DEUTERATION OF LIDOCAINE

Alfons Hädener

Institut für Organische Chemie der Universität Basel
St. Johanns-Ring 19, CH-4056 Basel, Switzerland

SUMMARY

Stepwise deuteration of the acidic methylene group of lidocaine (1) on a large scale using a moderate excess of ^2H_2O in triethylamine/pyridine at 200° is described (Table 1). The efficient and economical preparation of bideuterated lidocaine (3) facilitates the use of this compound as an excellent internal standard in lidocaine determination or as a tracer in lidocaine pharmacokinetics.

Keywords: 2-Diethylamino-N-2,6-dimethylphenyl [2-$^2H_2$]acetamide; lidocaine-d_2; lidocaine, determination of; lidocaine, internal standard for; lidocaine, pharmacokinetics of.

INTRODUCTION

Lidocaine (2-diethylamino-N-2,6-dimethylphenyl acetamide, 1), widely used as a local anesthetic and antiarrhythmic agent [1], possesses two sites suitable for direct exchange reactions with ^2H_2O. As one would expect for "active" hydrogen sites [2], the NH proton of 1 is easily exchanged at room temperature by addition of ^2H_2O to solutions of 1, yielding 2. On the other hand, deuteration of the acidic methylene group α to the amide carbonyl group requires more vigorous conditions. Hence, a bideuterated compound 3 is expected to be stable under physiological conditions and might therefore be useful in pharmacokinetic studies [3] or alternatively as an internal standard in lidocaine quantification [4].

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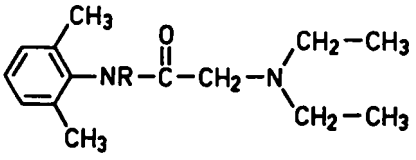

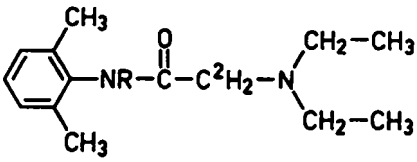

1 R = H

2 R = ^{2}H

3 R = H

4 R = ^{2}H

Bideuterated lidocaine (3) has previously been prepared by heating a mixture of 1, K_2CO_3, ^2H_2O and tetrahydrofuran at 90° for several days (Bauer et al. [3]). However, the large excess of ^2H_2O employed by these authors makes this method inappropriate for the preparation of large amounts of 3.

This paper presents a convenient and economical method for the preparation of bideuterated lidocaine (3) on a larger scale.

Results and Discussion

In order to perform the H/^{2}H-exchange reaction between 1 and ^2H_2O in homogeneous solution as well as to simplify the work-up procedure, a mixture containing 1, triethylamine, pyridine and ^2H_2O in a molar ratio of 1 : 6.0 : 9.3 : 17 was placed into a bomb tube and heated to ca. 200° for 2 h. After evaporation to dryness, the exchange reaction was repeated twice, using fresh ^2H_2O. The results of this deuteration sequence (Table 1) show that the acidic methylene group of lidocaine (1) may be deuterated nearly quantitatively in a large scale, using a moderate excess of ^2H_2O. The desired bideuterated compound 3 was isolated after shaking a solution of the crude product, which was a mixture of 4 and 3, with an excess of H_2O. Analysis of 3 using MS with chemical ionization (c.i.) and ^{13}C-NMR spectroscopy indicated that

Table 1. Stepwise deuteration of 15.5 g lidocaine (1) with ^2H_2O (20 ml in every step) in triethylamine/pyridine at 200°. Analysis was performed using the MS-signals of 1 at m/z 86-90 corresponding to the $(CH_2N(C_2H_5)_2)^+$-fragment.

Number of exchange reactions (2 h each)	1	2	3
Isotopomers containing CH_2	5.76%	0.05%	0.08%
Isotopomers containing CH^2H	35.3%	6.62%	4.44%
Isotopomers containing C^2H_2	58.9%	93.3%	95.5%
^2H-enrichment	76.6%	96.6%	97.7%

deuteration at the aromatic positions had occurred to an extent of less than 1%. In addition, no decomposition products could be detected. Nevertheless, if bideuterated lidocaine (3) prepared in this manner is designated to be used in pharmacokinetic studies, a purification including distillation in vacuo and recrystallization is recommended, in order to exclude the possibility of contamination of the preparation by minor toxic decomposition products.

