

## SYNTHESIS OF ORGANIC COMPOUNDS LABELLED WITH HYDROGEN ISOTOPES.

### I - EXCHANGE OF HALOGEN ATOMS IN HALOHYDRINS FOR HYDROGEN ISOTOPES TO PREPARE ALCOHOLS LABELLED WITH DEUTERIUM OR TRITIUM.

J. Egyed, A. Neszmélyi, I. Beke and E. Baitz.

Central Research Institute for Chemistry,  
Hungarian Academy of Sciences,  
Budapest.  
Hungary

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#### SUMMARY

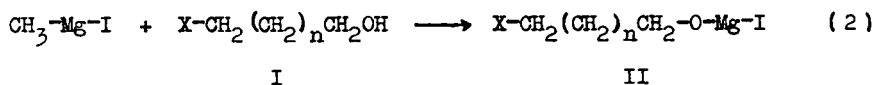
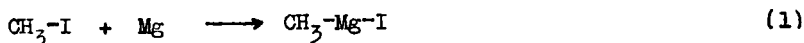
*A method has been developed for the preparation of alcohols labelled with hydrogen isotopes, from halohydrins. The synthesis has been performed via Grignard reagents in one step, in the course of which the halogen substituent has exchanged for magnesium which then exchanges for the hydrogen isotope required.*

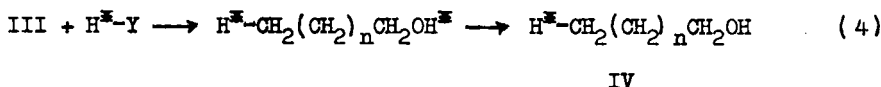
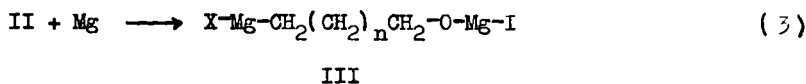
The preparation of compounds labelled with deuterium or tritium from halogen derivatives via a Grignard reagent is a generally accepted method <sup>(1)</sup>. The method is, however, limited, as other substituents in the molecule may either prevent formation of the Grignard reagent or lead to its immediate decomposition.

The same holds true for halohydrins, where the active hydrogen of the hydroxyl group may bring about the decomposition of the organometallic compound formed. In the case of  $\beta$ -halohydrins, on the other hand, the halogen is more reactive and tends to react with organometallic compounds <sup>(2)</sup>.

It is probably due to the above that there is no reference in the literature to the synthesis of Grignard reagents from halo-hydrins and to the practical application of these compounds.

Our aim was to synthesize alcohols labelled with hydrogen isotopes. The exchange of the halogen atoms of halo-hydrins for magnesium and subsequently for hydrogen isotopes seemed to be the most feasible method. We found that the procedure was practicable in case the hydroxyl hydrogen had been previously exchanged for magnesium (Equation 2). Magnesium halo-hydrinate (II) reacted with metal magnesium to form a carbon-magnesium bond (Equation 3). The organometallic compound thus derived (III) contained two magnesium atoms, one bonded to the carbon and the other to the oxygen atom. Magnesium-hydrogen exchange (Equation 4) takes place in the course of the reaction between III and the compound containing the corresponding chemically "active" hydrogen isotope. In the resultant labelled alcohol (IV), the hydrogen isotope takes the position of the halogen atom. (The hydroxyl-hydrogen isotope is completely exchanged for protium during the process).





$n = 1, 2, 3, 4$

The technical procedure is identical with the method used for the synthesis of labelled compounds through Grignard reagents, apart from the fact that half the amount of the initial metal magnesium is used for the synthesis of methyl magnesium iodide and activated metal magnesium while cooling. The formation of magnesium halohydrinate (II) is a momentary process (Equation 2) while development of the carbon-magnesium bond (III) required 4 to 6 hours (Equation 3).

Decomposition of the organometallic compound (III) was performed with acid both in the case of synthesis of alcohols labelled with deuterium and with tritium (Equation 4).

