NOTES

Synthesis of carbon-14 labelled S-ethyl hexahydro-1H-azepine-1-carbothiolate

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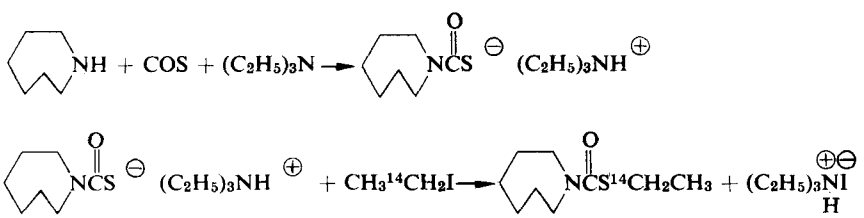
S-Ethyl hexahydro-1H-azepine-1-carbothiolate labelled in the ethyl moiety and in the azepine ring with carbon-14 was prepared to facilitate residue and metabolism studies. The ethyl labeled compound was prepared in 86% yield and 99+% radiochemical purity. The azepine labeled material was prepared in 60% yield and 99+% radiochemical purity.

INTRODUCTION

S-Ethyl hexahydro-1H-azepine-1-carbothiolate* is a promising herbicide for selectively controlling weeds in rice fields. To facilitate the study of residues and metabolism of this compound, it was labeled with carbon-14 in the ethyl moiety and in the azepine ring.

The reaction scheme for the preparation of these materials is illustrated in Figure 1. For the ethyl labeled compound, hexamethyleneimine was treated with carbon oxysulfide in the presence of triethylamine [4]. The thiocarbamic acid salt formed in this reaction was treated with ethyl iodide 1-^{14}C without isolation to give an 86% yield of S-ethyl hexahydro-1H-azepine-1-carbothiolate of 99+% radiochemical purity. The identity of the product was established by comparison with an authentic sample [5] by thin layer chromatography and infrared spectra.

Route 1. Ethyl labelled S-ethyl hexahydro-1H-azepine-1-carbothiolate



* Ordram, registered trademark of Stauffer Chemical Company.

Route 2. Azepine labelled S-ethyl hexahydro-1H-azepine-1-carbothiolate

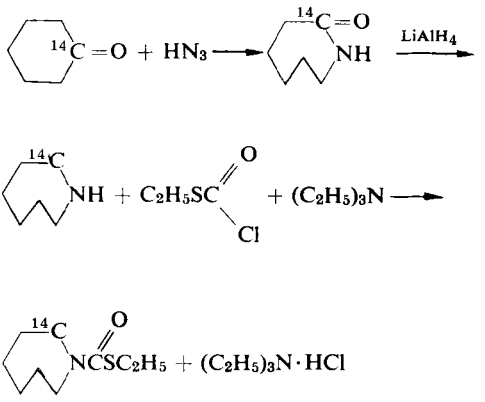


FIG. 1. — Reaction Schemes

The azepine labeled S-ethyl hexahydro-1H-azepine-1-carbothiolate was prepared by the following series of reactions: Cyclohexanone 1-^{14}C was converted by the Schmidt reaction to caprolactam [3] which was reduced to hexamethyleneimine with lithium aluminum hydride [2]. The hexamethyleneimine was converted without isolation to S-ethyl hexahydro-1H-azepine-1-carbothiolate by treatment with ethylchlorothiolformate [4]. The overall yield was 60% of a 99+% pure product. The identity of the product was established by infrared and thin layer chromatographic comparison with an authentic sample.

EXPERIMENTAL

S-Ethyl-1-^{14}C-hexahydro-1H-azepine-1-carbothiolate

Five ml of an ethereal solution containing 0.306 g (3.16 mmoles) of triethyl amine and 0.300 g (3.16 mmoles) of hexamethyleneimine was added to a 10 ml, two-necked flask, fitted with a rubber sealed inlet, magnetic stirrer, and dry ice condenser. An excess of carbonoxysulfide was passed into, and the thiolcarbamate salt precipitated out of, the solution. Ethyl iodide-1-^{14}C (0.437 g, 2.8 mmoles), with a specific activity of 2.5 millicuries per millimole, was added to the flask in one portion. The mixture was stirred at room temperature for 1½ hours. The mixture was washed with 3 ml of a dilute sodium hydroxide solution followed by washings with 3 ml of dilute hydrochloric acid and 3 ml of water. The product contained in the ether phase was further purified by passing the solution through a one-half inch column containing 1.5 g of florisil, 60-100 mesh, saturated with 2 ml of ether. The column was washed with an additional 2 ml of ether to remove any remaining product. The ether solution was evaporated

yielding 0.453 g of product, 86.3% of theory. The identity of the material was determined by infrared comparison with an authentic sample.

