NOTE

Synthesis and NMR-analysis of deuterated and tritiated cyclooctyl acetic acid.

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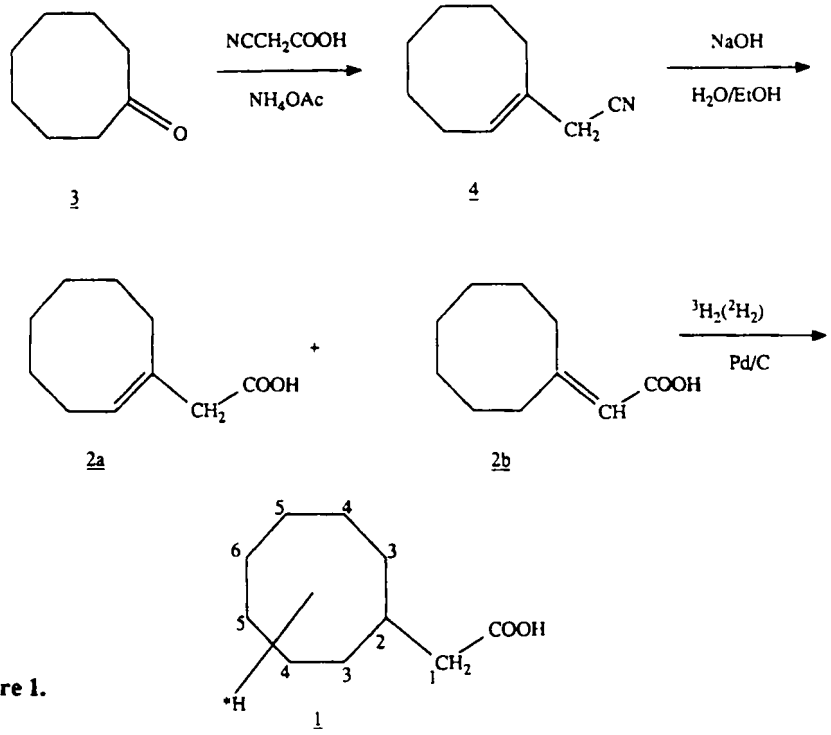
To increase the bio-availability of naturally occurring steroids, esterification of the 17-hydroxy position is a useful approach. Besides (branched) alkanecarboxylic acids[1] and cyclohexanecarboxylic acid[2] also cyclooctyl acetic acid (1) was applied. To establish the biological fate of the cyclooctyl acetic acid part of steroids the tritiated molecule was synthesized (Figure 1). Cyclooctanone (3) was condensed with cyanoacetic acid[3] and the resulting cyanide (4) was hydrolyzed to cyclooctenyl acetic acid (2a)[4] which contained according to ^1H NMR and ^{13}C NMR 20% of the isomeric 2b (^1H NMR (C^2HCl_3): 5,58 ppm (t,=CH of 2a) and 5,63 ppm (br.s=CH of 2b) ^{13}C NMR(C^2HCl_3): 129,6 ppm (=CH of 2a) and 115,0 ppm (=CH of 2b)).



3 4 2a 2b 1

Figure 1.

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Tritiation of this mixture of 2a and 2b with $^3H_2$ in ethanol with Pd/C as catalyst and subsequent purification of 1 gave a very complex ^3H NMR spectrum as illustrated in Figure 2. Similar results (Figure 2) were obtained for deuteration; mass spectrometry for the deuterated product indicated incorporation up to eight deuterium atoms.

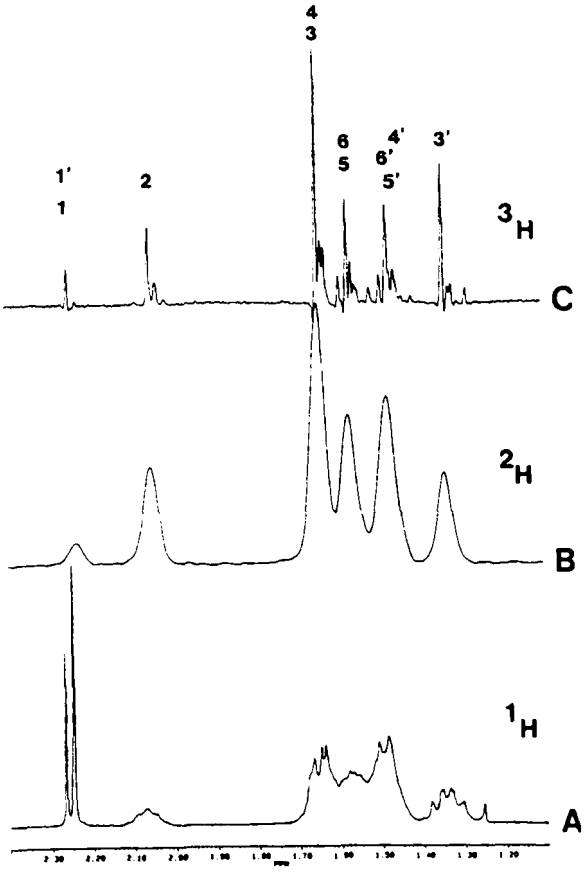

Figure 2.

NMR spectra of cyclooctyl acetic acid.

A: ^1H NMR of unlabelled material (360 MHz, C^2HCl_3)

B: ^1H-decoupled ^2H NMR spectrum (55 MHz, C^1HCl_3)

C: ^1H-decoupled ^3H NMR spectrum (384 MHz, C^2HCl_3)

Due to severe overlap of the signals an unambiguous assignment of the signals is not possible and an ^1H-^1H COSY spectrum of the unlabelled material did not clarify the situation. Also a ^3H-^3H correlation spectrum[5] (Figure 3) gave no complete assignment. The intensities of the singlets in the normal ^3H spectrum and the shape of the off-diagonal peaks in the ^3H-^3H correlation spectrum (all AX-systems) point to the predominance of mono- and ditritiated molecules, respectively.

