Tetrahedron. Vol 29, pp 3547 to 3551 Pergamon Press 1973 Printed in Great Britain

1,5-SHIFT OF HYDROGEN FROM CARBON TO CARBON IN THE LEAD TETRAACETATE OXIDATION OF 5,5-DIMETHYL-2-HEPTANOL†

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(*Received in the UK* 22 *March* 1973; *Accepted for publication* 25 *April* 1973)

Abstract—By using α-deuteriated substrate, it was established that in the thermal lead tetraacetate reaction (in benzene) of 5,5-dimethyl-2-heptanol (**1**) oxidation to the corresponding ketone **4** proceeds not only by way of direct elimination of the carbinol (α) hydrogen, but also, to the extent of 43·5%, by a route which involves 1,5-transfer of hydrogen from the carbinol (α) carbon atom to the ϵ-C atom.

In the lead tetraacetate oxidation of some secondary monocyclic and acyclic alcohols in non-polar solvents which afford as major products tetrahydrofuran-type ethers (Scheme 1, n = 1, VIII), it was found, by using α-deuteriated substrates,[2,3] that ketone (III) formation is not limited to direct removal of α-hydrogen, i.e. deuterium (Scheme 1, n = 1, I → II → IIIa) but occurs also, in part, by an alternative route corresponding in its first stages (Scheme 1, n = 1, I → II → IV → V) to the mechanism of cyclization to ether products (VIII), followed by intramolecular 1,4-shift of hydrogen (i.e. deuterium) from the carbinol (α) carbon atom to the electron deficient δ-carbon atom (Scheme 1, n = 1, V → VI (a or b) → VII → IIIb).[2,3] An analogous 1,5-hydrogen (i.e. deuterium) transfer to ϵ-carbon (Scheme 1, n = 2, V → VI (a or b) → VII → IIIb) could not be detected with aliphatic (open chain) alcohols,[2] but was observed only in the case of ketone formation from medium-sized secondary cycloalkanols and lead tetraacetate.[2]

Since transfer of hydrogen (as atom or hydride ion) from the carbinol (α) carbon to a remote carbon atom can occur only if the latter is electron deficient (as radical or cation), it was of interest to see if, and to what extent, in the lead tetraacetate reaction of a saturated open-chain secondary alcohol in which the δ-carbon is quaternary and which can therefore afford only tetrahydropyran-type ethers (Scheme 1, n = 2, VIII) via ϵ-carbon radicals (V, n = 2) (resulting from intramolecular homolytic 1,6-hydrogen abstraction in the corresponding alkoxy radical IV, n = 2),[4] the formation of ketone would involve 1,5-shift of hydrogen from carbon to carbon (Scheme 2, n = 2, V → VI (a or b) → VII → IIIb).

5,5-Dimethyl-2-heptanol (**1H**) and its α-deuterio derivative (**1D**) are convenient substrates of the type required, and were therefore subjected separately to the action of lead tetraacetate (molar ratio 1 : 1) in refluxing benzene in the presence of anhydrous calcium carbonate.[4,5] According to analysis of the reaction mixtures by gas chromatography combined with mass spectrometry, preparative gas chromatography and NMR spectroscopy, these oxidations afforded as major products the compounds which are given (together with yields) in Scheme 2.

The mass spectrum (Fig 1) of the ketone product **4**, obtained in 16·8% yield from **1D**, indicates that it consists of a mixture of nondeuteriated ketone **4H** (M = 142) and two monodeuterio derivatives **4De** and **4Dm** (M = 143), the intensity ratio of the molecular peaks 142 : 143 giving, after correction for ^{13}C, a percentage composition of 56·5% of **4H** and 43·5% of (**4De** + **4Dm**). The position of deuterium in, and the relative amounts of, the individual isomeric deuterio ketones **4De** and **4Dm** were deduced from the fragment ion peaks *m/e* 128, 127 and *m/e* 114, 113.

