[11-C]METHANOL AS A DIRECT LABELING AGENT : APPLICATION TO 3-METHOXYBENZODIAZEPINES.

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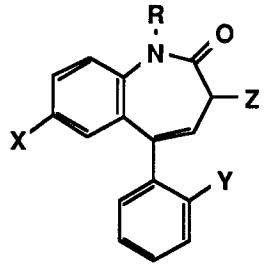
We wish to report the direct nucleophilic substitution of [^{11}C]methanol in 3-chlorobenzodiazepines under neutral conditions. These novel [^{11}C]methoxy-labeled benzodiazepines may have advantages over the known [^{11}C]N-methyl-labeled benzodiazepines for *in vivo* PET studies.



1 X=Cl,Y=Z=H,R=Me
2 X=NO_2,Y=F,Z=H,R=Me
3 X=Cl,Y=R=H,Z=OH
4 X=Cl,Y=H,Z=OH,R=Me
5 X=Y=Cl,Z=OH,R=H
6 X=Cl,Y=R=H,Z=OMe
7 X=Cl,Y=H,Z=OMe,R=Me
8 X=Z=Cl,Y=R=H
9 X=Z=Cl,Y=H,R=Me

Figure1. Structures of Benzodiazepines ıeferred to in the text.

Benzodiazepines (BZs), for example, diazepam 1, and flunitrazepam 2, are readily labeled with carbon-11 at the 1-amidic nitrogen (1). However, their use as *in vivo* ligands in PET of CNS BZ receptors is complicated by N-demethylation and by hydroxylation at position 3 (fig. 2). This latter route of metabolism in which the [^{11}C]N-methyl label is retained (fig. 2, C) is of particular concern for PET kinetic studies, since the metabolite is pharmacologically equipotent with its parent, but may exhibit different kinetic parameters. Pharmacologically A, B, C, and D, and the corresponding 3-methoxy BZs E and F (fig. 2) are all equipotent (2). Since both C and D are metabolically stable towards 3-hydroxylation they are candidates for labeling. Indeed oxazepam 3, temazepam 4, and lorazepam 5, (fig. 1) are all used clinically. With the availability of a general strategy for [^{11}C]O-methylation the relative merits of N- v. O-methylation could be studied. Using oxazepam, N-methylation to give 4 and O-methylation to yield 3-methoxynordiazepam 6 could be studied independently. Alternatively, in the case of 3-methoxydiazepam 7 the label could be incorporated into either the N-methyl- or O-methyl group in the same molecule.

[^{11}C]N-methylation of 3, 5, or 6 with [^{11}C]iodomethane is straightforward (3). Clearly 3 and 5 cannot be selectively alkylated at the 3-oxygen, since alkylation will occur preferentially at N-1 *vide supra*. BZs 6, and 7 were

prepared originally by reaction of the corresponding 3-chlorodiazepams 8, and 9 with methanol (2).

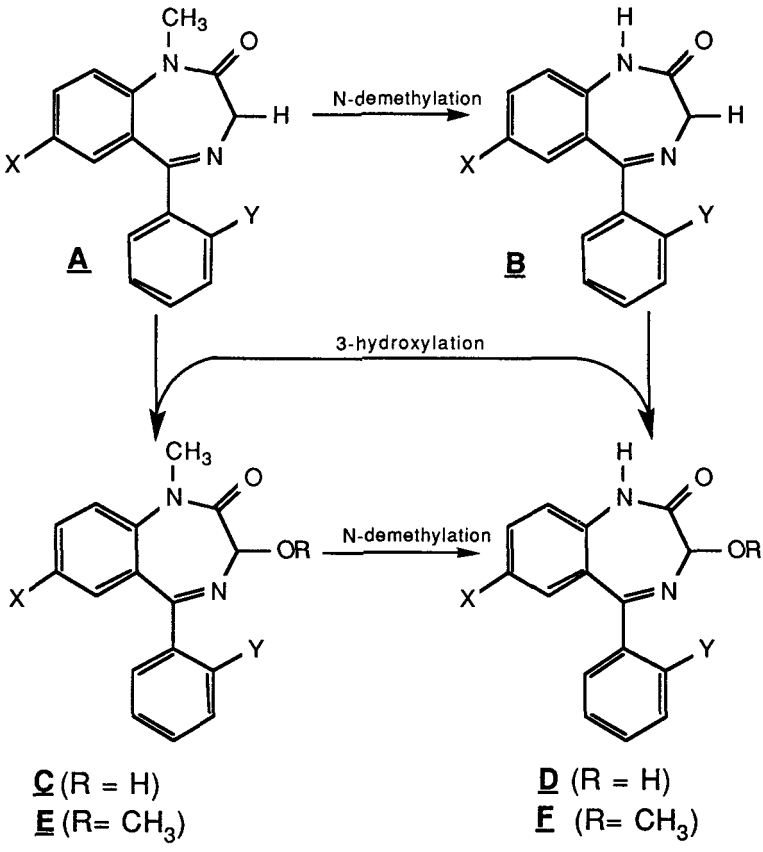


Figure 2. N-demethylation and 3-hydroxylation of Benzodiazepines

We thus attempted to prepare [^{11}C]3-methoxyBZs using [^{11}C]methanol as limiting reagent. The starting 3-chloro BZs, are readily obtained by treatment of corresponding 3-hydroxy compounds with thionyl chloride in the presence of polyvinyl pyridine. Removal of the polymer followed by washing with toluene, evaporation of the solvent, and trituration of the residue with hexane gave pale yellow solids which were stable on storage in a dessicator at ambient temperature for at least one year. Reaction of 3-chlorodiazepam 9, (obtained from temazepam 4) with n.c.a. [^{11}C]methanol (obtained from lithium aluminum hydride reduction of [^{11}C]carbon dioxide) in acetonitrile at 80°C for 15 min gave [^{11}C]3-methoxydiazepam 7. Water was added to the reaction mixture, which rapidly hydrolyzed unreacted 9 back to temazepam 4. Passage of this material through a C_{18} SEP-PAK and

washing with H_2O removed any unreacted [^{11}C]methanol. Desired 7 was obtained in > 50% radiochemical yield (EOB, based on [^{11}C]methanol) and > 99% radiochemical purity by eluting the C_{18} SEP-PAK with 95:5 pentane/ethanol and passing the effluent through an alumina SEP-PAK, which retained temazepam 4.

Avoiding the conversion of [^{11}C]methanol to [^{11}C]iodomethane, with its consequent reaction time and potential additional source of carrier, affords the opportunity of higher specfic activity over the corresponding [^{11}C]N-methylated BZ.

Surprisingly, [^{11}C]methanol itself has received scant attention as a labeling agent, although it is involved extensively as an intermediate in the formation of [^{11}C] iodomethane and [^{11}C]formaldehyde from [^{11}C]carbon dioxide. A search of the primary literature revealed only one prior use (4). In that case the [^{11}C]methanol was converted to the corresponding potassium methoxide with solid KOH, which in DMSO transformed simple n-alkyl- and benzyl-chlorides to the corresponding methyl ethers in 50-60% radiochemical yield. The success of the present method suggests that [^{11}C]methanol may be of potential use for other radiopharmaceuticals in which a reactive halogen can be displaced by methanol.

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4. Dischino, D.D., Welch, M.J., Kilbourn, M.R., and Raichle, M.E., J. Nucl. Med., 24, 1030 (1983).