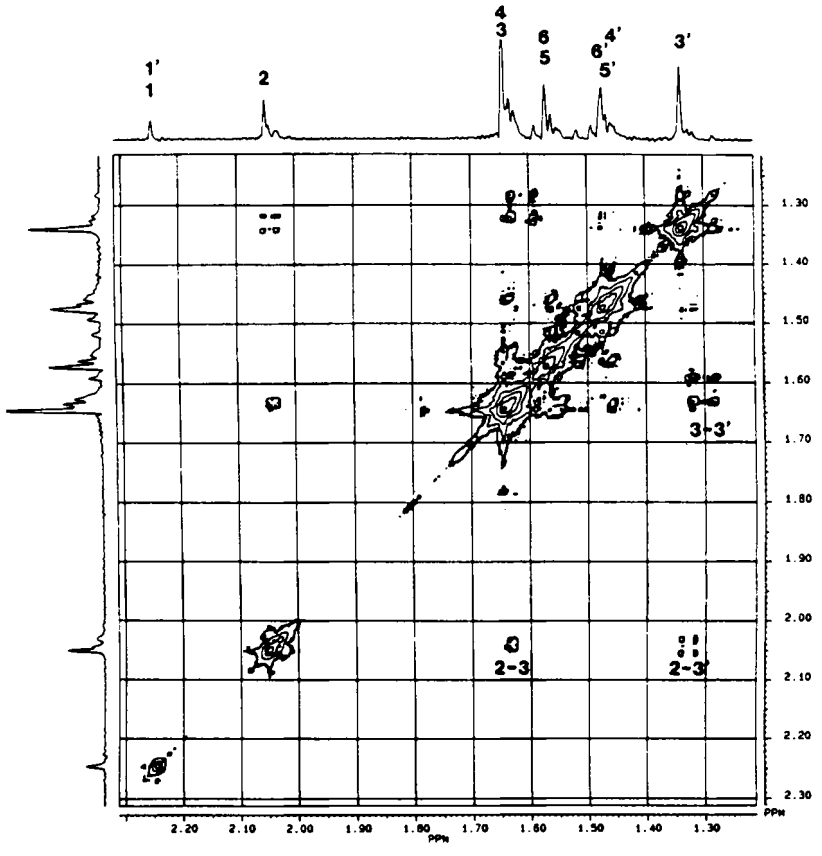

Figure 3: *^1H-decoupled[^3H-^3H]-correlation spectrum of 20 mCi of tritiated cyclooctyl acetic acid (C^2HCl_3).*

On the other hand the ^{13}C spectrum of cyclooctyl acetic acid could be assigned easily on basis of the signal intensities and chemical shifts. With a ^{13}C-^1H correlation spectrum (Figure 4) the complete assignment of the proton resonances and thus of the $^2H/^3H$-resonances was possible and complete scrambling of the label over the molecule was indicated; only no conclusion about labelling at position 6 could be obtained from these spectra.

The labelling pattern of this molecule can only partly be explained by vinylic or allylic exchange with $^3H_2$ in cyclooctenyl acetic (2). This suggests double bond isomerisation, -e.g. to position 3,4- during the interaction with Pd/C. Cyclooctyl acetic acid was -after conversion to the acid chloride- coupled to 17-hydroxy steroids and this product was used for metabolic studies[7].

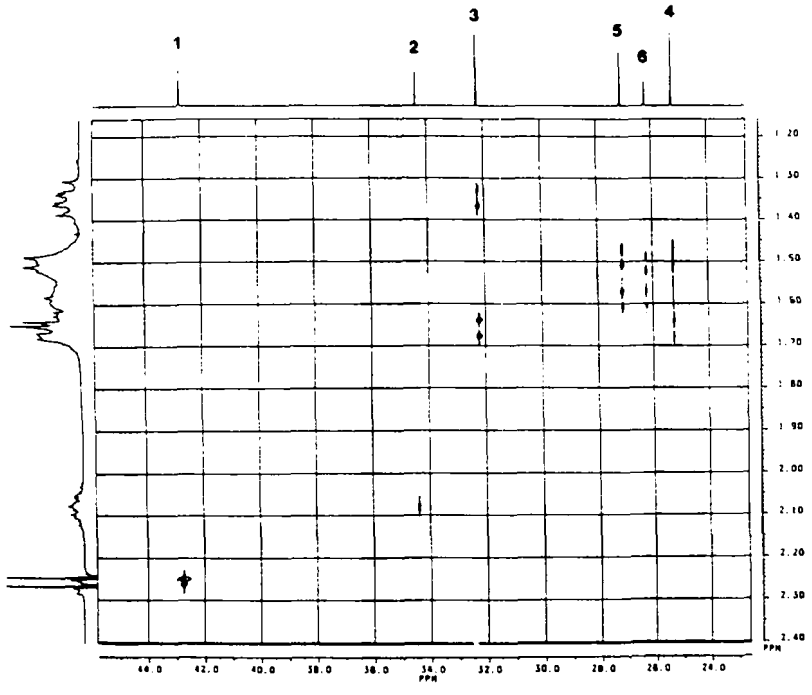

Figure 4: *^{1}H-^{13}C-correlation spectrum of cyclooctyl acetic acid (C^2HCl_3).*

References.

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