The deuterium content of deuterated alcohols is shown in the Table 1.

### Experimental

The starting material:  $\beta$ -chloro-1-propanol was a FLUKA product;  $\beta$ -bromo-2-methyl-1-propanol was prepared from methyl

Table 1.  
Preparation of hydrogen labelled alcohols from haloalcohols

Initial haloalcohol	Deuterated alcohol	Yield %	Extent of deuterium incorp. %	Tritiated alcohol	Yield % calcd. for initial radioactivity
3-Chloro-1-propanol	1-Propanol-3-d <sub>1</sub>	48	92.3	1-Propanol-3- <sup>3</sup> H	58
3-Bromo-2-methyl-1-propanol	2-Methyl-1-propanol-3-d <sub>1</sub>	76	90.7	2-Methyl-1-propanol-3- <sup>3</sup> H	71
4-Chloro-1-butanol	1-Butanol-4-d <sub>1</sub>	41.3	89.6	1-Butanol-4- <sup>3</sup> H	55
5-Bromo-1-pentanol	1-Pentanol-5-d <sub>1</sub>	42.4	92.1	1-Pentanol-5- <sup>3</sup> H	52
6-Iodo-1-hexanol	1-Hexanol-6-d <sub>1</sub>	39.3	90.1	1-Hexanol-6- <sup>3</sup> H	43

$\beta$ -bromo- $\alpha$ -methylpropionate (3); 4-chloro-1-butanol was synthesized from tetrahydrofuran (4); 5-bromo-1-pentanol was obtained by reduction of ethyl  $\gamma$ -bromovalerate with  $\text{LiAlH}_4$  (5); and 6-iodo-1-hexanol was prepared from 6-chloro-1-hexanol (6).

#### Determination of the hydrogen isotopes incorporation

Mass spectrometric measurements was performed with an MI-1305 type mass spectrometer with the application of the trimethylsilyl ether of deuterated alcohol (7).

The results were checked by NMR measurements performed at 60 MHz with an AEI RS-2 spectrometer. Proton spectra were taken at room temperature in  $\text{CDCl}_3$ , and integrated with an electronic integrator (accuracy 3%). The value of deuterium incorporation, calculated on the basis of the decrease in the intensity of H-lines agreed with the results of mass spectrometric measurements, within the experimental error.

Radioactivity measurements were carried out in liquid phase in toluene solution with a PACKARD TRI-CARB Scintillation Spectrometer Model 574.

#### Preparation of alcohols from halohydrins

A solution of 7.1 g (0.05 mole) methyl iodide in 30 ml ether is added to 2.64 g (0.11 g-atom) of metal magnesium contained in a 3-necked flask equipped with stirrer, condenser and dropping funnel.

After the formation of methyl magnesium iodide (approx. 2 hrs.) , a solution of 0.05 mole halohydrin in 25 ml ether is added dropwise to the reaction mixture while cooling. Following this, the mixture is heated for 4-6 hrs. and vigorously stirred, which is required for in some cases two phases develop during the course of the reaction.

After the reaction is completed, the mixture is cooled to  $-20^{\circ}\text{C}$  and decomposed with the acid containing the corresponding hydrogen isotope. It is feasible to use methane sulphonic acid- $^3\text{H}$  (which is easily soluble in ether) for the preparation of tritiated alcohols, and deuterium chloride or deuterium bromide for the synthesis of deuterated alcohols. Total exchange (Equation 4) generally requires further 3 hrs. of heating and stirring. Finally, after addition of 100 ml of water, the alcohol is obtained by azeotropic distillation and purified by the usual method.

In all cases, purity of the products was checked by gas chromatography (FRACTOVAP CARLO ERBA; packing: Carbovax 1000; flame ionization indication) . As there is generally considerable difference in the boiling points of the initial halohydrins and the alcohols formed, normal distillation proved to be a satisfactory method of purification.

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