SYNTHESIS OF N-ALKANE DERIVATIVES LABELLED WITH SEVERAL ^{13}C

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SUMMARY

The introduction of several ^{13}C-atoms in the alkane chain is described. A maximum number of compounds, with up to six ^{13}C labels, are obtained with a minimum of different reactions.

INTRODUCTION

For a mass-spectroscopic study we needed labelled 1-heptyl- and 1-nonyl iodides, 1-heptene and 1-nonene. The seven-membered chain was to be labelled in the 1,2,3-positions and the nine-membered chain in the 4,5,6-positions with one, two or three ^{13}C-atoms. In order to simplify the calculations, the same batch of Ba $^{13}CO_3$ had to be used with an enrichment of the ^{13}C over 90%. 0.5 m mol was considered sufficient yield for the final products. Using only classical reactions, we tried to obtain a maximum of different labelled products with a minimum of different steps compatible with small quantities. We decided to prepare the alkyl-iodides, alkanes and alkenes from the corresponding bromides obtained from their alcohols. All the final products were purified by gas chromatography. This technique was also used to isolate the n-alkanes with 10 to 14 carbon atoms that were side-products of the syntheses. The yields given are average values for purified intermediate products, such that the multiplication of the yields gives the overall yield for the final product before the gas chromatographic purification.

2. Syntheses

The reaction schemes are given in Fig. 1 and 2. We used chain-prolongation by either one or two carbon atoms at the time. Most of the products labelled with one ^{13}C-atom have already been prepared [1].

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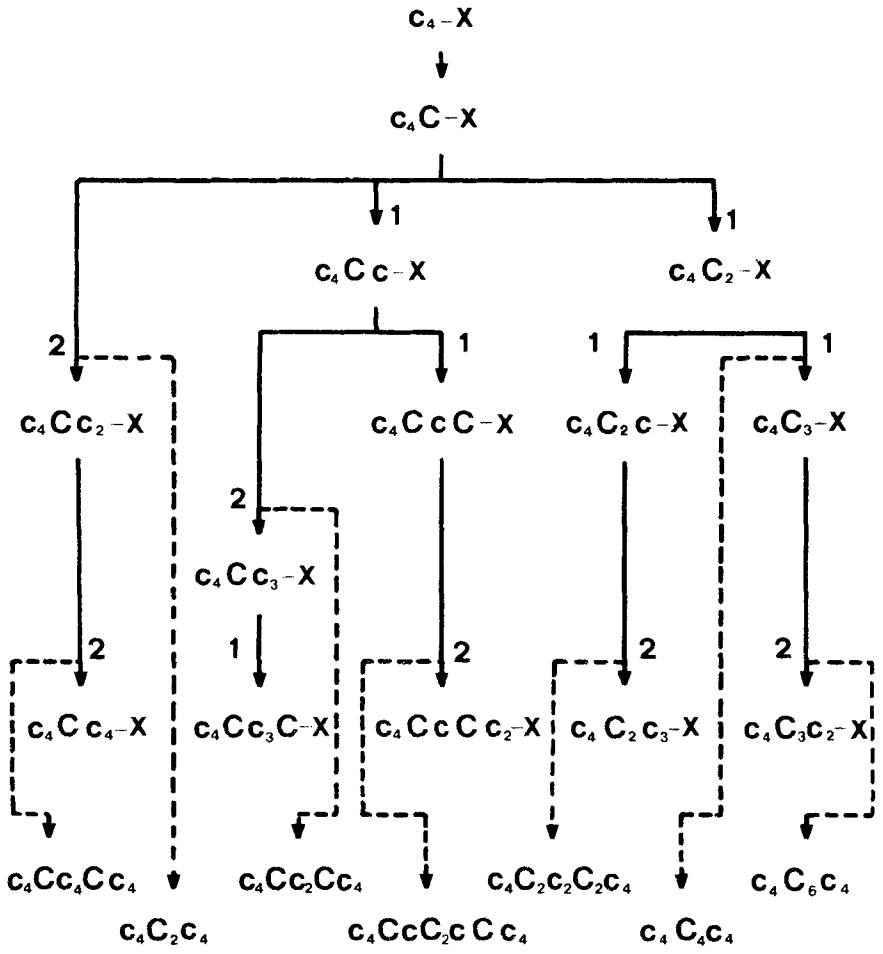
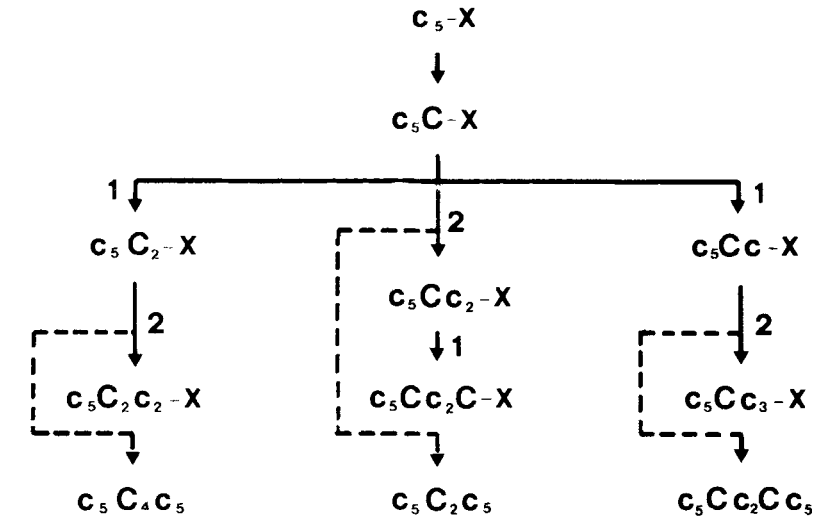
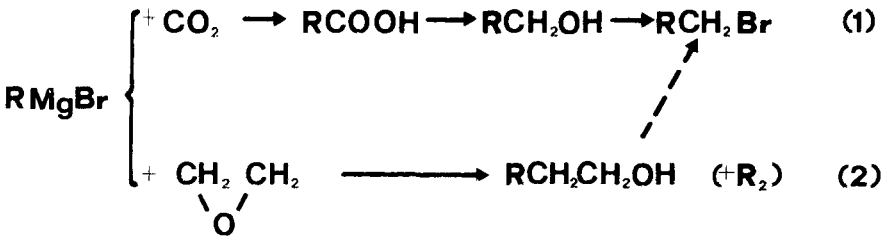


