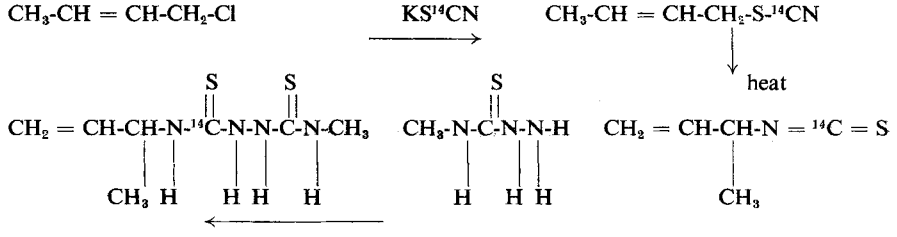
Synthesis of 1-α-Methylallylthiocarb-^{14}C-amoyl-2-methylthiocarbamoylhydrazine

Received April 3, 1970.

1 - α - Methylallylthiocarbamoyl - 2 - methylthiocarbamoylhydrazine [1] (MATCH*), a compound which inhibits pituitary gonadotrophic function [2] and is an effective estrus synchronizing agent in swine [3,4,5], was synthesized with a ^{14}C label in the 1 position through the reaction sequence :



The reaction was carried out on a 10-mmole scale, and the product was purified by recrystallization.

Synthesis on a 1-mmole scale was also briefly investigated and appeared to give good results. In this case the reaction mixture was chromatographed on a column of Sephadex LH-20 with methanol, and the effluent was monitored continuously with a radioactive flow detector. A major peak (50 % of the original activity) was obtained, which was MATCH of fair purity. MATCH was consistently chromatographed without degradation on LH-20 with methanol.

MATCH was also chromatographed on alumina or silica gel thinlayer plates with benzene-methanol (9:1). Further purification was effected with these systems, but some degradation (primarily to 2-methylamino-5-methylallylamino-1, 3, 4-thiadiazole) occasionally resulted. Because of the uncertainties in purification of MATCH by chromatography, synthesis with the larger amount of mass and purification by recrystallization was used.

* The compound has also been referred to in previous literature as methallibure, ICI 33,828 and Aimax (a premix containing 1.2 % methallibure).

1-α-methylallylthiocarb-^{14}C-amoyl-2-methylthiocarbamoylhydrazine.

A solution of 0.97 g (0.01 mole, 3.0 mCi) of potassium thiocyanate and 1.2 g (0.013 mole) of crotyl chloride (1-chloro-2-butene) in 3 ml of dimethylformamide was allowed to stand at room temperature for 10 minutes. The mixture was then warmed to 50-60° C and kept at this temperature for 90 min (a thick slurry of finely divided potassium chloride was obtained). The reaction mixture was distilled at aspirator vacuum without removing the KCl; this resulted in a considerable, but not prohibitive, amount of bumping. The distillate, which contained the desired methylallyl isothiocyanate in dimethylformamide, was collected by cooling with Dry Ice. Additional Dry Ice traps were used to trap volatile radioactive materials. To the solution of the isothiocyanate in dimethylformamide was added a solution of 0.80 g (0.008 mole) of 4-methylthiosemicarbazide in 10 ml of ethanol (the 0.008 mole used represented a small excess based on yields of isothiocyanate determined by nmr in several cold runs). The reaction was refluxed for 90 min, cooled to room temperature and allowed to stand overnight to yield crystalline MATCH. The crude MATCH was recrystallized from ethanol to yield 0.49 g (605 μCi), mp 198.5-200° C (sealed capillary). By addition of 0.60 g of pure unlabelled MATCH to the mother liquors and further recrystallization, 0.80 g (482 μCi) mp 198.5-199.5° C was obtained. Both fractions gave infrared spectra that were identical to that of an authentic sample. When the reaction was repeated using 6 mCi of activity and the same mass as above, comparable results were obtained.

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