PESTICIDES LABELLED WITH ^{14}C III. SYNTHESIS OF [6-^{14}C]METRIBUZINE

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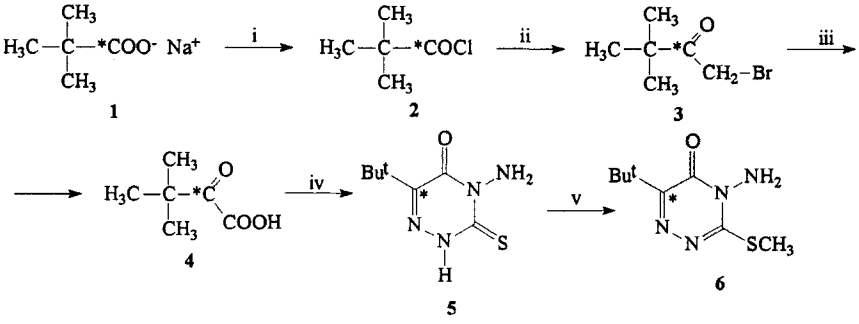
SUMMARY

^{14}C labelled Metribuzine was synthetised in a five step synthesis from sodium [1-^{14}C]pivalate (trimethyl acetic acid) via ω-bromo-[2-^{14}C]pinacoline (1-bromo-3,3-dimethyl-butan-2-on) and trimethyl [2-14C]pyruvic acid. The total yield was 30% (calculated on sodium pivalate).

INTRODUCTION

Metribuzine {4-amino-6-tert.-butyl-3-methylthio-1,2,4-[6-^{14}C]triazin-5(4H)-on} is a pre- or postemergency herbicide, used to control weeds in asparagus, lucerne, potatoes, soyabeans sugarcane, tomatoes and other crops[1]. Environmental degradation studies needed ^{14}C ring labelled Metribuzine.

Scheme 1.



i = phthaloyl dichloride, 160°C, 2 h.; ii = 1) diazomethane, ether, 0°C 2) HBr; iii = $KMnO_4$, NaOH, water, reflux, 10 min.; iv = $(H_2NNH)_2CS$, water, reflux, 1.5 h; v = MeI, NaOEt, etanol, r.t., 1 h.

The key intermediate of the synthesis[2] is trimethyl pyruvic acid (4), which can be prepared by the oxidation of pinacoline (3,3-dimethyl-butan-2-one). As the preparation of pinacoline seemed to be complicate, we tried the more plausible synthesis of α-keto acids by the hydrolysation of pivaloyl cyanide (on the analogia of the synthesis of pyruvic acid[3]). Though we could prepare pivaloyl cyanide[4] by the reaction of pivaloyl chloride and CuCN, but all our efforts were unsuccessful to hydrolyze it to 4, in accordance the observation of Chelintzev and Schmidt: "the method is only applicable to the synthesis of straight chain α-keto acids with no more than five carbon atoms."[5,6]

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Then we had to follow the well known route, but we modified that. Instead of one of the complicated keton syntheses we prepared ω-bromo-pinacoline (1-bromo-3,3-dimethyl-butan-2-on; **3**) via diazoketone by the reaction of pivaloyl chloride (**2**) and diazomethane, as the Scheme 1. shows. Then, **3** was oxidized with $KMnO_4$ to **4**. **4** was obtained as an oil, which crystallizes in several days (m. p.: 90°C), but the oil form was also suitable to the following steps. It was heated with thiocarbohydrazide to form **5**, then it was S-methylated with methyl iodide to give **6**. Row **6** was purified by chromatography and pure **6** was obtained with 30% yield (calculated on sodium [1-^{14}C]pivalate).

EXPERIMENTAL

Melting points are uncorrected and were determined by a PHMK microscope. Chromatography was performed on Silica gel 60 HF_{254} plates (MERCK) and Siliuca gel 60 (0,063-1.00 mm), respectively. The spots were visualised by UV light and evaluated on an Berthold Tracemaster 20 scanner. HPLC and gas chromatography were performed by a Gilson HPLC system on a Nucleosil 5C-18 column, and a Carlo Erba Fractovap 2101 apparate using flame ionisation detector, respectively, and radioactivity was measured on an LKB 1217 rackbeta liquid scintillation counter.

Sodium [1-^{14}C]pivalate was prepared in our laboratory by known procedure[7] from Ba[^{14}C]O_3.

