# PREPARATION OF $^{14}$C-LABELLED POLY(ℓ-MENTHYL ISOPROPENYL CARBONATES)

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## SUMMARY

The synthesis of $^{14}$C-labelled poly(ℓ-menthyl isopropenyl carbonate) is described. Experimental conditions are included for incorporation of $^{14}$C into each of the carbon atoms in the molecule. High pressure liquid chromatography conditions are given for separation and purification of the labelled intermediates.

Key Words: Carbon-14, Poly(ℓ-menthyl isopropenyl carbonate), HPLC, Tobacco, Flavor

## INTRODUCTION

The synthesis of a series of menthyl carbonate esters has been a segment of an on-going project based on the study of stable, nonmigratory, pyrolytic precursors of key tobacco flavor components.(1,2) Due to the volatility of many of the important blend components, tobacco product storage stability has been less than satisfactory. A study of the use of poly(ℓ-menthyl isopropenyl carbonate)[poly(MIC)] as a pyrolytic precursor for menthol is currently under way. This material offers a potential solution to the volatility problems associated with the use of ℓ-menthol.

Current evaluation of poly(MIC) has proceeded to the point where a detailed analysis of the thermal decomposition products is needed. Carbon-14 labelled materials offer the best means of studying thermal breakdown processes. Three different $^{14}$C-poly(MIC) systems have been prepared. The structures of these compounds are shown in Figure 1.

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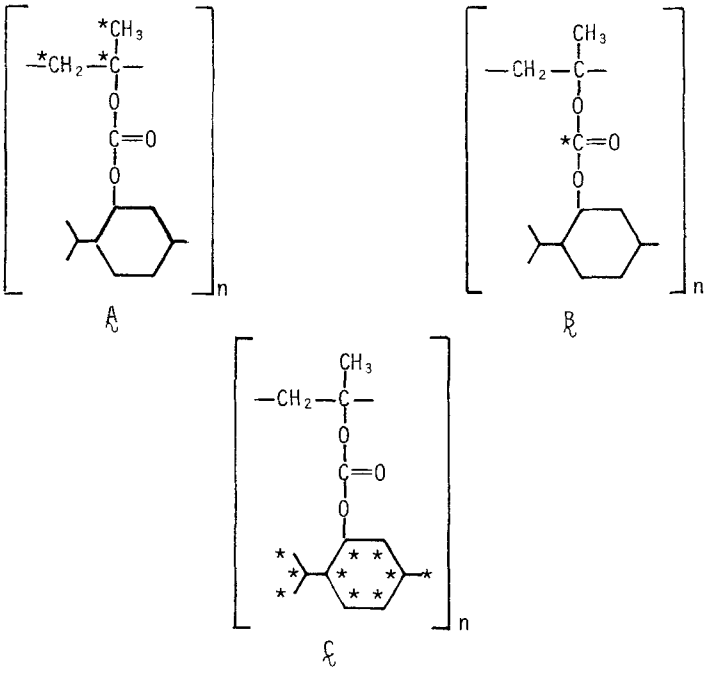

Fig.1. $^{14}C$-Labelled poly(ℓ-menthyl isopropenyl carbonate)

The preparation of the labelled polymers (Figure 2) involves the treatment of acetone with potassium hydride in THF. The acetone is quantitatively converted to the soluble potassium enolate salt, 2. This salt, on treatment with menthyl chloroformate (MCF, 1), yields a mixture from which pure menthyl isopropenyl carbonate (MIC, 3) is isolated by high pressure liquid chromatography (HPLC). Bulk polymerization of 3 in the presence of dibenzoyl peroxide yields polymer 4 of sufficient purity for the pyrolytic studies.

