[Contribution from the Department of Chemistry, Clark University]

CARBOXYMETHYLATION OF AMINES. III. PREPARATION OF SUBSTITUTED GLYCINES[1]

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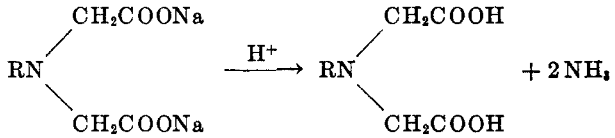
In previous publications the use of the carboxymethylation reaction for the preparation of ethylenediamine tetraacetic acid (1) and of triglycine (2) has been described. The purpose of the present paper is to demonstrate the usefulness of this reaction as a general method for the preparation of substituted α-amino acids by using benzylamine, *p*-aminobenzoic acid, isoamylamine, ethylamine, diethylamine, piperidine, and ethanolamine.

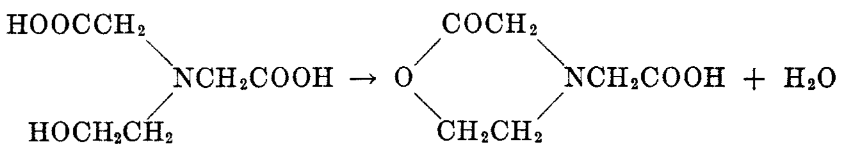
It was found that maximum yields of the substituted glycines were obtained when a dilute solution of formaldehyde was added slowly to an alkalized aqueous solution of the amine and sodium cyanide. The ammonia formed was completely removed by intermittent distillation under reduced pressure. The resulting solution was then neutralized or acidified, evaporated to dryness under reduced pressure, and the product separated from inorganic salts by extraction with organic solvents or by fractional crystallization. N-benzyliminodiacetic acid, N,N-*bis*-(carboxymethyl)anthranilic acid, and N-ethyliminodiacetic acid were separated in this manner. The general reaction may be represented by the equation:

$RNH_2 + 2\,NaCN + 2\,CH_2O + 2\,H_2O \rightarrow$



$$RN\begin{cases}CH_2COONa\\CH_2COONa\end{cases} \xrightarrow{H^+} RN\begin{cases}CH_2COOH\\CH_2COOH\end{cases} + 2\,NH_3$$

The lactone of N-(2-hydroxyethyl)iminodiacetic acid was obtained from the acidified reaction product resulting from dicarboxymethylation of ethanolamine:



Diethylglycine, piperidinoacetic acid, and N-isoamyliminodiacetic acid were not obtained in crystalline form from their respective reaction mixtures. These substances were isolated as the corresponding butyl esters by direct esterifica-

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tion of the reaction mixture and by subsequent fractional distillation under reduced pressure. The esters were colorless liquids which darkened slowly on standing over a period of several weeks. The isoamyl derivative, however, seemed aprticularly unstable and darkened appreciably in the course of 24 hours.

The crystalline products were characterized by carbon, hydrogen, and nitrogen analyses, while the liquid esters were identified by nitrogen and molecular weight determinations. Insofar as it has been possible to ascertain, the substances reported, with the exception of N-ethyliminodiacetic acid prepared by Heintz (3) and of N,N-*bis*-(carboxymethyl)anthranilic acid prepared by Schwarzenbach, *et al.* (4), have not previously been described. On the other hand, diethylglycine has been prepared by Heintz (5) and piperidinoacetic acid has been reported by Kraut (6).

EXPERIMENTAL

N-Benzyliminodiacetic acid. A solution of 30.0 g. (0.75 mole) of sodium hydroxide’ 58.8 g. (1.2 moles) of sodium cyanide, and 71.8 g. (0.5 mole) of benzylamine hydrochloride in 500 ml. of water was placed in a two-liter three-neck flask equipped with a stirrer, a dropping-funnel, and a reflux condenser. Then 81.8 g. of 37% formaldehyde solution was diluted to 500 ml., and 100 ml. of this solution was added, over a period of an hour, to the reaction flask with stirring at 75°. The addition was followed by the removal of 100 ml. of solvent under reduced pressure. The remainder of the formaldehyde was added in four successive batches at 80, 85, 90, and 95°, each addition requiring one hour. Each addition was followed by distillation of 100 ml. of solvent to insure complete removal of the ammonia. After the last distillation, the reaction mixture was neutralized with hydrochloric acid and evaporated to dryness under reduced pressure. The salt-like product was extracted with butyl alcohol in a Soxhlet apparatus for 6 hours. Upon cooling, crystals of *N*-benzyliminodiacetic acid precipitated from the alcoholic solution. An additional batch of crystals was obtained by a second extraction. Both batches proved to be free from sodium chloride and melted at 214° dec. The combined weight was 90 g. (84% yield).

Anal. Calc'd for $C_{11}H_{13}NO_4$: C, 59.3; H, 5.83; N, 6.27.
Found: C, 59.1; H, 5.29; N, 6.12.

N,N-bis-(carboxymethyl)anthranilic acid. The method of addition and the reaction conditions were the same as described for the previous preparation. The resulting reaction mixture was then refluxed for two hours. The product, slightly contaminated with *p*-aminobenzoic acid, was precipitated by cooling, acidifying to *p*H 4 with sulfuric acid, and washing with cold water. The unchanged *p*-aminobenzoic acid was removed by extraction with ethyl ether (Soxhlet). From 35.0 g. of *p*-aminobenzoic acid, 41 g. (65% yield) of pure material (m.p. 228° dec.) was obtained.

