SYNTHESIS OF ^{14}C-LABELLED ANTITUMOR AGENTS. II. A FACILE SYNTHESIS OF RING-^{14}C-LABELLED PARA-TOLUIC ACID AS AN INTERMEDIATE FOR SYNTHESIS OF RING-^{14}C-LABELLED PROCARBAZINE

SUMMARY

p-Toluic acid-ring-^{14}C was synthesized by the Friedel-Crafts p-carbamylation of toluene-ring-^{14}C with N,N-disubstituted carbamyl chloride and subsequent hydrolysis. The radiochemical yield was 61%. An attempt was made to apply this method for the synthesis of benzoic acid-ring-^{14}C from benzene-ring-^{14}C.

Key Words: p-Toluic acid-ring labelled-^{14}C, N-methyl-N-Phenyl-p-toluamide-ring-^{14}C

INTRODUCTION

In the synthesis of ring-^{14}C-labelled procarbazine, an antitumor agent,[1] the patented method for nonlabelled procarbazine[2] was adapted. The ring-^{14}C-labelled p-toluic acid was the key intermediate for the synthesis.

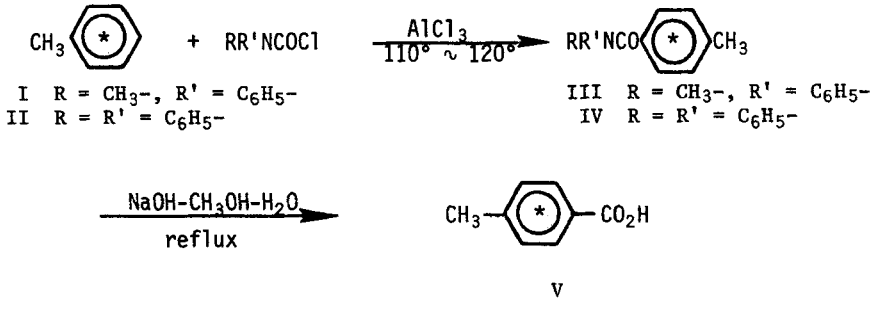
We are unaware of any reported synthesis for p-toluic acid-ring-^{14}C. Therefore, we wish to report a facile method for synthesizing p-toluic acid-ring-^{14}C from commercially available toluene-ring-^{14}C. This method is also applicable to the synthesis of p-toluic acid-$^{14}CH_3$.

Gross et al.[3] reported an efficient carboxylation of toluene (78% yield), involving Friedel-Crafts reaction with catechol carbonate dichloride and subsequent hydrolysis. However, this method is not practical because it requires isolation of the p-isomer from a mixture of o- and p-toluic acid (40/60 by weight). Thus, it is desirable to find a reaction that would undergo almost exclusively p-carboxylation of toluene or its derivatives.

Morgan and Coulson[4] reported the Friedel-Crafts p-carbamylation of o-xylene with N,N-diphenyl-carbamyl chloride (II) and subsequent hydrolysis to yield 3,4-dimethyl-benzoic acid (39% yield from excess o-xylene and 76% from II). Wilshire[5] described similar synthesis of p-methoxybenzoic acid from anisole in 54% yield

(from anisole and II). In addition, Weygand and Mitgau[6] prepared N-methyl-N-phenyl-p-toluamide (III) from toluene, N-methyl-N-phenyl carbamyl chloride (I), and aluminum chloride (23% yield from excess toluene and 49% from I). These reports suggested that predominant p-carboxylation of toluene may be achieved by p-carbamylation of toluene with I or II and subsequent hydrolysis. Hence, the carbamylations of toluene with I or II under various conditions were investigated. The results indicated that the best condition is to heat a mixture of toluene, I, and $AlCl_3$ (molar ratio of 1:1.1:1.2) in ethylene dichloride at 105° for 17 to 18 hr and to hydrolyze the unpurified carbamate (III) in sodium hydroxide-methanol-water solution. p-Toluic acid of high purity based on nmr analysis was obtained. The procedure is simple, and further purification is not required for the procarbazine sequence. When the carbamyl chloride (II) was used, further purification was required, since the isolated toluic acid was not pure.

An attempt was made to extend this method to carboxylation of benzene. In contrast with carbamylation of toluene, benzoic acid was obtained in poor yield (5% from benzene).



EXPERIMENTAL

The thin-layer chromatographic system used was Brinkman glass plate, MN Sil G-25 UV 254, using chloroform-methanol (9-1 by volume).

N-Methyl-N-phenyl-p-toluamide-ring-^{14}C (III-ring-^{14}C)

To 3.07 g (23.4 mmole) of anhydrous aluminum chloride in 7 ml of dry ethylene dichloride was added 3.58 g (21.1 mmole) of the carbamyl chloride (I) in portions. A mild exothermic reaction occurred. Then toluene-ring-^{14}C (1.77 g, 19.2 mmole, 150 mCi at 7.8 mCi/mmole; supplied by New England Nuclear, Boston, Mass.) dis-

solved in 2.6 ml of ethylene dichloride was added. The reaction mixture was heated at 105° (oil bath) for 18 hr while it was protected from the moisture. The mixture was hydrolyzed in 40 ml of ice water containing 4 ml of concentrated hydrochloric acid. The II-ring-^{14}C was extracted with chloroform (3 X 30 ml). The combined extracts were dried with anhydrous Na_2SO_4, filtered, and evaporated to a syrupy residue (4.65 g, 1.98 mmole, quantitative) that was shown by tlc to be homogeneous. The crude product (III-ring-^{14}C) was used directly for the next step.

p-Toluic acid-ring-^{14}C (V-ring-^{14}C)

Under a nitrogen atmosphere, a stirred mixture of the crude III-ring-^{14}C (4.65 g) and sodium hydroxide solution [3.76 g (94 mmole) of NaOH, 6 ml of water and 100 ml of methanol] was refluxed for 48 hr. The reaction mixture was cooled and evaporated to dryness at reduced pressure. The residue was mixed with 80 ml of water, and the resulting mixture was washed with ether (3 X 40 ml). The aqueous solution was carefully acidified with 10 ml of concentrated hydrochloric acid to cause precipitation. The mixture was cooled to 4°, and the precipitate was collected by filtration, washed with water, and dried at reduced pressure in the presence of P_2O_5. A pure product of V-ring-^{14}C (1.67 g, 12.3 mmole; 64% yield from toluene ring-^{14}C; specific activity 7.50 mCi/mmole; total activity 92 mCi) was obtained. The radiochemical yield was 61%. The radioautograms of the product by tlc (R_f 0.68, identical to that of the nonlabelled p-toluic acid) indicated that V-ring-^{14}C is 97% pure.

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REFERENCES

1. Zeller, P., et al. - *Experientia* 19: 129 (1963); Bollag, W., and Grunberg, E. - *ibid.*: 130; Falkson, G., deVillier, P. C., and Falkson, H. C. - *Canc.*

Chemoth. Rep. No. 46: 7 (1965).

2. F. Hoffmann-LaRoche & Co. - Brit. Patent 968,460.
3. Gross, H., Rusche, J., and Mirsch, M. - *Chem. Ber.* 96: 1384 (1963).
4. Morgan, G. T., and Caulson, E. A. - *J. Chem. Soc.*: 2323 (1937).
5. Wilshire, J.F.K. - *Aust. J. Chem.* 20: 575 (1967).
6. Weygand, F., and Mitgau, R. - *Chem. Ber.* 88: 301 (1955).

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