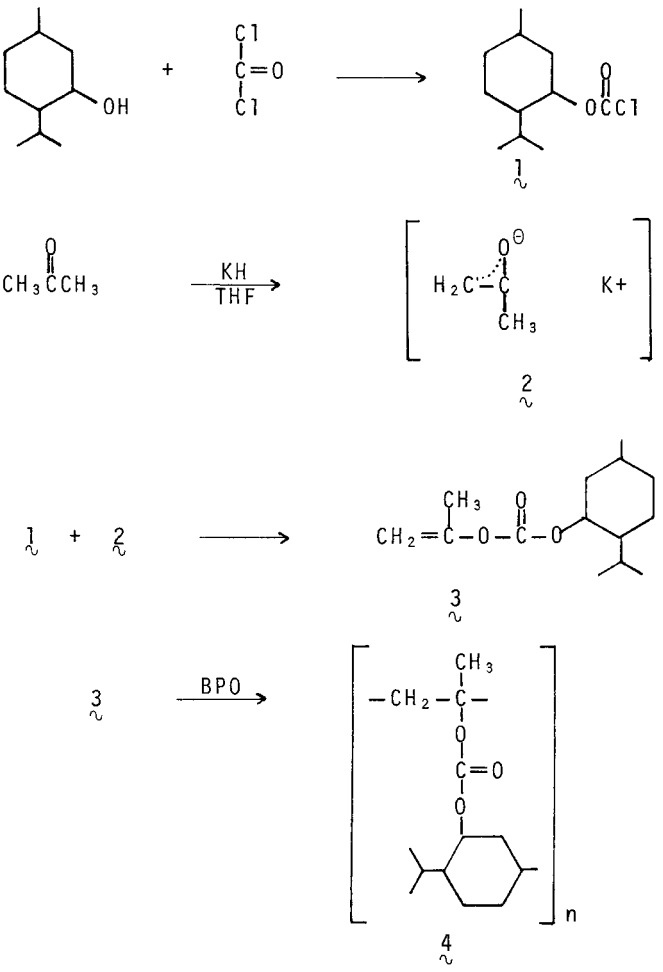


Fig.2. Synthesis of poly(ℓ-menthyl isopropenyl carbonates)

## EXPERIMENTAL[1]

### POLY(ℓ-MENTHYL ISOPROPENYL CARBONATE-$^{14}$C-ISOPROPENYL LABELLED)-A

Acetone (U-$^{14}$C) (58.1 mg, 1 mmol-5 mCi)[2] in 1.5 mL of THF[3] was added dropwise by syringe to a suspension of KH (196 mg of a mineral oil suspension containing 43.9 mg, 1.1 mmol of KH) in 1 mL of THF under $N_2$. The reaction was stirred at room temperature under $N_2$ for 15 min and the contents were transferred dropwise by syringe to a stirred solution of MCF (243 mg, 1.1 mmol) in 1 mL of THF under $N_2$. After the addition was completed, stirring was continued for one h at room temperature. Five mL of abs $Et_2O$ was added and the reaction mixture then extracted with three 6 mL portions of $H_2O$. The organic layer was dried over $MgSO_4$ for 1.5 h and evaporated to dryness *in vacuo* to give 343.5 mg of a viscous oil. The oil was dissolved in a small quantity of isooctane and the MIC isolated by trapping from a high pressure liquid chromatograph.[4] Four cuts were taken. The material eluting between 14.6 and 21.7 min (third cut) was pure monomer. The solvent was removed *in vacuo* to yield 101.7 mg (42.3%) of oily monomer with an activity of 1.91 mCi. Specific activity - 18.78 μCi/mg.

The monomer (101.7 mg - 1.91 mCi) was polymerized by the addition of 7.1 mg of dibenzoyl peroxide and heating at 80°C under $N_2$ for 24 h. A solid, pale yellow mass was obtained on cooling. To this mass was added 2 mL of MeOH and a fluffy white powder formed on scraping and stirring. After stirring for 1 h, the solid was collected by filtration, washed with 0.5 mL of MeOH and air dried for 2 h to yield 68.8 mg (67.6% yield from monomer) of white polymer (A) with an activity

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1 Physical and chemical properties of the intermediates and final products were identical to those previously obtained on non-labelled materials.

2 Acetone (U-$^{14}$C) was purchased from ICN Pharmaceuticals, Inc. (5 mCi - 5mCi/mmol).

3 The THF described throughout the experimental section was distilled from and stored over Na.

4 Waters Assoc. Model ALC-202/401, 2 - 7.8 mm x 61 cm Porasil A columns, 4 mL/min flow of 3% ethyl acetate in isooctane.

of 1.36 mCi (71.2% activity yield from monomer). Specific activity - 19.76 μCi/mg polymer.

