[Contribution from the Los Alamos Scientific Laboratory of the University of California]

Micro Syntheses with Tracer Elements. III. The Synthesis of Thiourea Labeled with C^{14} and of Thiourea Labeled with S^{35}

By C. Wayne Bills and Anthony R. Ronzio[1]

Thiourea labeled with S^{35} and with C^{14} was desired for a study of the metabolism of the compound and of the mode of action on the thyroid gland.

Experimental

I. **Thiourea Labeled with C^{14}.**—Three-tenths of a gram (1.52 millimoles) of C^{14} barium carbonate was converted to barium cyanamide in the manner described by Murray and Ronzio.[2] Twenty-five ml. of water was added to the fusion mixture and 0.3 g. of barium hydroxide monohydrate was also dissolved in the mixture; this in order to ensure an excess of the hydroxide. Hydrogen sulfide from a tank was slowly bubbled through the solution at room temperature for 2 hours.[3] The flask was then tightly stoppered and the stopper wired tightly to the flask. The contents of the flask were then warmed in a water-bath to 85° and allowed to react at this temperature for 20 hours. After cooling, the flask was unstoppered and all the barium precipitated as the carbonate by saturating the mixture with carbon dioxide gas (about 30 minutes) until the solution gave a neutral reaction with indicator paper. The barium carbonate was filtered off through a sintered glass funnel, alcohol being used to wash the flask and funnel. The filtrate was then evaporated to dryness using a gentle stream of air under an infrared lamp. When the residue was anhydrous, it was scraped away from the sides of the container and extracted several times with alcohol. The extract was treated with decolorizing carbon, and then filtered into a tared centrifuge cone. The solvent was removed by evaporation. The crude weight of the product at this stage was 0.2228 and was recrystallized from 3.5 ml. of *n*-butanol. The solution was allowed to cool slowly until crystals appeared, then was cooled in an ice-bath. The mother liquor was removed with a medicine dropper, the point of which had been drawn down to a fine capillary. The product so obtained after another recrystallization from 2 ml. of *n*-butanol, and washing with ether before drying, melted at 171–172° and weighed 0.1761 g. (87%).

If instead of allowing the product to crystallize, the decolorized solution was filtered into a vacuum sublimator and the solvent removed by evaporation, the residue gave a 97% yield of thiourea melting at 171–173° when sublimed at a temperature of 70–90° and a pressure of 0.025–0.030 mm.

II. **Preparation of H_2S^{35}.**—The sulfur isotope, S^{35}, as obtained from the Atomic Energy Commission, is in the form of barium sulfide in 0.05 *N* barium hydroxide solution. The quantitative precipitation of the sulfur was accomplished by first transferring the solution into a 40-ml. centrifuge cone, the tip of which had been drawn down to a diameter of about 7 mm. and a length of about 30 mm., then adding an excess of a solution which was 0.05 *N* in hydrochloric chloride and 0.1 *N* in cadmium chloride. The quantity of reagent should be sufficient to neutralize all the barium hydroxide and give an acidic reaction to the mixture. The sulfur was thus precipitated as cadmium sulfide. The precipitate was separated by centrifuging and decanting the clear solution. After washing with water several times and centrifuging, the precipitate was dried while still in the cone.

The quantitative conversion of cadmium sulfide to hydrogen sulfide without the introduction of other gases was accomplished by breaking off the tip of the cone containing the cadmium sulfide into a 200-ml. flask into which had been introduced 20 g. of metaphosphoric acid. Connecting the flask to a vacuum system, evacuating to a pressure of 0.005 mm., then heating the acid to boiling, smoothly freed the sulfur as H_2S. As quickly as generated, the H_2S was removed from the system, while still under vacuum, by freezing out the gas with liquid nitrogen into a round-bottomed flask located at the end of a $CaCl_2$–P_2O_5 purifying train. This receiver flask was equipped with a micro stopcock so that the flask and contents could be weighed. Cadmium sulfide, 71.9 mg., containing 8.2% of CdS^{35}, by this procedure gave 17.8 mg. of hydrogen sulfide (105%).