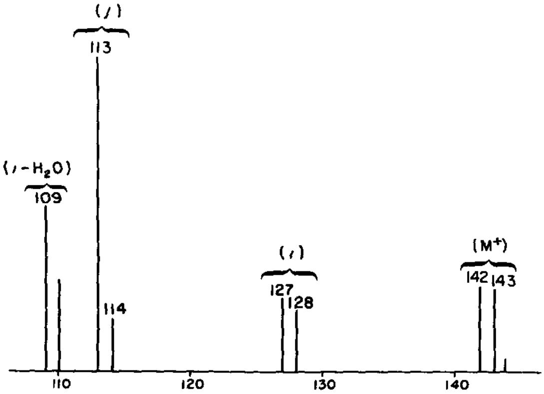

Fig 1. Part of the mass spectrum used for the analysis of the ketone mixture (**4H** + **4De** + **4Dm**) produced from alcohol **1D**

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†Paper XXVI: *Reactions with lead tetraacetate.* For communication XXV see Ref 1.

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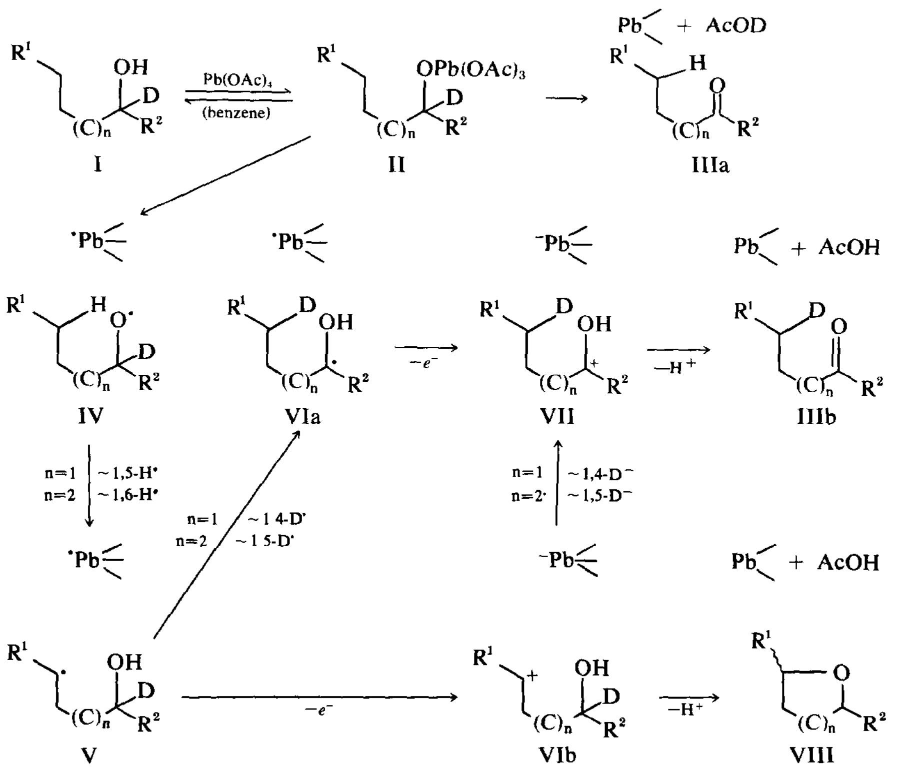

SCHEME 1

Ions *m/e* 127 and 128 (*i*) arise by elimination of a methyl radical from the respective molecular ions (M^+); on the example of 1,1,1,3,3-d_5-5,5-dimethyl-2-heptanone[*] it was found (Scheme 3) that 34% of this elimination occurs by way of α-cleavage to give ion (*i'*), and 66% by a process of δ-fragmentation to give ion (*i''*).[7] Ions *m/e* 113 and 114 (*j*) arise exclusively by δ-cleavage of the ethyl radical (Scheme 3), from the respective molecular ions (M^+). On the basis of these considerations and relative abundance ratios of mass peaks at (*i*) and at (*j*), it follows that the mixture of ketones **4** (obtained in reaction **b** from **1D**, Scheme 2) contains 35·6% of **4De** and 7·9% of **4Dm**.

Comparison of NMR spectra of ketone **4H** and ketone mixture (**4H**+**4De**+**4Dm**) confirms that the major monodeuterio ketone, formed in oxidation **b** (Scheme 2), is **4De**, with deuterium at C-6; namely, the signal at 1·23 ppm of the C-6 methylene group is weaker in the spectrum of pure **4H**, and the multiplet at 0·83 ppm of the three C-7 methyl protons (which partly overlaps with the singlet due to the six 5-Me protons) is considerably narrower in the spectrum of the ketone mixture, because of the presence of deuterium on the adjacent (C-6) carbon atom.

