NOTE

Synthesis of *m*-Bromophenol- $^{14}\text{C}_6$ with High Specific Activity†

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1. Introduction

m-Bromophenol- $^{14}\text{C}_6$ with high specific activity of ca. 20 mCi/mmol has been required as the intermediate for labeling O,O-dimethyl-O-(3-methyl-4-nitrophenyl) phosphorothioate; Sumithion, a famous insecticide.

We previously prepared this phenol with specific activity of 6.5 mCi/mmol on 15 mmol scale. The synthesis involved the conversion of benzene- $^{14}\text{C}_6$ with the mixture of nitric acid and sulfuric acid, bromination of the nitrobenzene- $^{14}\text{C}_6$ with bromine in the presence of iron powder¹⁾, reduction of *m*-bromonitrobenzene- $^{14}\text{C}_6$ to *m*-bromoaniline- $^{14}\text{C}_6$ with tin and hydrochloric acid²⁾ and hydrolysis of the diazotized *m*-bromoaniline- $^{14}\text{C}_6$ to form *m*-bromophenol- $^{14}\text{C}_6$ ³⁾. Yoshitake, et al. prepared ringlabeled Sumithion using this *m*-bromophenol- $^{14}\text{C}_6$ ⁴⁾.

In our previous work, every stage except the bromination step resulted satisfactory. We encountered difficulty in isolation of *m*-bromonitrobenzene- $^{14}\text{C}_6$ from the reaction mixture after completion of the bromination reaction. Repetition of fractional distillation using non-radioactive nitrobenzene as a carrier was required to remove the unreacted nitrobenzene- $^{14}\text{C}_6$, which lowered yield.

Since the present work necessitated smaller scale synthesis, the previous method became of less value. Therefore, special emphasis was laid on establishing an alternative method

for the preparation of *m*-bromonitrobenzene- $^{14}\text{C}_6$ on the scale we wished to achieve. Ponoomarenko reported the substitution reaction between the nitro groups in *m*-dinitrobenzene and chlorine derived from carbon tetrachloride on heating at 270-290° in a sealed tube⁵⁾. We found that bromination also took place with the use of carbon tetrabromide instead of carbon tetrachloride. Monosubstituted product was obtained when the reaction was carried out under moderate conditions (270°, 60-80 minutes). Although this method represents the disadvantage of converting only ca. 35% of *m*-dinitrobenzene to *m*-bromonitrobenzene, the result seemed satisfactory because of the following reasons:

(1) Separation of *m*-bromonitrobenzene from the reaction mixture can easily be achieved by column chromatography.

(2) About 50% of *m*-dinitrobenzene remains unreacted and can be recovered. Therefore, reutilization of this material affords an additional yield.

(3) *m*-Dinitrobenzene- $^{14}\text{C}_6$ can be prepared in a single step from benzene- $^{14}\text{C}_6$ in good yield⁶⁾. This compound is easier to handle and less hazardous owing to its non-volatile property.

The ratio of the composition in the reaction products varied depending on the reaction conditions: when the reaction was carried out at higher temperature, the ratio of *m*-dibromobenzene increased, whereas that of *m*-bromonitrobenzene did only slightly, with decrease of that of *m*-dinitrobenzene.

Eventually, 50 mCi of *m*-bromophenol- $^{14}\text{C}_6$ with specific activity of 23.5 mCi/mmol was

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prepared from 205 mCi of benzene- $^{14}\text{C}_6$ according to the synthetic scheme as shown in Figure 1. Purity of the product at each stage was determined both chemically and radiochemically by radiogaschromatography. Confirmation of the identities was accomplished by comparison of the retention times with those of the authentic samples.

2. Experimental

2.1 *m*-Dinitrobenzene- $^{14}\text{C}_6$ Benzene- $^{14}\text{C}_6$ (6.1 mmol, 205 mCi) was converted to *m*-dinitrobenzene- $^{14}\text{C}_6$ of such a way as described in the preceding paper⁶. The product thus obtained was recrystallized from 90% ethanol to remove a small amount of *o*-isomer. The yield was 758 mg (149 mCi, 33.0 mCi/mmol; 73%).

2.2 *m*-Bromonitrobenzene- $^{14}\text{C}_6$ *m*-Dinitrobenzene- $^{14}\text{C}_6$ (1.5 mmol, 50 mCi) and CBr_4 (0.75 mmol) were sealed in a Pyrex tube (12×150 mm) and heated in an electric furnace at 270° for 80 min. The contents of the tube were then chilled with liquid nitrogen and the tube was opened in a vacuum line. After the volatile

substances had been removed under reduced pressure (ca. 100 Torr), the tube was detached from the vacuum line and a small amount of *n*-hexane was added to the residue. The solution was poured onto a column of silica gel (Merck, 70-230 mesh, 12×150 mm) and elution was made first with 50 ml of *n*-hexane, then with 100 ml of 95% *n*-hexane/ether and finally with 100 ml of 85% *n*-hexane/ether. The unreacted *m*-dinitrobenzene- $^{14}\text{C}_6$ which was eluted in the third fraction and remained insoluble in *n*-hexane was recovered by recrystallization after evaporation of the eluent. In this procedure, an appropriate amount of pure *m*-dinitrobenzene was employed as a carrier to aid recovery of the labeled material. The recovered *m*-dinitrobenzene- $^{14}\text{C}_6$ was subjected to the same reaction. The result of six runs including reutilization of the recovered material is summarized in Table 1. The second fractions from each run which contained radiochemically pure *m*-bromonitrobenzene- $^{14}\text{C}_6$ were combined and evaporation of the eluent gave the desired product. The yield was 690 mg (82.5 mCi, 24.1 mCi/mmol; 55%).