In a series of six experimental runs using cold cadmium sulfide the average yield of hydrogen sulfide was 95.4% with a lowest yield of 90.7%.

III. **Thiourea Labeled with S^{35}.**—The standard syntheses of thiourea using hydrogen sulfide utilize an excess of this gas. Since in this instance the hydrogen sulfide is the limiting factor, the procedure was modified in such a manner as to utilize completely all of the hydrogen sulfide containing the radioactive isotope. The procedure used is based on the method described by Heuser.[4]

The flask containing the metaphosphoric acid was removed from the system and replaced by a 10-ml. flat-bottomed reaction flask containing a magnetic stirrer, 0.8 ml. of distilled water and 25 mg. of cyanamide (freshly prepared), and one small drop of concentrated ammonium hydroxide. The contents of the flask were frozen with liquid nitrogen, the vacuum was re-established and the H_2S was transferred into it by warming the flask containing the frozen gas. The reaction vessel was closed off from the system and was allowed to warm to room temperature.

The mixture was then warmed to 40° and was stirred continuously for 24 hours with a magnetic stirrer. The solution was colored a faint yellow, which disappeared after 6 hours, followed by the appearance of a faint cloudiness. At the end of this period the contents of the flask were transferred into a vacuum sublimator using alcohol. All solvent was removed by evaporation and the thiourea was sublimed in a vacuum (0.02–0.03 mm.) at a temperature of 70–90°. A higher temperature causes the sublimation of impurities which lowered the melting point of the thiourea.

Since films of oils or waxes materially raise the temperature of sublimation, it was found advantageous to remove all oil films by washing the residues first with petroleum ether, then removing the ether and dissolving the thiourea in ethanol. The solvent was then removed by evaporation and the residue was sublimed in a vacuum. The isolation of thiourea by this method is quantitative. The thiourea obtained, 35 mg. (92.2% of the theoretical yield) melted at 171–173°. The compound possessed an activity of 0.535 mc./mg.

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Summary

A method of labeling thiourea with C^{14} has been

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[1] This document is based on work performed at Los Alamos Scientific Laboratory of the University of California under Government Contract W-7405-Eng-36.

[2] Murray and Ronzio, This Journal, **71**, 2245 (1949).

[3] W. F. Lewis, U. S. Patent 2,393,917 (1946).

[4] R. V. Heuser, U. S. Patent 1,991,852 (1935); *C. A.*, **29**, 2180 (1935).

described. A method for the quantitative formation of hydrogen sulfide-S^{35} from cadmium sulfide-S^{35} has been described. A method of labeling thiourea with S^{35} has been described. The thiourea possessed an activity of 0.535 mc./mg.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Reduction of α-Haloketones to Halohydrins by Lithium Aluminum Hydride[1]

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The reduction of α-bromoketones by lithium aluminum hydride is of particular interest in connection with reductive elimination of bromine by the Grignard reagent which has been shown in one case to occur as a 1,4-reaction process or "reductive enolization."[2]

Trevoy and Brown[3] have reported the reduction of *p*-bromophenacyl bromide (I) to α-(*p*-bromophenyl)-ethanol using 30–100% excess of lithium aluminum hydride. In attempted repetitions of their experiment we obtained in addition to this (the predominant product) very small amounts of the *p*-bromophenylbromohydrin. By using an amount of reagent only slightly in excess of that needed for a one-stage reduction we obtained the bromohydrin in 69% yield of purified material. Desyl chloride (II) and *p*-chlorophenacyl bromide (III) under these conditions were reduced in 76 and 77% yields, respectively, to *erythro*-stilbene chlorohydrin and *p*-chlorophenyl bromohydrin. This synthesis of *erythro*-stilbene chlorohydrin appears to be more economical in respect to labor and materials than the synthesis through *meso*-hydrobenzoin.[4] Varying the temperature from 0–35° did not seem to affect the results appreciably, but reversing the order of addition, *e. g.*, adding the reducing agent slowly to desyl chloride, lowered the yield sharply, due doubtless to condensation between desyl chloride and the reaction product.