POLY(ℓ-MENTHYL ISOPROPENYL CARBONATE-$^{14}$C-CARBONYL LABELLED)-B

$^{14}$C-(Carbonyl labelled) MCF was prepared in two runs from $^{14}$C-phosgene.[5] To 156 mg (1 mmol) of menthol and 137.5 mg (1.1 mmol) of quinoline in 10 mL of abs $Et_2O$ at 0°C under $N_2$ was added phosgene over a 10 min period:

Run 1 - 15.5 mg (0.15 mmol $^{14}$C-phosgene) in 1 mL of toluene plus 103 mg (1.05 mmol unlabelled phosgene) - 5.3 mL of 9.65 g phosgene/500 mL toluene

Run 2 - 16.7 mg (0.17 mmol $^{14}$C-phosgene) in 1 mL of toluene plus 101.9 mg (1.03 mmol unlabelled phosgene) - 5.2 mL of 9.65 g phosgene/500 mL toluene

The solution was stirred at 0°C for an additional 15 min and the bath then removed to allow the reaction mixture to come slowly to room temperature. The reaction was stirred overnight at room temperature under $N_2$. The precipitated solid was filtered off and washed well with abs $Et_2O$. The $Et_2O$/toluene organic phase was evaporated to dryness *in vacuo* to yield a yellow oil. Pure MCF was isolated by HPLC trapping.[6]

Run 1 - 1.18 mCi (47.2% radioactivity yield)

Run 2 - 0.92 mCi (36.9% radioactivity yield)

These solutions were combined and taken to dryness *in vacuo*.

Acetone (87.2 mg, 1.5 mmol) in 1 mL of THF was added dropwise by syringe to a suspension of KH (269 mg of a mineral oil suspension containing 60.2 mg, 1.5 mmol KH) in 1.5 mL of THF under $N_2$. The reaction was then stirred at room temperature for 15 min. The

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[5] Phosgene, ($^{14}$C) was purchased from ICN Pharmaceuticals, Inc.
Run 1 - (2.5 mCi - 16 mCi/mmol) phosgene in 1 mL of toluene
Run 2 - (2.5 mCi - 14.8 mCi/mmol) phosgene in 1 mL of toluene

[6] Waters Assoc. Model ALC-202/401, 2 - 7.8 mm x 61 cm Porasil A columns, 8 mL/min flow of 10% ethyl acetate in isooctane, MCF collected at 5.2 - 9.4 min.

previously prepared $^{14}$C-MCF [weight unknown but calculated from activity yields to be 183.9 mg (0.84 mmol) - total activity 2.10 mCi] and unlabelled MCF (35.0 mg, 0.16 mmol) were combined in 1 mL of THF and placed in a separate flask under $N_2$. The enolate was added in portions dropwise by syringe to the MCF solution. The reaction was followed by gas chromatography.[7] At the conclusion of the addition, the reaction mixture was stirred for 3 h at room temperature under $N_2$. To the reaction mixture was added 5 mL of abs $Et_2O$ and the mixture washed with two 5 mL and one 10 mL aliquots of $H_2O$. The $Et_2O$ layer was dried overnight over $MgSO_4$, filtered and the $MgSO_4$ washed with $Et_2O$. The $Et_2O$ was stripped to dryness *in vacuo* to yield 441.1 mg of a viscous yellow oil. The MIC was isolated from the oil by HPLC, collecting the material eluting between 14.1 min and 22.2 min. Concentration *in vacuo* yielded 129.2 mg (53.8% weight yield assuming 1 mmol of MCF to start) and 794.5 μCi (37.8% activity yield).

The $^{14}$C-carbonyl labelled MIC (129.2 mg - 794.5 μCi) was polymerized by the addition of 8.02 mg dibenzoyl peroxide to the viscous oil and heating at 80°C for 24 h. The addition of 2 mL of MeOH followed by scraping and stirring for 30 min yielded 80.6 mg (62.4% based on starting MIC) of white polymer ($\beta$) on filtration and air drying - activity 422 μCi (53.1%). Specific activity - 5.25 μCi/mg polymer.