The relatively high percentage (43·5%) of ketones **4D** arising by 1,5-shift of deuterium from carbon to carbon (according to Scheme 1, n = 2, V → VIa or VIb → VII) in the lead tetraacetate oxidation of **1D**, when compared to the amount of ketones IIIb (Scheme 1, n = 1) formed via a similar 1,4-deuterium transfer from unbranched secondary aliphatic α-deuteriated alcohols I (2-heptanol 13%, 2-octanol 18%),[2] reflects a more favourable situation in the cyclic transition state which controls 1,5-hydrogen rearrangement.[†] This fact, namely that 1,5-shifts of hydrogen from carbon to carbon in conformationally mobile acyclic systems (in solution) occur readily and are much preferred over 1,4-shifts, has been demonstrated in a number of other cases, both in homolytic[8] and heterolytic[9] processes.

A deuterium isotope effect (which intervenes in both the direct removal of α-deuterium to give ketone IIIa and in the sequence involving 1,5-deuterium shift from carbon to carbon to afford IIIb, Scheme 1) is probably responsible for the fact that the α-deuterio alcohol **1D** produces ketone **4** in lower yield than the nondeuteriated alcohol **1H** (Scheme 2); a similar difference in the

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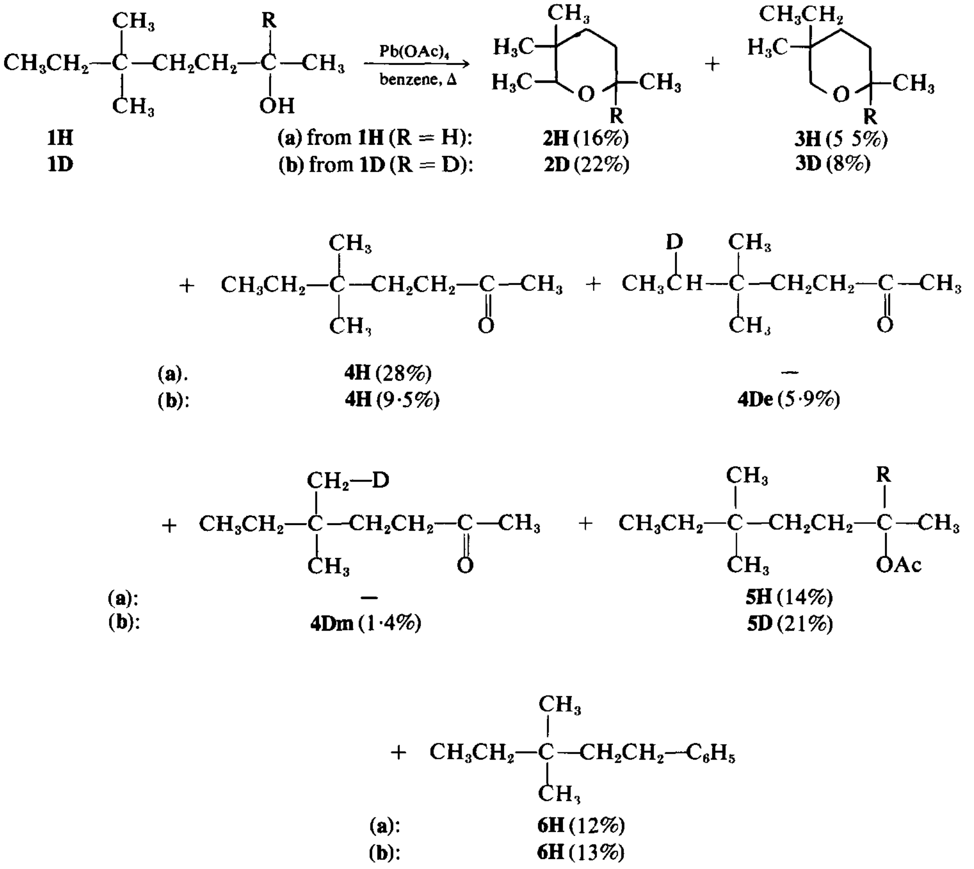
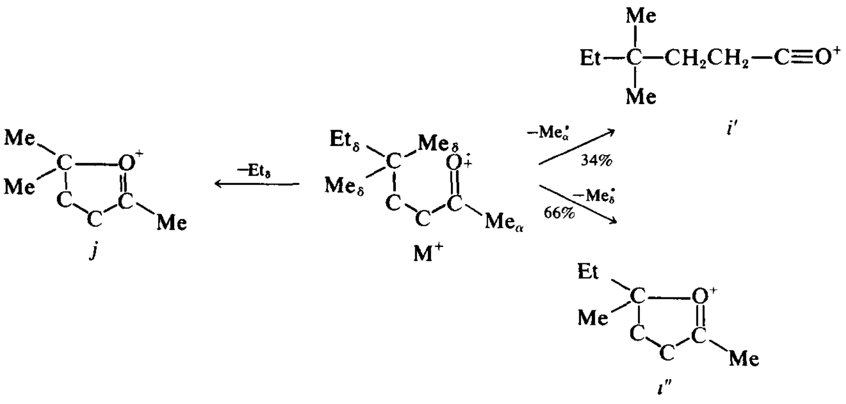
[*] Prepared by gas chromatographic α-deuteriation of 5,5-dimethyl-2-heptanone (**4H**).[6]