Fig. 1 Synthetic scheme for the preparation of *m*-bromophenol- $^{14}\text{C}_6$.

Table 1 The result of the synthesis of *m*-bromonitrobenzene- $^{14}\text{C}_6$.
The bromination products separated by column chromatography on silica gel with three kinds of eluents

Starting material mg mCi			Products							
			Fraction 1 ^a <i>m</i> -dibromobenzene mCi %yield		Fraction 2 <i>m</i> -bromonitrobenzene mCi %yield		Fraction 3 <i>m</i> -dinitrobenzene mCi %yield		Residue ^b <i>m</i> -dinitrobenzene mCi %yield	
1.	254	49.8	8.0	16.1	18.5	37.1	7.2	14.4	15.6	31.3
2.	248	48.7	6.2	12.7	17.3	35.5	8.0	16.4	14.8	30.4
3.	247	48.5	5.5	11.3	15.6	32.2	6.8	14.0	20.5	42.2
4.	244 ^c	32.0	7.0	21.8	12.6	39.4	5.0	15.6	8.2	25.6
5.	240 ^c	31.4	6.1	19.4	10.0	31.8	5.5	17.5	8.8	28.0
6.	281 ^d	22.0	6.0	27.3	9.2	41.8	2.6	11.8	...	...

a. also contained a slight amount of tri- and tetrabromobenzenes.

b. also contained a small amount of *m*-bromonitrobenzene.

c. recovered from fraction 3 and residue in exp. 1, 2 and 3 with the aid of 168 mg carrier.

d. recovered from fraction 3 and residue in exp. 4 and 5 with the aid of 168 mg carrier.

2.3 *m*-Bromoaniline- $^{14}\text{C}_6$ *m*-Bromonitrobenzene- $^{14}\text{C}_6$ (698 mg, 82.5 mCi) was dissolved in 5 ml of warm ethanol/water (3:2 v/v) in a flask equipped with a reflux condenser. Granulated tin (2 g) was added and the solution was warmed at 50° for a few min. Concentrated HCl (6.5 ml) was added portionwise to the solution during 20 min and the solution was refluxed for 30 min. Concentrated NaOH solution was then added to make the solution alkaline and the solution was extracted three times with ether. The combined ether solution was dried over Na_2SO_4 and concentrated to ca. 50 ml. Dry HCl gas was then introduced into the ether solution and the precipitate of *m*-bromoaniline- $^{14}\text{C}_6$ hydrochloride formed was collected by filtration. The yield was 592 mg (67.6 mCi, 23.8 mCi/mmol; 82%).

2.4 *m*-Bromophenol- $^{14}\text{C}_6$ *m*-Bromoaniline- $^{14}\text{C}_6$ hydrochloride (592 mg, 67.6 mCi) was dissolved in 12 ml solution of conc H_2SO_4 and water (1:5 v/v). To the precipitate formed on cooling with ice at 0-5°, NaNO_2 (210 mg) in 3 ml of water was added dropwise during 15 min with stirring. Stirring was continued for another 15 min and then urea (20 mg) in 3 ml of water was added to the solution with stirring. The diazotized aniline solution was filtered into the

solution of conc H_2SO_4 (5 ml) and water (40 ml). Then the mixture was distilled with steam and 350 ml of the distillate was collected. The distillate was saturated with NaCl and extracted three times with ether. The ether solution was dried over Na_2SO_4 and the solvent was evaporated to leave chemically and radiochemically pure *m*-bromophenol- $^{14}\text{C}_6$. The yield was 370 mg (50.2 mCi, 23.5 mCi/mmol; 74%).

References

- 1) H. Gilman and H. Blatt: *Organic Syntheses Col. Vol. 1*, 2nd Ed. p. 123, John Wiley & Sons, New York (1963)
- 2) A. Weissberger: *Technique of Organic Chemistry Vol. 6*, Micro and Semimicro Methods, p. 335, Interscience, New York (1954)
- 3) A. Rieker, K. Scheffler and E. Muller: *Liebigs Annal. Chem.*, **670**, 23 (1963)
- 4) A. Yoshitake, K. Kawamura, T. Kamada and M. Endo: *J. Labelled Compounds and Radiopharmaceuticals*, **13**, (3) 323 (1977)
- 5) A.A. Ponomarenko: *Zh. Obshch. Khim.*, **32**, 4035 (1963); *Chem. Abstr.*, **58**, 13744g (1963)
- 6) T. Moriya: *J. Labelled Compounds and Radiopharmaceuticals*, in press.