Owing to the high ^2H-enrichment, no problems arise when mixtures of unlabelled lidocaine (1) and the bideuterated analog (3) are to be analysed by routine GLC/MS methods. It is sufficient to examine the ratio of intensities at m/z 86 and 88 (cf. Table 2). A reliable analysis using the M^+-signals around m/z 234 - 236 is not possible with electron impact (e.i.) ionization, because these signals are too weak and protonation/deprotonation effects occur. In order to obtain strong MH^+-signals, c.i. techniques are recommended [4].

Table 2. Mass spectra[a] of unlabelled lidocaine (1) and bideuterated lidocaine (3) from m/z 84 to 90.

m/z :	84	85	86	87	88	89	90
1 :	0.76	0.37	100	5.75	0.12	0	0
3 :	0	0	0.86	5.01	100	5.76	0.13

a) e.i., 70 eV, 100°; signal intenstities are given in % of the base peak.

In summary, the efficient and economical preparation of bideuterated lidocaine (3) facilitates the use of this compound as an ideal internal standard in lidocaine determination or as a tracer in lidocaine pharmacokinetics.

Experimental Part

Materials and methods. Lidocaine (1) was purchased from Sigma. ^2H_2O (99.8 atom % ^2H) was obtained from Ciba-Geigy Ltd., Basel. All solvents were of analytical grade. In addition, pyridine and triethylamine were refluxed over CaH_2 for 16 h, distilled and kept over molecular sieves (4 Å). Lidocaine preparations were dried in vacuo (0.02 Torr, 16 h) prior to analysis. Mass spectra were recorded on a VG 70-250 instrument using e.i. ionization at 70 eV and 100° or c.i. (isobutane) at 170-200°. The composition of deuterated lidocaine with respect to isotopomers containing a CH_2, CH^2H, or C^2H_2 group was calculated using the MS-signal-intensities between m/z 84 and 90, which were compared to those of unlabelled lidocaine (1) (cf. Table 2). Where necessary, data reduction was effected using a least-squares approximation according to Givens [5]. NMR-spectra were measured on a Bruker WH 90 instrument with Fourier transform (^1H, 90 MHz; ^{13}C, 22.63 MHz). Chemical shifts are given in ppm relative to tetramethylsilane.

2-Diethylamino-N-2,6-dimethylphenyl [2-$^2H_2$]acetamide (bideuterated lidocaine, 3). A solution of 15.5 g (66.2 mmol) lidocaine (1) in 56 ml (0.40 mol) triethylamine, 60 ml (0.74 mol) pyridine and 20 ml (1.11 mol) ^2H_2O was heated to 200° for 2 h in a sealed bomb tube, allowed to cool down to r.t., combined with 150 ml of toluene and evaporated to dryness. The residue was subjected to two additional evaporation steps from toluene (150 ml each), and finally dried in vacuo. The entire procedure was repeated twice, MS-analysis being performed after each deuteration step (cf. Table 1). The mixture of 3 and 4 thus obtained was taken up in 150 ml toluene and converted into 3 by shaking with 150 ml H_2O. The crystalline crude product, obtained after evaporation of the organic layer and additional evaporation from toluene, was distilled in vacuo (b.p. 173-175°/2 Torr) and finally recrystallized from 45 ml n-hexane, yielding 11.1 g (47.0 mmol, 71%) of bideuterated lidocaine (3), m.p. 66-67° (corr.). Calc. for $C_{14}H_{20}{}^2H_2N_2O$ (236.35): C 71.15, N 11.85%; found: C 71.01, N 11.82%. MS (e.i.): cf. Table 2; additional signals at m/z 236 (M^+), 72,60. MS (c.i., isobutane): 237 (MH^+), 88; $(MH^+{+}1)/(MH^+)$ = 0.175 ± 0.009 for 3 (0.160 ± 0.002 for 1). ^{1}H-NMR ($CDCl_3$); 1.13 (t, J=7.2, 6H, CH_3-CH_2); 2.23 (s, 6H, CH_3-ar); 2.69 (q, J=7.2, 4H, CH_2-CH_3); 7.08 (s, 3H, aromatic); 8.91 (br. s, 1H, NH; disappears after addition of ^2H_2O); no signal at 3.22 (s, CH_2) was detected. ^{13}C-NMR ($CDCl_3$): no signals due to aromatic ^{13}C-^2H were detected.

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