It is shown by the above results that in three typical instances the straightforward 1,2-reduction of the carbonyl group proceeds more rapidly than reductive replacement of the halogen of either the haloketone or the halohydrin. The preferential 1,2-reduction of the carbonyl groups of the α-bromoketones is in sharp contrast with the "reductive enolization" which is commonly brought about by the Grignard reagent.[1]

Some consideration has been given to the distinction between the first hydride reducing equivalent of the reagent and the other hydride hydrogens which may involve the equivalent of aluminum hydride.[5] It was found that the aliphatic halogen of one typical bromohydrin (the *p*-bromophenyl) was readily removed by the action of a molecular equivalent of lithium aluminum hydride, and the bromoketone was reduced to *p*-bromophenylethanol by reagent in which the first hydride reducing equivalent had been destroyed in advance. The formation of the halohydrins from the haloketones in reductions using close to one-fourth of a molecule of the rea-

TABLE OF RESULTS

Compound[a]	Mole LiAlH$_4$	Temp., °C.	Product	Yield, %
I	0.007	25	V	69[b]
I	.026	35	VI	[c]
I	.026	0	VI	[c]
I	.026[d]	35	VI	90[e,f]
V	.026	35	VI	90[e]
II	.007	25	VII	76[b]
II	.015	0	VII	60[b]
II	.015	34	VII	60[b]
II	.026	35	VII	50[b]
II	.007	35	VII[g]	30[b]
III	.007	25	VIII	77[b]
IV	.007	35	IX	10[h]

[a] The amount of compound used in each case was 0.02 mole. The compounds and products are as follows: I = *p*-$BrC_6H_4COCH_2Br$ (*p*-bromophenacyl bromide); II = $C_6H_5COCHClC_6H_5$ (desyl chloride); III = *p*-$ClC_6H_4COCH_2Br$; IV = $C_6H_5COCHBrC_6H_5$; V = *p*-$BrC_6H_4CHOHCH_2Br$; VI = *p*-$ClC_6H_4CHOHCH_3$; VII = $C_6H_5CHOHCHClC_6H_5$ (*erythro*); VIII = *p*-$ClC_6H_4CHOHCH_2Br$; IX = $C_6H_5CHOHCHBrC_6H_5$ (*erythro*). [b] Purified material, identified by the sharp and characteristic melting points (within one degree of reported values), and in the case of stilbene chlorohydrin by mixture melting points with an authentic sample. In view of losses entailed in purification of these products by crystallization methods, it is clear that the actual production of the halohydrin in all cases must have been higher than the yields stated. [c] The results were similar to those of Trevoy and Brown[3] except that a very small amount of the bromohydrin (V) was also isolated and identified. [d] In this reduction in two separate experiments the first hydride–hydrogen equivalent had been destroyed by addition of the calculated amount of (a) allyl iodide or (b) ethyl iodide (and refluxing for a half hour). [e] The product was isolated as a distilled oil and identified by boiling point,[f] and also by conversion to the phenylurethan.[3] [g] The lithium aluminum hydride solution was added slowly to the ether solution of desyl chloride. [h] This experiment was a preliminary one carried out by Mr. J. W. Baker, and it is cited only as evidence that the bromohydrin can be isolated here.

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[1] This work was incidental to the synthesis of amino alcohols as tumor-necrotizing agents; supported in part by a grant from the National Institutes of Health.

(2) (a) Lutz and Kibler, THIS JOURNAL, **62**, 360 (1940); (b) Lutz and Reveley, *ibid.*, **63**, 3180 (1941).

(3) Trevoy and Brown, *ibid.*, **71**, 1675 (1949).

(4) (a) Reulos and Letellier, *Compt. rend.*, **216**, 698 (1943); (b) *cf.* modifications of this method, Bauer, Master's thesis, University of Virginia, 1949 (to be published shortly).

(5) Johnson, Blizzard and Carhart, THIS JOURNAL, **70**, 3664 (1948).