100 cc.; yield, 32.0–32.5 g. or 90–91% of material melting at 102–103°. This material is satisfactory for the following oxidation without further purification. A sample of the 2-benzoylamino-1-propanol was recrystallized several times from acetone when it melted at 107–108°.

Anal. Calcd. for N, 7.82. Found: N, 7.65.

Benzoylalanine.—In a liter 3-necked flask equipped with a stirrer and a thermometer was placed 30.3 g. of the above benzoylated amino alcohol, 300 cc. of water and 2 g. of sodium hydroxide. To the vigorously stirred mixture was added 35.6 g. of solid potassium permanganate at such a rate that the temperature did not rise above 40°. Stirring was continued until practically all of the potassium permanganate was consumed. The manganese dioxide was filtered out and the cake washed with two 25-cc. portions of water. The combined filtrates were heated with a few cc. of methyl alcohol to destroy the excess of permanganate, and again filtered. The filtrate was cooled to room temperature and the product precipitated by chilling after the addition of concentrated hydrochloric acid. A small additional amount was obtained by neutralizing the filtrate and evaporating to about 150 cc. under reduced pressure; yield 21.2–22.8 g. (65–70%) of material that melts over a two degree range between 156 and 163°. Recrystallized material melts at 166°.

Alanine.—The above material (22.2 g.) was refluxed for eight hours in 200 cc. of 18% hydrochloric acid. The mixture was cooled and the benzoic acid filtered off. The filtrate was evaporated to dryness and pure alanine was isolated according to the method of Pacsu and Mullen[3]; yield, 7.2–7.3 g. (70–71%).

Summary

1. A method for the preparation of 2-benzoylamino-1-propanol has been developed.

(1) Submitted to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University.

(2) Billman and Parker, THIS JOURNAL, 65, 761 (1943).

(3) Pacsu and Mullen, *J. Biol. Chem.*, 136, 335–342 (1940).

2. Alanine has been synthesized by a new method using 2-amino-1-propanol as the starting material.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE PENNSYLVANIA SALT MANUFACTURING CO.]

The Reciprocal Salt Pair NaClO₃ + KCl ⇌ NaCl + KClO₃ in Water at 0 and 40°

BY PAUL A. MUNTER[1a] AND RALPH L. BROWN[1b]

Introduction

In the course of an investigation of the production of potassium chlorate from sodium chlorate cell liquors and potassium chloride, it was necessary to secure solubility data on the quaternary system of the reciprocal salt pair $NaClO_3$ + KCl ⇌ NaCl + $KClO_3$ in water.

The only significant experimental work previously reported for this quaternary system was that given by C. Di Capua and U. Scaletti,[1c] who investigated this reciprocal salt pair and the various component ternary systems involved at 20°.

In view of the fact that in the interpretation of their data for the ternary systems $KClO_3$–KCl–H_2O and $KClO_3$–$NaClO_3$–H_2O at 20°, Di Capua and Scaletti arrived at isothermally invariant point compositions which were at considerable variance with other reported data, new determinations of these invariant points for the two ternary systems were also undertaken. Rather than repeat their work at the same temperature (20°), the quaternary system and the ternary systems were studied at 0 and 40°.

Materials.—All the salts employed in this study were of c. p. grade and were used without further purification. The chlorate salts employed were found to average 99.9 + % pure based on the determination of chlorate content.

Apparatus.—Two types of apparatus were used in this investigation. For the 0° experiments, the mixtures of the solid salts and water sealed in Pyrex bottles were fastened to a rotor suspended in a constant temperature

with mercury seals. A thermometer was inserted in each flask. The temperature was maintained at 40 ± 0.05° by a heater controlled by a mercury thermoregulator.

The actual bath temperature in each instance was set and checked by means of a U. S. Bureau of Standards calibrated thermometer.

Procedure.—For each system studied, a preliminary experiment was carried out in which an original mixture of the solid salts and water was gradually augmented by small additions of the solid salts until the density and composition of the resultant solution became constant. From these data, mixtures of the solid salts and water known to result in a solution saturated with respect to the salts were prepared for the final tests. Saturation with respect to the salts was checked in the 40° tests by X-ray analysis of the dried and ground solid residues.

Sampling and Analysis.—The equilibrium solutions were sampled by withdrawing the clear supernatant solutions through cotton filtering plugs directly into the density pipet. After determining the density, the samples were diluted to a convenient volume and aliquots taken for analysis. The chloride ion was determined by the Volhard method as modified by Caldwell and Moyer.[2] The chlorate ion was determined by the method of Ditz as described by Kolthoff and Furman.[3] The sodium ion was determined by direct precipitation with zinc uranyl acetate as described by Barber and Kolthoff.[4] The potassium ion was determined by calculation based on the ionic balance. The water content was found by difference. The volumetric ware employed was recalibrated.

Results

The compositions of the solutions at the quaternary isothermally invariant points determined at 0° and 40° are presented in Table I along with the data of Di Capua and Scaletti. The composi-

TABLE I

Temp., °C.	Solid phases present	Cl	ClO₃	Na	K	H₂O	Density	Observer
		— Wt. % composition of solution at isothermally invariant point						
0	KClO₃ + NaCl + KCl	16.54	0.91	8.63	3.99	69.93	1.235	
0	KClO₃ + NaCl + NaClO₃	9.52	19.64	11.39	0.34	59.11	1.349	Munter and Brown
20	KClO₃ + NaCl + KCl	16.95	1.41	7.98	5.82	67.84	...	
20	KClO₃ + NaCl + NaClO₃	8.50	22.80	11.20	1.00	56.50	...	Di Capua and Scaletti
40	KClO₃ + NaCl + KCl	17.17	2.84	7.60	7.34	65.05	1.257	
40	KClO₃ + NaCl + NaClO₃	5.60	33.41	12.02	1.39	47.58	1.450	Munter and Brown

bath. An aqueous glycol solution was used as the bath liquid. The temperature was maintained at 0 ± 0.1° by intermittent circulation of a brine solution (−15 to −5°) through a cooling coil immersed in the well lagged bath. The circulation of the brine was controlled by a mercury thermoregulator.

In the 40° experiments, the mixtures of the solid salts and water were placed in a 250 ml. 3-necked flask and immersed in a constant temperature water-bath. The contents of the flasks were agitated by glass stirrers provided

tions of the solutions at the ternary isothermally invariant points determined are presented in Tables II and III along with the previously reported data of other workers, i. e., J. Fleck,[5] M. Donald,[6] and Iljinski.[7]

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(1c) C. Di Capua and U. Scaletti. *Gazz. ital. chem.*, **57**, 391 (1927).

(2) Caldwell and Moyer, *Ind. Eng. Chem., Anal. Ed.*, **7**, 38 (1935).

(3) Kolthoff and Furman, "Volumetric Analysis," Vol. II, p. 388 (1929).

(4) Barber and Kolthoff, THIS JOURNAL, **50**, 1625 (1928).

(5) J. Fleck, *Bull. soc. chim.*, 350 (1936).

(6) M. Donald, *J. Chem. Soc.* London, 1325 (1937).

(7) "International Critical Tables," Vol. IV, p. 315.