[CONTRIBUTION FROM THE LOS ALAMOS SCIENTIFIC LABORATORY OF THE UNIVERSITY OF CALIFORNIA, LOS ALAMOS, NEW MEXICO]

Micro-syntheses with Tracer Elements. I. A New Synthesis of Cyanamide. The Synthesis of Urea Labeled with C^{14} [1]

BY ARTHUR MURRAY, III, AND ANTHONY R. RONZIO

Since urea is a compound of great biochemical interest and also is a starting material for the preparation of a number of organic compounds of pharmacologic importance, this synthesis was undertaken.

Barium carbonate is the most readily available source of C^{14}. Accordingly, a method was desired which used this compound.

Urea may be synthesized by a number of methods[2,3,4,5,6] all of which either give low yields or complex mixtures difficult to separate.

Calcium cyanamide may be prepared from calcium carbide and nitrogen by heating to a high temperature. Since barium carbide is formed by the heating of barium carbonate with metallic barium to a high temperature, experiments were made to determine whether the barium carbide so formed would react with barium amide at high temperatures to yield barium cyanamide. The method developed and herein reported gives quantitative yields of barium cyanamide which, upon hydrolysis, gives high yields of urea.

Experimental

One to five millimoles of barium carbonate was placed in a 50-ml. long-necked, round-bottomed flask equipped with a ground-glass joint and dried at 120° for sixteen hours. The flask was connected to a Dry Ice reflux condenser as shown in Fig. 1. The system was then alternately evacuated and filled with purified nitrogen several times in order to remove all traces of carbon dioxide. In a stream of nitrogen, 4–7 g. of freshly cut, shiny barium metal which had been well washed with dry ether was introduced into the flask at X. A crystal of ferric nitrate catalyst was added and the system then was closed. The reflux condenser B was filled with Dry Ice chips. From another flask liquid ammonia containing sodium was allowed to distil into flask A through inlet D until $^{2}/_{3}$ full. The mixture was allowed to react until all of the barium was converted to the amide (as was indicated by the disappearance of the blue color). This conversion could be effected within twenty-four hours by adding a second crystal of ferric nitrate after the reaction had proceeded for twelve hours. When the flask A was allowed to stand overnight, it was immersed in a Dewar tube filled with Dry Ice in order to prevent the ammonia from boiling off. The excess ammonia was allowed to distil off at the end of the reaction by opening clamp F. The system was then slanted at an angle of 45 degrees and flask A, while still connected to the apparatus, was slowly heated with a Fisher burner (clamp F still open). The heat was slowly increased until the flask was dull red. The contents of the flask were white before heating, then turned gray, yellow, brown and finally black. At this point the glass began to soften and the contents ceased to froth and set to a black mass, whereupon it was allowed to cool. The flask then was shattered into a 400-ml. beaker and the mass washed with three 100-ml. portions of boiling distilled water.[7] The washings were decanted through a filter and the filtrate was treated with carbon dioxide gas until all of the barium was precipitated as the carbonate. The solution was neutral at this point. The barium carbonate was filtered off and washed with distilled water.

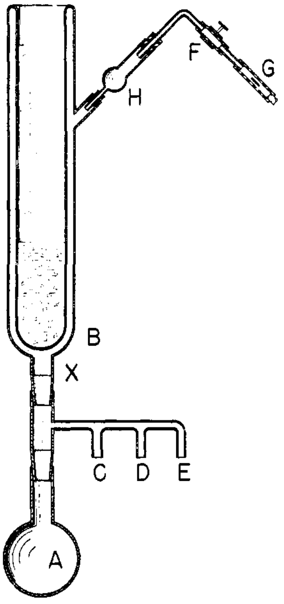

Fig. 1.

The precipitate should be kept until the end of the experiment. The filtrate and washings were treated with 0.6 ml. of concentrated sulfuric acid in order to hydrolyze the cyanamide formed. The solution was allowed to evaporate slowly at a temperature of 40° to a few milliliters of sirupy residue (two to three days). The sirup was diluted to 25 ml. with distilled water and filtered in order to remove a small amount of barium sulfate. The filtrate then was made alkaline with ammonium hydroxide and evaporated to dryness at room temperature under a gentle stream of air. The drying was completed in a vacuum desiccator over calcium chloride. As the drying progressed it was necessary to break the crust over the liquid as often as it formed. The dried residue was then extracted with four 10-ml. portions of hot propyl alcohol. It was necessary that the precipitate be crushed to a fine powder during the extraction and that the solvent be allowed to cool before filtration. The solvent was removed from the filtrate under vacuum at room temperature. The yield of crude product was 102% (average of eight runs) and melted from 110–118° to 129–130°. When the yields fell below 90%, it was necessary to work up the barium carbonate precipitate in the following manner: The barium carbonate, which was saved, was treated with a slight excess over the calculated amount of warm dilute hydrochloric acid and filtered. The filtrate was then treated with the calculated amount of ammonium sulfate and filtered. The filtrate, already acidic from the hydrochloric acid, was evaporated to dryness at room temperature. The residue was diluted with water, made to *p*H 5–6 with dilute potassium hydroxide, made basic with ammonium hydroxide, and evaporated to *absolute* dryness. The precipitate was extracted with propyl alcohol as before. The final purification was carried out by dissolving the product in methanol, decolorizing with Norite, evaporating to dryness, and finally recrystallizing from isoamyl alcohol.[8] Products

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[1] This document is based on work performed under Contract No. 7405-eng-36 for the Atomic Energy Commission.

[2] Krase, Gaddy and Clark, *Ind. Eng. Chem.*, **22**, 289 (1930).

[3] Laude, *Compt. rend.*, **194**, 2070 (1932).