POLY(ℓ-MENTHYL ISOPROPENYL CARBONATE-$^{14}$C(U)-MENTHYL LABELLED)-$\zeta$

To 3.78 g (0.024 mol) of $^{14}$C(U)-menthol-2.8 mCi, (isolated from $^{14}CO_2$ grown mint plants) was added, under $N_2$ with stirring, a solution of 11.9 g (0.12 mol) phosgene in 34 mL of abs $Et_2O$. The reaction was stirred at room temperature for 24 h under a slight $N_2$

[7] Stainless steel column (1.5 ft), 3% SE30, 70cc/min He flow, on column injection at 85°C, held isothermal at 85°C for one min then programmed at 25°C/min to 135°C followed by 50°C/min to 275°C, isothermal at 275°C for ten min.

pressure, after which $N_2$ was bubbled in for 1 h to remove excess phosgene and HCl. The solution was then taken to dryness *in vacuo* to yield an oil. Pure MCF was isolated from the oil by HPLC injection and trapping.[8] The MCF was collected between 350 mL and 700 mL of solvent throughput. On concentration, a yield of 4.67 g (89.0%), 2.29 mCi (81.8%) of pure MCF [$^{14}$C(U)-menthyl] was obtained.

Acetone (1.74 g, 0.03 mol) in 20 mL of THF was syringe added to KH (5.4 g of a mineral oil suspension containing 1.2 g, 0.03 mol KH) in 30 mL of THF under $N_2$. In a separate flask under $N_2$ was placed 4.67 g (0.021 mol) $^{14}$C-MCF (2.29 mCi). The acetone enolate was added in portions to the $^{14}$C-MCF and the reaction followed by gas chromatography.[7] After >95% conversion to MIC had been carried out, the reaction mixture was stirred an additional two h. Abs $Et_2O$ (100 mL) was added to the stirred reaction mixture. The $Et_2O$/THF was extracted twice with 100 mL of $H_2O$ and once with 200 mL of $H_2O$. The organic layer was dried over $MgSO_4$ for 1 h, filtered and the $MgSO_4$ washed well with $Et_2O$. The $Et_2O$ was stripped to dryness *in vacuo* to yield 7.71 g of oil which was purified by HPLC.[9] Pure MIC was isolated in the volume eluting between 1450 mL and 2400 mL. Concentration of this fraction yielded 2.29 g (45.3%) of $^{14}$C-MIC with an activity of 945.6 μCi (41.3%).

To this oil was added 136.8 mg dibenzoyl peroxide under $N_2$. The temperature was slowly raised to 80°C and heating continued at 80°C for 22 h yielding a solid mass. After cooling to room temperature, the mass was dissolved in 10 mL of hexane and the hexane solution added dropwise to 75 mL of rapidly stirred MeOH. A fine white solid precipitated. The mixture was stirred for an additional 15 min, filtered through a medium porosity filter, and the precipitate

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[8] Waters Assoc. Prep. 500, one silica cartridge, 100 mL/min flow of 10% ethyl acetate in hexane.

[9] Waters Assoc. Prep. 500, two silica cartridges, 100 mL/min flow of 1.5% ethyl acetate in hexane.

washed three times with 10 mL of MeOH. After air drying for 1-1/4 h, 1.17 g (51.1%) of white polymer (C) with an activity of 425 μCi (45.0%) was obtained. Specific activity - 0.36 μCi/mg.

## $^{14}$C-MENTHOL BIOSYNTHESIS AND ISOLATION

Mint plants (*Mentha arvensis L.* var *piperascens*) were chamber grown in a $^{14}CO_2$ atmosphere for a period of 32 days.(3) Harvesting was accomplished by cutting the stems approximately 1-1/2 in. above ground level. Leaves were immediately pulled (cut) from the stems and frozen in liquid $N_2$. A yield of 605 g of leaf was obtained from 1116 g total stems and leaves. After freezing, the leaves were ground with a mortar and pestle and transferred to round bottom flasks imbedded in dry ice. Steam distillation of the leaf material was accomplished after warming to room temperature and adding $H_2O$. Pentane extraction of the steam distillate yielded 2.8 mCi of total extract. This was combined with 1.9 mCi of oil similarly isolated from a previous chamber run. Menthol isolation was accomplished by HPLC.[10] Pure menthol (3.78 g - 2.8 mCi) was obtained after solvent removal *in vacuo*.

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[10] Waters Assoc. Prep. 500, one silica cartridge, 100 mL/min flow of 8% ethyl acetate in hexane.