c = CH_2 or CH_3 C = $^{13}CH_2$

fig. 1


c_5-X
c_5C-X
1
2
1
c_5C_2-X
c_5Cc_2-X
c_5Cc-X
2
1
2
$c_5C_2c_2$-X
c_5Cc_2C-X
c_5Cc_3-X
$c_5C_4c_5$
$c_5C_2c_5$
$c_5Cc_2Cc_5$


RMgBr
+ CO_2 → RCOOH → RCH_2OH → RCH_2Br (1)
+ CH_2 CH_2 → RCH_2CH_2OH (+R_2) (2)
O

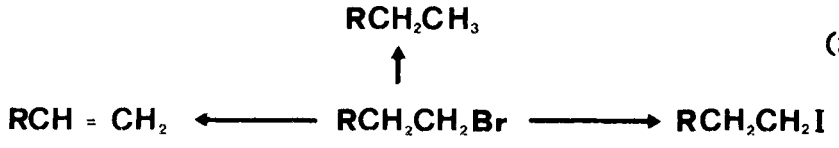

RCH_2CH_3
(3)
$RCH=CH_2$ ← RCH_2CH_2Br → RCH_2CH_2I

fig. 2

The reaction of the Grignard compound of the bromide with frozen CO_2 was used to lengthen the chain either by one ^{12}C-atom [2] or by a ^{13}C-atom from $Ba^{13}CO_3$ [3] (cf. (1) of Fig. 2). In the first case equimolar amounts were taken producing a yield of 75% for 1-bromopentane, 70% for 1-bromohexane, 60% for 1-bromoheptane and 55% for 1-bromooctane. In the latter case an excess of 30% unlabelled bromide was used and a yield of 90% for the carboxylic acid was obtained.

From the neutral fraction the corresponding bialkanes were isolated by gas chromatography (dotted lines in Fig. 1 and 2). The carboxylic acids were reduced to alcohols with $LiAlH_4$ in diethylether with 95% yields [4].

Chain lengthening by two (unlabelled) carbon atoms was obtained from the reaction of the Grignard compound of the bromides with ethylene oxide in excess (Ref. (2) of Fig. 2) [5]. The yield dropped with increasing length from 70% with bromopentane as starting material to 55% for the 1-nonylalcohols from 1-bromoheptane. The corresponding bialkanes could again be isolated. The alcohols were converted to the bromides with PBr_3 with a yield of 80% [6].