The 0.453 g of the product was dissolved in 4 ml of ether, and 10 λ of the ethereal solution was dissolved in 100 ml of toluene. 100 λ of the toluene solution was spotted on a thin layer chromatography plate coated with a layer of 250 microns of silica gel G (Brinkman Co., Westbury, New York). The plate was developed in a 19 to 1 solution of chloroform and ethyl acetate for 20 min. The plate was dried, and the resulting chromatograph was covered with Eastman Kodak SP351 X-ray film for 4 days. The film was developed and exhibited only one spot, indicating that the radiochemical purity was 99+%.

S-Ethyl-hexahydro-1H-azepine-2-^{14}C-1-carbothiolate

Conc. H_2SO_4 (0.22 ml, 3.9 mmoles) and 0.67 ml of chloroform were placed in a 10 ml round-bottom flask fitted with a magnetic stirrer and a rubber sealed inlet vented by a syringe needle. The contents of the flask were cooled in an ice-salt bath. Cyclohexanone (9.40 mg, 0.959 mmoles) and 60 mg (1.40 mmoles) of hydrazoic acid in 0.7 ml of chloroform were added to 3.85 mg (0.041 mmoles) of cyclohexanone-1-^{14}C, with a specific activity of 2.54 millicuries per millimole. This solution was added over a period of 30 min to the rapidly stirred sulfuric acid-chloroform mixture. After the addition was complete, the solution was washed with 3 ml of water. The chloroform phase was separated, and the aqueous phase was extracted with 3 ml of $CHCl_3$. The combined chloroform extracts were evaporated and the resulting caprolactam-2-^{14}C was dissolved in 2 ml of ether. The ether solution was stirred and heated under reflux under an argon atmosphere. Lithium aluminum hydride (33.0 mg, 0.86 mmoles) in 0.75 ml of ether was added over a period of 10 min. After the addition was complete, the mixture was stirred and heated under reflux for 16 hours. The mixture was cooled, and 2 ml of water was cautiously added to decompose any unreacted lithium aluminum hydride. The mixture was stirred and cooled to 0 °C, and ethylchlorothioformate (87.0 mg, 0.70 mmoles) was added over a period of 15 min. After the addition was complete, the ice-bath was removed; and the mixture was stirred for 2 hours at room temperature. Five ml of ether was added, and the mixture was washed with 3 ml of water. The ether phase was subsequently washed with 3 ml of dilute sodium hydroxide, 3 ml of dilute hydrochloric acid, and 3 ml of water. The product contained in the ether phase was further purified by passing the solution through a one-half inch column containing 1.5 g of florisil, 60-100 mesh, saturated with ether. The column was washed with 2 ml of ether to remove any remaining product. The ether solution was evaporated, giving 114 mg of product, 60.1% of theory based on cyclohexanone. The identity of the material was determined by infrared comparison with an authentic sample.

The radiochemical purity was determined in the same manner as the previous example. The radiochemical purity proved to be 99+%.

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A simple method for preparation of labelled halides*

It is well known that labelled halides can easily be produced by direct activation. This method, however, with very few exceptions, produces doubly-labelled salts. In the course of an investigation on thermal decomposition of halides, a method was developed for preparing hydrochloric acid labelled with Cl-38 by an easy and quick procedure which is suitable for the preparation of practically any chloride singly-labelled. The method permits the use of the short-lived and readily available Cl-38 instead of the long-lived but very costly Cl-36, in those cases where both isotopes are suitable. This method may be of help in many investigations of chemical reactions, reaction mechanisms, reaction kinetics, etc., of halide acids and salts, provided a neutron source of sufficient flux is available for the activation.

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