[4] Werner, *J. Chem. Soc.*, **113**, 694 (1918).

[5] Cavalieri, Blair and Brown, THIS JOURNAL, **70**, 1241 (1948).

[6] Nagai and Yamaguti, *J. Soc. Chem. Ind.* (*Japan*), **43**, 219 (1940).

[7] When the run is on a scale greater than 5 millimoles there is danger of fire and consequent lowering of yield at this point. With runs greater than 5 millimoles it was advisable to add the water to the mixture in an atmosphere of carbon dioxide.

[8] Fifty milligrams of urea in 1 ml. of isoamyl alochol gave a 91% recovery when cooled to −30°. Acetone may also be used for this purification. In this case, fifty mg. of urea in 7 ml. of acetone gave an 85% recovery of urea at −40°; all without working up any mother liquors.

obtained from syntheses on the one millimole scale by this procedure melted at 110-129°, and melted at 125-130° after purification. On a five millimole scale the products melted at 123-131°, and melted at 131-133° after purification. These products were considered sufficiently pure for syntheses and were not purified further.

A typical isotopic synthesis, using 2.53 millimoles (0.500 g. containing 5 mc. of C^{14}) of barium carbonate gave a yield of 144.8 mg. of urea (95.2%) melting at 125-130°. Recrystallized from acetone, the yield was 123 mg. melting at 132-133°. This product contained 1.98 millicuries/millimole.

Summary

Urea has been synthesized using barium carbonate containing C^{14} to give a 95.2% yield of product containing 1.98 millicuries of radioactivity per millimole. The method employed involved a new synthesis of cyanamide.

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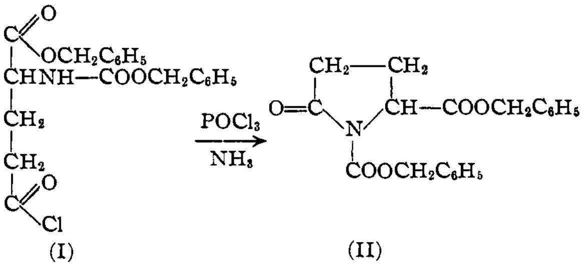
NOTES

The Preparation of Benzyl N-Carbobenzoxypyrrolidone-2-carboxylate-5

BY MAX BERENBOM[1] AND JULIUS WHITE

In the synthesis of glutamine by the method of Bergmann, Zervas and Salzmann,[2] one of the steps is the formation of α-benzyl N-carbobenzoxyglutamoyl chloride (I) by treating the corresponding carboxylic acid with phosphorus pentachloride. The phosphorus oxychloride formed in this reaction is washed out with petroleum ether. (I) is then treated with an ice cold solution of ammonia in ether to form the amide which is subsequently hydrogenated to yield glutamine. We wish to point out that if the phosphorus oxychloride is not removed in the preparation of (I), subsequent treatment with ammonia yields benzyl N-carbobenzoxypyrrolidone-2-carboxylate-5 (II), instead of the desired amide.



(I) (II)

This compound (II), m. p. 110° (uncorrected), $[\alpha]^{25}D$ − 39.5 (in ethanol), which has not been described previously can be obtained in 70% yield. It is insoluble in water, ether, petroleum ether, and benzene, soluble in ethanol and methanol.

Anal. Calcd. for $C_{20}H_{19}NO_5$: C, 68.0; H, 5.7; N, 4.0. Found: C, 68.1; H, 5.7; N, 3.9.

(II) was identified by hydrogenation in methanol in the presence of palladium to yield 90% of 2-pyrrolidone-5-carboxylic acid, m. p. 162-164° (uncorrected), $[\alpha]^{25}D$ − 11.4 (in water).[3] A mixed melting point of the hydrogenated product with synthetic 2-pyrrolidone-5-carboxylic acid showed no depression.

Anal. Calcd. for $C_5H_7NO_3$: C, 46.5; H, 5.7; N, 10.9. Found: C, 46.8; H, 5.7; N, 10.9.

[1] Senior Research Fellow, National Cancer Institute.

[2] M. Bergmann, L. Zervas and L. Salzmann, *Ber.*, **66**, 1288 (1933).

[3] M. Bergmann and L. Zervas, *Z. physiol. Chem.*, **221**, 51 (1933).

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The Exchange between a Formamido Group and Formamide, Studied with C^{13},[1]

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Adenine (I) may be prepared by heating 4,6-diamino-5-formamidopyrimidine (II) in formamide.[2] In order to prepare adenine labeled with C^{13} in the 8-position, 4,5,6-triaminopyrimidine (III) as the sulfate was converted to II by formylation with C^{13} labeled formic acid. When the sulfate of II was heated in formamide, extensive exchange with the formamide occurred and only 25% of the carbon isotope contained in II was found in the adenine (I) which resulted. Formamide decomposes to ammonia and carbon monoxide when heated[3] and it is probable that the mechanism for the exchange involves ammonolysis of the formyl group.[4]

Evidence in support of this mechanism is found in the fact that the triamine (III) when heated with formamide is converted to adenine in 62% yield. Further, it appears that once the adenine is formed it remains intact, since a sample of adenine subjected to the reaction conditions was recovered in quantitative yield (95%).

[1] The authors wish to acknowledge the assistance of the Office of Naval Research and the National Cancer Institute of the United States Public Health Service.

[2] Cavalieri, Tinker and Bendich, THIS JOURNAL, **71**, 533 (1949).

[3] Freer and Sherman, *Am. Chem. J.*, **20**, 223 (1898).

[4] In general when pyrimidine sulfates are cyclized to purines in formamide one mole of ammonium sulfate is recovered: Bendich, Tinker and Brown, THIS JOURNAL, **70**, 3109 (1948).