NOTES

SYNTHESIS OF DEUTERATED ANALOGS OF CHLOROMETHYL METHYL ETHER

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INTRODUCTION

Chloromethyl methyl ether (CMME) has been known for almost 100 years (1). The compound is used extensively in the manufacture of polymers, and has been employed in the laboratory to introduce the chloromethyl (2) or methoxymethyl groups (3,4) into organic molecules. Some barbituric acid derivatives, for example, have been methoxymethylated on nitrogen using CMME to give compounds with potent anticonvulsant properties (3,4). Our interest in the disposition of these drugs has prompted us to synthesize the deuterated analogs IIIa and IIIb of CMME, to be used in the preparation of deuterated N-methoxymethyl barbituric acid derivatives. These compounds in turn will be used as internal standards in studies of the metabolic fate and pharmacokinetics of the unlabelled analogs employing combined gas chromatography - mass spectrometry as analytical tool.

Recently clear evidence was obtained linking human lung cancer and exposure to CMME (5,6). This finding, of great concern in view of the extensive use of CMME in the chemical industry, has led to a study (7) of the stability of CMME in humid air using mass spectrometry. Deuterated analogs of CMME may also be of interest in this connection.

CH_3OCH_2Cl

CMME

$$CX_3OX + (CY_2O)_n \xrightarrow{HCl} CX_3OCY_2Cl$$

Ia IIa IIIa
b b b

	X	Y
a:	D	H
b:	H	D

S C H E M E 1

$ClCH_2OCH_2Cl$

IV

$(C_6H_5)_3\overset{\oplus}{P}CH_2O\overset{\ominus}{C}H_3Cl$

V

DISCUSSION

CMME may be conveniently prepared from aqueous formaldehyde, methanol, and hydrogen chloride (8). However, since commercial aqueous formaldehyde contains methanol as stabilizer we turned to an earlier method employing non-aqueous starting materials (9,10). This procedure uses paraformaldehyde as the source of formaldehyde (Scheme 1). Methanol-d_4 and paraformaldehyde gave CMME labelled in the methyl group (IIIa) while paraformaldehyde-d_2 and methanol led to the ether labelled in the methylene group (IIIb). Nmr analysis of unlabelled CMME prepared in this fashion and purified by simple distillation through a Vigreux column showed the presence of several impurities with resonances at δ 3.35, 3.42, 4.57, 4.58 and 5.56 (all singlets). Commercial CMME (Aldrich Chem. Co.) had an essentially identical nmr spectrum. The identity of these impurities was not established. Bis(chloromethyl) ether (IV, b.p. 104-5°, nmr δ 5.57 (11)) is known (7) to be an impurity in CMME. Considerably purer CMME can be obtained by careful fractionation of the crude material in a spinning-band still. This procedure removes the impurities except for traces of material with resonance at δ 3.35.

In order to determine the isotopic purity of the deuterated compounds they were reacted with phenobarbital (3), and the product 1,3-bis(methoxymethyl) derivatives were analyzed by mass spectrometry.

An alternative method for the preparation of IIIb (isotopic purity 92%) has been published (12). The three step sequence uses the key intermediate phosphonium salt V to introduce deuterium into the methylene group by exchange in D_2O, catalyzed by potassium carbonate. While the overall yield (75%) reported was superior to those obtained by our procedure, the sequence is longer and there seems to be incomplete incorporation of deuterium.

EXPERIMENTAL

Caution! CMME is a potent carcinogen; in the United States its handling, use, and preparation are governed by regulations of the Occupational Safety and Health Administration.

Nmr spectra were recorded on Varian A60 D Instrument in chloroform-d. Chemical shifts were expressed as parts per million (δ) downfield from TMS internal standard. A Perkin-Elmer Model 251 Teflon still was used in the distillations. Mass spectra were obtained on a DuPont 21-491 instrument at 70 eV ionizing energy.

Chloromethyl Methyl-d_3 Ether (IIIa). Methanol-d_4 (10.0 g, isotopic purity 99%) and paraformaldehyde (10.0 g) were placed in 100 ml round bottom flask equipped with reflux condenser and a gas inlet tube reaching below the surface of the liquid. The mixture was cooled in an ice bath and vigorously stirred magnetically while hydrogen chloride gas was bubbled in at a rate to produce a gentle reflux. The exothermic reaction subsided after ca. 10 min., the ice bath was removed and the gas bubbled in for an additional 1 hr. The two layers formed were separated, the organic layer dried ($CaCl_2$) and distilled through a spinning-band column to obtain 6.3 g (26.4%) of IIIa, b.p. 57-57.5°. Nmr δ 5.45 (S, $\underline{CH_2}$). Reaction of IIIa with phenobarbital was carried out as described (3). Mass spectrometric analysis of the product 1,3-bis(methoxymethyl)phenobarbital showed an isotopic purity of 98%.

Chloromethyl-d_2 Methyl Ether (IIIb). Paraformaldehyde-d_2 (10.0 g, isotopic purity 98%) and methanol (10.0 g) gave, using the above procedure, 5.8 g (22.5%) of IIIb, nmr δ 3.48 ($\underline{CH_3}$), isotopic purity 98%.

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