THE PREPARATION OF CARBON-14 LABELED TOBACCO CONSTITUENTS. I. THE SYNTHESES OF BENZYL, PHENETHYL, AND UNDECYL ACETATE-^{14}C-1,2.

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SUMMARY

The syntheses and purifications of benzyl, phenethyl, and undecyl acetate-^{14}C-1,2 are described. These compounds were prepared by reaction of the appropriate alkyl or aryl halide with ^{14}C-labeled sodium acetate in the presence of acetic acid. Isolation of the acetates was accomplished by trapping from a gas chromatograph. The technique of gas-liquid radiochromatography in activity determinations is described.

INTRODUCTION AND DISCUSSION

The mechanism of cigarette smoke formation has been under investigation in our laboratories for some time. The use of ^{14}C-labeled compounds has been a valuable tool in determining the fate of tobacco constituents in the burning cigarette.[1,2] In this regard benzyl acetate,[3] phenethyl acetate,[4] and undecyl acetate,[5] compounds which had previously been reported in tobacco, but not in tobacco smoke,[6] were synthesized by the route shown:

$$R\text{-}CH_2Cl + NaO\overset{\overset{O}{\|}}{\underset{**}{C}}CH_3 + HO\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[xylene]{Et_3N} R\text{-}CH_2O\overset{\overset{O}{\|}}{\underset{**}{C}}CH_3$$

$R=C_6H_5\text{-}$, $C_6H_5CH_2\text{-}$, $CH_3(CH_2)_8CH_2\text{-}$

Sodium acetate [1,2-^{14}C] (New England Nuclear Corp.) was converted to acetic acid [1,2-^{14}C] by introduction of "cold" glacial acetic acid to the purchased ^{14}C-sodium acetate. The required aryl or alkyl chloride was then added and an equivalent of triethylamine was introduced as an acid scavenger. The progress of the reaction was followed by gas chromatography and the best yields were realized with a 24 hr. reflux in dry xylene. Shorter reflux time and/or other solvents (i.e., benzene, toluene) led to lowered yields due to unreacted starting materials, whereas longer reaction times resulted in decomposition of the desired esters.

Precipitation of the by-product salts was accomplished with an excess of dry n-hexane. After filtration and concentration, the crude oily residue was purified by gas chromatographic injection of 75 μl samples and trapping into a disposable pipette cooled in dry ice. Gas-liquid radiochromatography (GLRC) of the trapped products indicated chemical and radiochemical purity of >99.5% in all cases.

The specific activities were found to be 1.28, 1.09, and 0.66 mCi/mM for the benzyl, phenethyl, and undecyl acetates, respectively. The activities were determined by GLRC and were confirmed by liquid scintillation counting. The values obtained by both measurements were in excellent agreement.

In preparation for the labeled syntheses, the reactions were run on cold materials and the products identified by gas chromatographic retention time and infrared and nuclear magnetic resonance spectra.

EXPERIMENTAL

Liquid scintillation counting was accomplished on a Packard

Model 3310 Tri-Carb Liquid Scintillation Spectrometer. The scintillation solution was prepared from Liquiflour (New England Nuclear Corp.) and spectral grade toluene (Packard). ^{14}C-Toluene (New England Nuclear Corp.) was used as an internal standard for applying proper quenching corrections.

Gas-Liquid Radiochromatography

A F&M Model 720 Gas Chromatograph was utilized for isolation and purity evaluation. The columns (1/4 in. O.D. by 10 ft. copper) contained 5% Carbowax 20M on 80-100 mesh Chromosorb G, AW-DMCS. The oven temperature was maintained at 150°C and helium flow was 60 ml/min. Injection port and detector temperatures were 215°C.

Gas-liquid radiochromatography was accomplished by standard injection and detection by thermal conductivity, followed by passage of the sample through a stainless steel combustion tube (3/8 in. O.D. by 13 in., containing CuO at 720°C) and a copper drying tube (1/4 in. O.D. by 10 in., containing $MgClO_4$ followed by cobalt oxide). The oxidized sample was then mixed with the counting gas (propane) in the ratio 2.5:1 (propane:helium) and passed into a 10 cc flow through counting tube (Lab. Prof. Dr. Berthold). A Berthold preamplifier was coupled to a Hewlett-Packard Model 5201L Scaler-Timer. Digitized data was printed on a Hewlett-Packard Model 562A Digital Recorder. Efficiency determinations were conducted with toluene-^{14}C (New England Nuclear).

Benzyl Acetate [acetate 1,2-^{14}C]

Sodium acetate [1,2-^{14}C], (New England Nuclear, 1.0 mCi; 1.4 mg in 10 ml EtOH) was isolated by concentration of the EtOH solution *in vacuo* with a minimum of heat. To the residue was added 60 mg (0.001 mole) gl. HOAc, 127 mg (0.001 mole) benzyl

chloride, 101 mg (0.001 mole) triethylamine and 1 ml xylene. The mixture was heated at reflux for 24 hr. On cooling to room temperature, triethylamine hydrochloride crystallized out. Dilution with hexane, filtration, and washing with hexane (a total of 50 ml used) yielded a light, mobile oil on concentration in vacuo. The oil was purified by trapping from a gas chromatograph. A total of 74.3 mg (50% yield) of ^{14}C-benzyl acetate was isolated. This material had a specific activity of 1.28 mCi/mM.

Phenethyl Acetate [acetate 1,2-^{14}C]

Sodium acetate [1,2-^{14}C],(New England Nuclear, 1.0 mCi; 1.4 mg in 10 ml EtOH) was isolated by concentration of the EtOH solution in vacuo with a minimum of heat. To the residue was added 60 mg (0.001 mole) gl. HOAc, 140 mg (0.001 mole) phenethyl chloride, 101 mg (0.001 mole) triethylamine and 1 ml xylene. The mixture was heated at reflux for 24 hr. On cooling to room temperature, triethylamine hydrochloride crystallized out. Dilution with hexane, filtration, and washing with hexane (a total of 50 ml used) yielded a light, mobile oil on concentration in vacuo. The oil was purified by trapping from a gas chromatograph. A total of 85.5 mg (52% yield) of ^{14}C-phenethyl acetate was isolated. This material had a specific activity of 1.09 mCi/mM.

Undecyl Acetate [acetate 1,2-^{14}C]

Sodium acetate [1,2-^{14}C], (New England Nuclear, 1.0 mCi; 1.4 mg in 10 ml EtOH) was isolated by concentration of the EtOH solution in vacuo with a minimum of heat. To the residue was added 60 mg (0.001 mole) gl. HOAc, 190 mg (0.001 mole) undecyl chloride (prepared from 1-undecanol and thionyl chloride), 101 mg (0.001 mole) triethylamine and 1 ml xylene. The mixture was heated at

reflux for 24 hr. On cooling to room temperature, triethylamine hydrochloride crystallized out. Dilution with hexane, filtration, and washing with hexane (a total of 50 ml used) yielded a light, mobile oil on concentration in vacuo. The oil was purified by trapping from a gas chromatograph. A total of 67.9 mg (32% yield) of ^{14}C-undecyl acetate was isolated. This material had a specific activity of 0.66 mCi/mM.

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