[1-^{14}C]Pivaloyl chloride (trimethyl acetyl chloride; 2)

Powdered sodium [1-^{14}C]pivalate (**1**) (3.44 mmoles, 106 mCi) was placed into a micro destillation apparatus (the collector was cooled with dry-ice/aceton bath) and phthaloyl dichloride (5 ml) was added and the mixture was heated at 160-170°C for 1.5 hours in a nitrogen stream. The weight of the distillate was 450 mg, somewhat more, than 100%.

1-Bromo-3,3-dimethyl-[2-^{14}C]butan-2-on (3)

2 (450 mg, about 3.4 mmoles, 100 mCi) was dissolved in dry ether (10 ml) and slowly dropped at 0°C into an ethereal diazomethane solution (prepared from 3 g of N-nitroso-N-methyl urea and dried over KOH[8]). The solution was stirred for 1 hour at room temperature, the the excess of diazomethane was expelled by evaporating about the half of the ether in vac and slowly 10 ml of conc. hydrogen bromide was added. The mixture was stirred overnight, then saturated NaCl solution (10 ml) was added, the phases were separated and extracted with ether (3x15 ml), washed with a 5% solution of $NaHCO_3$ and brine (10-10 ml), dried over $MgSO_4$ and ether was evaporated. **3** was obtained as a colourless oil (810 mg, more, than 100%), which contained ether and other impuritiy (about 10%) by GC (3% Silicon SE-30; 140°C). It was used for the next step without purification.

Trimethyl-[2-^{14}C]pyruvic acid (4)

3 (810 mg; about 3 mmoles, 90 mCi), $KMnO_4$ (1.6 g; 10 mmoles) and NaOH (0.5 g; 12 mmoles) were mixed with water (30 ml) and the mixture was refluxed for 10 minutes, then methanol (1 ml) was added to destroy the excess of $KMnO_4$. The warm colourless solution was separated from the dark brown solid (MnO_2) by filtration. The filtrate was cooled and acidified with 10N H_2SO_4 (about 2 ml) to pH 1. Then the solution was saturated with NaCl and extracted with ether (4x15 ml), dried over $MgSO_4$, then ether was evaporated. **4** was obtained as colourless oil (600 mg, more, than 100%), which was immediately used for the next step. (In inactive runs this oil crystallized in several days. The yield was 60-70%, calculated on sodium pivalate.)

4-Amino-6-tert.-butyl-3-thio-1,2,4-[6-14C]triazin-3,5(2H,4H)-dion (5)

Thiocarbohydrazide (300 mg, 2.8 mmoles) was dissolved in warm water (30 ml) and this solution was added to **4** (about 2.5 mmoles, 70-75 mCi). The mixture was refluxed for 1.5 hours. During reflux white crystals separated. Then the mixture was cooled, stored in refrigerator overnight, then filtered and washed with cold water, dried in vacuum exsiccator. 490 mg (63%) of **5** was obtained as white crystals. A_{sp} = 137.5 mCi/g; A_m = 27.51 mCi/mmole; A_t = 67.37 mCi. M. p.: 208-213°C (Lit: 214-216°C). According to TLC it was contaminated about 5% active and about 10% inactive impurities (benzene - ethyl acetate 95:5; R_f 0.5).

4-Amino-6-tert.-butyl-3-methylthio-1,2,4-[6-14C]triazin-5(4H)-on (6)

5 (490 mg, 2.4 mmoles, 67 mCi) was dissolved in ethanol (5 ml) and a solution of sodium ethylate (about 3 mmoles in 5 ml of ethanol) was added. A yellowish solution was obtained. Then methyl iodide (400 µl, 912 mg, 6.4 mmoles) was added and the mixture was stirred for one hour at room temperature. Then the most of the solvents were evaporated in vac., the residue was treated with brine (15 ml), extracted with dichloromethane, washed with brine, dried over Na_2SO_4 and evaporated. 546 mg of row **6** was obtained, as an oil. It was purified by chromatography (benzene, benzene - ethyl acetate 97:3) and 329 mg (68%) of pure **6** was obtained. M. p.: 125-126°C (Lit.: 124-6°C). A_{sp} = 140.6 mCi/g, A_m = 30.09 mCi/mmole, A_t = 46.2 mCi. It was pure by TLC (benzene - ethyl acetate 95:5; R_f = 0.8) and HPLC (water - acetonitrile -water 75:25; detection at 254 nm).

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