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A SIMPLE PREPARATION OF DEUTERIUM LABELLED O-METHYL GROUPS FOR MASS SPECTROMETRY

K.J. van der Merwe, P.S. Steyn and S.H. Eggers

National Chemical Research Laboratory, Council for Scientific and Industrial Research, P.O. Box 395, Pretoria, South Africa

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Previously described methods (1) for preparing deuterium labelled O-methyl groups used either methyliodide-d_3, methanol-d_4, or diazomethane-d_2 [prepared from N-nitroso-N-methyl-d_3-tosylamide (2)] to obtain fully deuterated O-methyl groups. The preparation of completely deuterated O-methyl groups is, however, often not essential for labelling such groups for mass spectrometry. We have found that a partial deuteration is conveniently effected by methylation of an acid or phenol with diazomethane in the presence of an excess of deuterium oxide. Mass spectra of the reaction products showed the introduction of mainly three deuterium atoms per O-methyl group in addition to smaller amounts of the partially deuterated species.

The n.m.r. spectrum of diazomethane in chloroform at 5° showed a single peak at τ 6.72 which was not altered by treatment with an excess of deuterium oxide over ten minutes. On subsequent addition of catalytic amounts of either benzoic acid, propionic acid, phenol, or ammonium chloride, yellow solutions resulted which showed practically no absorption in the τ 6.6 - 6.8 region, but which still reacted vigorously with large amounts of acid.

These results suggest that exchange of the hydrogen atoms of diazomethane for deuterium is acid catalysed.* Methylation of an acid or phenol would seem to be preceded by a much faster, and reversible, protonation of diazomethane. Such a reaction mechanism would resemble that recently proposed for the acid catalysed hydrolysis of diazoketones (2,3) while contradicting that proposed for the acid catalysed hydrolysis of diazoalkanes (3).

The following simple procedure is recommended to give at least a fifty per cent yield of trideuterated O-methyl compounds. An ethereal diazomethane solution is prepared in the standard way from N-nitroso-N-methyltosylamide or N-nitroso-methylurea and dried over solid potassium hydroxide. The diazomethane is then carried over into dry dioxane in a stream of dry nitrogen. An excess of deuterium oxide is added to this diazomethane solution followed by a slow addition of a dioxane-deuterium oxide solution of the acid or phenol over a period of at least ten minutes. Substitution of chloroform or ether for dioxane results in the formation of two phases and a corresponding decrease in the efficiency of deuterium exchange.

Groups unreactive towards diazomethane but which might have become deuterated during the reaction can be re-exchanged by treatment of the deuterio-methylated product with water.

This method proved useful in the interpretation of the mass spectra of ochratoxin A (5), a fungal metabolite containing a carboxy, a phenolic hydroxyl and an amide group.

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* It is to be noted that this exchange can also be catalysed by alkali; T.D. Goldfarb and G.C. Pimentel, J. Am. Chem. Soc. 82, 1865 (1960).

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