Anal. Calc'd for $C_{11}H_{11}NO_6$: C, 52.0; H, 4.33; N, 5.53.
Found: C, 51.8; H, 4.05; N, 5.25.

N-Ethyliminodiacetic acid. This substance was prepared by a method similar to that described for *N*-benzyliminodiacetic acid, but the temperature was maintained at 25° during the addition of sodium cyanide and formaldehyde. Upon cooling the butyl alcohol extracts, 148 g. of precipitate containing appreciable amounts of sodium chloride was obtained from 45.0 g. of ethylamine. Fractional crystallization from aqueous alcohol resulted in the isolation of the hydrochloride of N-ethyliminodiacetic acid, m.p. 185–190° dec.

Anal. Calc'd for $C_6H_{12}ClNO$: N, 7.08; HCl, 18.45.
Found: N, 6.99; HCl, 18.40.

N-(2-Hydroxyethyl)iminodiacetic acid lactone. A one-liter aqueous solution of 30.5 g. of ethanolamine, 3 g. of sodium hydroxide, and 58.5 g. of sodium cyanide was placed in an apparatus similar to that previously described and was treated in a similar manner with 100 g. of 37% formaldehyde solution diluted to 375 ml. The formaldehyde was added in five equal portions at temperatures of 25, 30, 35, 40, and 45°. After the last addition the mixture was distilled under reduced pressure to 250 ml. and acidified with sulfuric acid to *p*H 1.5. The resulting precipitate, which weighed about 108 g., was contaminated with about 30% sodium sulfate. The colorless crystalline product was purified of all traces of sulfate by two successive recrystallizations from hot concentrated aqueous solutions. The 75 g. of pure product (m.p. 185° dec.) obtained indicated nearly quantitative conversion to the lactone of N-(2-hydroxyethyl)iminodiacetic acid.

Anal. Calc'd for $C_6H_9NO_4$: C, 45.5; H, 5.90; N, 8.80.
Found: C, 45.3; H, 5.70; N, 8.80.

n-Butyl N,N-diethylglycinate. A solution of 36.6 g. of diethylamine, 5 g. of sodium hydroxide, and 30 g. of sodium cyanide dissolved in two liters of water was placed in an apparatus of 5-liter capacity similar to that used in the foregoing preparations. To this was added in 250-ml. portions (at the rate of 125 ml. per hour) 50 ml. of 37% formaldehyde diluted to one liter. The initial temperature of 20° was raised 5° during each subsequent addition. At the end of each addition the system was evacuated to 15 mm. for five minutes. After the last addition the temperature was maintained at 35° for four hours more. The solution was subsequently neutralized to *pH* 7 and evaporated at 15 mm. until no more solvent could be distilled. The residue was boiled with 500 ml. of butyl alcohol, filtered hot, cooled, and 30 ml. of conc'd sulfuric acid added; the solution was kept at 80° for 24 hours. A mixture of 500 ml. of butyl alcohol and 200 ml. of toluene was then added. The reaction flask was fitted with a thermometer, stirrer, and water separator, and the solution was refluxed gently for 12 hours, after which the amount of water being collected became negligible. The reaction mixture was distilled under reduced pressure to remove toluene and butyl alcohol, and the residue was then made alkaline with excess 20% sodium carbonate solution. The oil was removed with a separatory funnel, dried over calcium chloride, and finally distilled under reduced pressure. Yield, 54 g. of a clear colorless oily liquid boiling at 66°/1 or 55%. Index of refraction, 1.4270^{20}; density, 0.9091^{20} g./ml.

Anal. Calc'd for $C_{10}H_{21}NO_2$: N, 7.47; M.W., 187.
Found: N, 7.40; M.W., 180.

n-Butyl piperidinoacetate. By a method similar to that just described, piperidine was converted to a colorless liquid, b.p. 94–95°/1. Index of refraction, 1.4515^{20}; density, 0.9609^{20} g./ml.; Yield, 101 g. (50%).

Anal. Calc'd for $C_{11}H_{21}NO_2$: N, 7.07; M.W. 199.
Found: N, 6.98; M.W., 180.

Di-n-butyl N-isoamyliminodiacetate. Isoamylamine was carboxymethylated and esterified in a manner similar to that described for diethylamine. Upon distillation of the product, only 10 ml. of ester was collected at 49°/12 before extensive decomposition of the boiling liquid took place. The index of refraction of the clear colorless product was 1.420^{20}.

Anal. Calc'd for $C_{17}H_{33}NO_4$: N, 4.44; M.W., 315.
Found: N, 4.32; M.W., 298.

SUMMARY

The extension of the carboxymethylation reaction to benzylamine, *p*-aminobenzoic acid, isoamylamine, ethylamine, diethylamine, piperidine, and ethanolamine is described. The products which were prepared and characterized are: N-benzyliminodiacetic acid, N,N-*bis*-(carboxymethyl)anthranilic acid, N-ethyliminodiacetic acid, N-(2-hydroxyethyl)iminodiacetic acid lactone, butyl N,N-

diethylglycinate, butyl piperidinoacetate, and dibutyl N-isoamyliminodiacetic acid.

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