Starting from the bromides, the iodides, alkanes and alkenes were obtained (Ref.(3) of Fig. 2). The iodoalkanes were obtained with NaI in acetone. The yield after purification by gas chromatography was 65%. The reduction of the bromides with $LiH/LiAlH_4$ in THF gave the alkanes with 70% yield after gas chromatographic purification [7]. The bromide was dehydrohalogenated with dicyclohexylethylamine to the alkene with 50% yield after gas chromatographic purification [8].

3. Experimental

3.1. Carbocyclic acid. 1-Bromoalkene (24 m mol) labelled with ^{13}C and Mg-chips (26 m mol) in ether (40 ml) gave the Grignard compound, which, after dilutiom with ether (40 ml) was connected with a CO_2-generator (24 m mol $Ba^{13}CO_3$ with 50 ml H_2SO_4 conc.). The resulting solution was frozen in liq. N_2, evacuated, the CO_2 condensed on to the solution, left to react at -20° and the magnesium salt decomposed with 2n HCl (30 ml). The carboxylic acid was isolated as a Na-salt with a yield of 55-75%.

3.2. Alcohols from acid. Carboxylic acid (20 m mol) labelled with ^{13}C was dissolved in ether (30 ml) and added dropwise to a suspension of $LiAlH_4$ (22.5 m mol) in ether (20 ml) within 15 min. and then refluxed for 2.5 h.

After cooling to 0°, water was added until no further H_2- evoluement could be observed. H_2SO_4 (30 ml, 2n) added, well stirred, the organic phase separated, washed with NaOH (2n), with water and dried with $MgSO_4$. The yield after filtration and evaporation of the ether was 95%.

3.3. Chain lengthening with ethylene oxide. Alkylbromide (15 m mol) and Mg-chips (16 m mol) in ether (10 ml) gave the Grignard compound. The solution was cooled to 0° and during 4 h; ethylene oxide (60 m mol) was dissolved from the gas phase while stirring. Other methods of addition of ethylene oxide gave smaller yields. The resulting gel was then warmed, benzene (10 ml) added and approx. 8 ml ether (with small amounts of ethylene oxide) distilled off. Cooling to 0 ÷5, 1 ml water was added and the solution well stirred. The solution was dried with $MgSO_4$, filtered through a glass-sintered dish and the residue washed with benzene. Ether and benzene were distilled off the solution and the rest distilled at 15 Torr in a high-efficiency column. Yield after distillation : 55 ÷ 70%.

3.4. 1-bromoalkane. To labelled alcohol (15 m mol), cooled to 0°, PBr_3 (10 m mol) was added with stirring and heated during 2.5 h to 120-140°. The orange coloured emulsion was cooled, ether (10 ml) added and the solution filtered. $NaHCO_3$ (40 m mol) was added to the clear solution and then water was added while cooling until the bicarbonate was dissolved. After separation of the organic phase, drying with $MgSO_4$, filtration, evaporation of the ether and distillation, the yield was 80%.

3.5. 1-iodoalkane. Labelled bromoalkane (0.5 m mol), NaI (1.5 m mol) and acetone abs. (1 ml) were left react during 5 h in the dark, in a closed flask and then distilled in a closed and evacuated system. Acetone was evaporated from the distillate at room temperature and 15 Torr. The 100% yield after the reaction dropped to 65% after gas chromatographic purification.

3.6. Alkane. LiH (1.5 m mol) and $LiAlH_4$ (1.0 m mol) were added to tetrahydrofurane (THF) (0.5 ml). 1-bromoalkane (0.5 m mol) in THF abs. (0.5 ml) was added and the solution refluxed for 20 h. THF and alkane were distilled off in a closed and evacuated system and the alkane separated by gas chromatography with a 70% yield.

3.7. Alkene. A 25 cm long Pyrex-tube of 7 mm outer and 5 mm inner diameter was sealed at one end and bent to form a V. 1-Bromoalkane (1.5 m mol)

and dicyclohexylethylamine (2.25 m mol) were added and the other end of the tube also closed. The end of the inverted tube with all the substances was heated to 205° for 5 h, while the other end was cooled with water and at the end of the reaction briefly with liq. N_2 in order to collect all the olefin. The yield after gas chromatographic separation was 50%.

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