PESTICIDES LABELLED WITH ^{14}C I. SYNTHESIS OF [6-^{14}C]HEXAZINONE

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SUMMARY

Hexazinone - a s-triazine type contact herbicide - was labelled with ^{14}C for the investigation of metabolic pathways. A convenient synthesis was elaborated for labelling of the carbon atom in the 6 position of the triazine ring. The molar activity of Hexazinone was 797.0 MBq/mmole (21.54 mCi/mmole).

Key words: Hexazinone; herbicides; synthesis; ^{14}C

INTRODUCTION

Hexazinone: (3-cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazine-2,4(1H,3H)-dione) is a postemergency contact herbicide against some annual and biennal weeds[1], introduced by duPont Nemours & Co.[2]. We elaborated an improved synthesis of ^{14}C labelled Hexazinone (4) required for pharmacokinetic and metabolism investigations.

RESULTS

Our synthesis differs from the patented route[2], because the labelling process of their starting material, N-methyl-thiourea would have been very tedious. Thus we started our synthesis from thiourea (Scheme I). shows. The first steps of the synthesis (ring closure and SMe - NMe_2 change) were carried out without difficulties, but the methylation of the nitrogen in the position 1 caused troubles. We used methyl iodide as methylating agent. Applying of the conventional NaOMe/methanol base-solvent system the main product was an O-methyl derivate (its structure was not investigated), so we changed over to a NaH/toluene base-solvent system which resulted in the desired 4. In the second case the product rate (N-methyl/O-methyl) was about 8:2, so 4 was obtained with an acceptable yield. Then 4 was separated from the O-methyl isomer and other contaminants by chromatography and it was recrystallized from diethyl ether and hexane. The purity of the product prepared this way was about 98% (checked by HPLC), and other physical parameters were identical with the authentic standard. The overall radiochemical yield (starting from [1-^{14}C]thiourea) was 23%.

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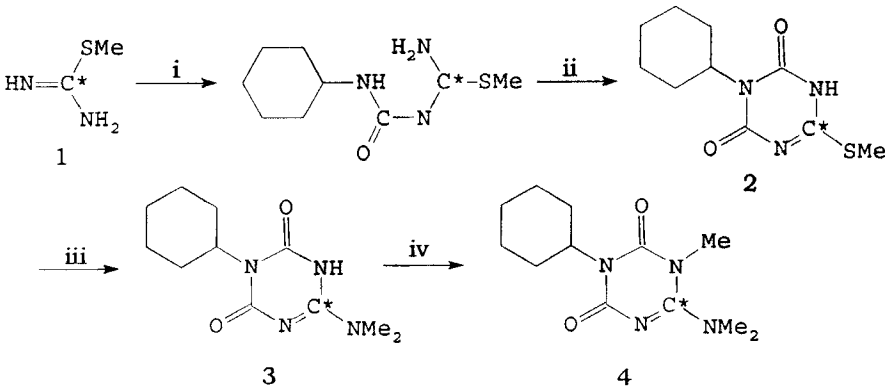
Scheme 1.



i = cyclohexyl isocyanate, NaOH; ii = ethyl chloroformate, NaOH; iii = dimethylamine; iv = methyl iodide, NaH

EXPERIMENTAL

Melting points are uncorrected and were determined with a PHMK microscope. Chromatography was performed on Silica gel 60 HF_{254} plates and Silica gel 60 (0.063-0.10 mm), respectively. HPLC was performed by a Gilson HPLC system with ABI UV detector and Berthold 503 radiomonitor on a Nucleosil 5C-18 column.

S-Methyl-isothiourea [2-^{14}C] methosulphate (1).

It was prepared from $Ba^{14}CO_3$ via thiourea[^{14}C] as described earlier.[3-5]

3-Cyclohexyl-6-methylmercapto-1,3,5-triazine[6-^{14}C]-2,4(1H,3H)-dione (2)

1 (386 mg; 2.8 mmoles, 1.99 GBq) was dissolved in water (5 ml), chloroform (5 ml) was added and the mixture was cooled under 5°C and cyclohexyl isocyanate (0.40 ml; 3.1 mmoles) was added slowly (about 5 min). 2 N NaOH (1.4 ml) was added to the mixture in 1 h, so that the aqueous phase not to exceed pH 9. Then let the mixture to warm up and ethyl chloroformate (0.6 ml; ~ 0.6 mmoles) was added. The pH of the aqueous phase was maintained at 9 by adding 2N NaOH. About 3 hours later the pH of the mixture was not changing, the organic phases were separated and the aqueous phase was extracted with chloroform. The collected organic phases were washed with brine, dried over $MgSO_4$ and evaporated. The residue was treated with hexane to give a white solid. Weight: 620 mg (94%), M.p.: 110-113°C. Specific activity: 3.019 GBq/g; molar activity 709.3 MBq/mmole; total activity 1.872 GBq. The compound was almost pure by TLC (benzene - ethyl acetate 8:2; R_f 0.8).

3-Cyclohexyl-6-dimethylamino-1,3,5-triazine[6-^{14}C]- 2,4(1H,3H)-dione (3)

2 (620 mg; 2.63 mmoles; 709.3 MBq) was dissolved in chloroform (5 ml) and 2 ml of dimethylamine in ethanol (33%) was added. The solution was stirred for 3 hours at room temperature (the reaction must be carried out in a hood with good ventilation, because of the evolution of methylmercaptan). By this time the spot of 2 almost disappeared on TLC (but two other spots of contaminations appeared nearby). Then the solvents were evaporated, the residue was a light brown oil (752 mg, purity is about 75% by TLC (benzene:ethylacetate = 1:1; Rf 0.5)) which was used for the next step without purification.

3-Cyclohexyl-6-dimethylamino-1-methyl-1,3,5-triazine[6-^{14}C]-2,4(1H,3H)-dione (4)

Compound 3 was dissolved in toluene (10 ml) and NaH (50% suspension in mineral oil; 400 mg; 8 mmoles) was slowly added. The mixture was stirred for 30 minutes (while the evolution of hydrogen was ceased), then methyl iodide (3 ml; ~50 mmoles) was added, the flask was closed and stirred overnight. The next day ethanol (1 ml) and (10 minutes later) water (10 ml) were added and the phase were separated. The aqueous phase was extracted with chloroform, the collected organic phase was washed with brine, dried over $MgSO_4$ and evaporated. The residue was a brown oil (896 mg), which was purified by chromatography (benzene : tetrahydrofuran = 2:1). A light yellow oil was obtained, which was crystallized treating with ether-hexane. 163.5 mg of white crystals were obtained (23% calculated on thiourea) M.p.: 116-7°C (Lit[1]: 115-7°C). Specific activity: 3.17 GBq/g ; molar activity: 797.0 MBq/mmole; total activity: 517.6MBq. The material showed only one detectable peak on HPLC (acetonitrile : water = 60 : 40; Rt = 5.69 min; detector: UV - 245 nm).

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