[†] Work is in progress in order to establish if in the lead tetraacetate oxidation (Scheme 1) of alcohols (I) to ketones (IIIb) hydrogen migrates from the carbinol (α) carbon to the remote (δ^2 or ε) electron-deficient carbon as a radical (atom) species (V → VIa) or as a hydride ion (VIb → VII).



SCHEME 2



SCHEME 3

ease of ketone formation was observed previously in the lead tetraacetate oxidation of other monocyclic and open-chain secondary alcohols.[2]

That ε-methylene hydrogens are more reactive than ε-methyl hydrogens toward intramolecular homolytic 1,6-abstraction by alkoxy radical[4] (Scheme 1, n = 2, IV → V)* was confirmed in the lead tetraacetate oxidation of **1H** and **1D**, since of the two possible six-membered cyclic ethers **2** and **3**, and the two possible monodeuterio ketones **4De** and **4Dm** (from **1D**), 2,3,3,6-tetramethyl-

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*The same is true for intramolecular homolytic 1,5-hydrogen abstraction from δ-carbon by alkoxy radicals.[5]

tetrahydro-2*H*-pyran (**2**) and 6-d_1-5,5-dimethyl-2-heptanone (**4De**), respectively, are formed in predominant amounts (Scheme 2).

The relatively high yield of 3,3-dimethyl-1-phenylpentane (**6**, Scheme 2), which results from β-fragmentation of **1** and reaction of the so formed alkyl radicals with solvent (benzene), is probably due to long reaction times (22–23 hr until disappearance of tetravalent lead), i.e. to the slow rate of the competing 1,6-hydrogen abstraction and oxidation processes (leading to cyclic ether and ketone products).

EXPERIMENTAL

Gas chromatography: preparative Varian Aerograph instrument, Model A-700 (thermistor detector), and analytical Varian Aerograph instrument, Series 1200 (flame-ionization detector). IR spectra: Perkin-Elmer Grating Spectrophotometer, Model 337. NMR spectra: Varian spectrometer A-60A (60 MHz), TMS as internal standard (chemical shifts in δ units, coupling constants J in Hz). Mass spectra: Massenspektrometer Varian MAT, Model CH-5, at 70 eV.

Starting materials. 5,5-Dimethyl-2-heptanol (**1H**) was prepared starting from t-amylmagnesium chloride and allyl bromide, which afforded 4,4-dimethyl-1-hexene;[4, 10] hydroboration[11] to 4,4-dimethyl-1-hexanol,[4, 10] followed by esterification with *p*-toluenesulphonyl chloride[12a] gave the corresponding tosylate, which was oxidized by dimethyl sulphoxide[13] to 4,4-dimethylhexanal; treatment of the crude aldehyde with methylmagnesium iodide afforded *5,5-dimethyl-2-heptanol* (**1H**), which was purified by preparative gas chromatography (20% Carbowax 20M on Chromosorb W, 60–80, 1 m × 0·6 cm, 120°); IR (film), ν_{max}: 3300 (OH), 1370 and 1360 (*gem*-diMe), 1350 (Me), 1118 (C—O) cm^{-1}; NMR (CCl_4), δ: 0·82 (s, 6H, 5-CMe_2), ~0·82 (m, 3H, 7-Me), 1·13 (d, $J = 6$, 3H, 1-Me), 3·62 (m, 1H, 2-CH—O), 2·50 (s, 1H, OH) which disappears by addition of D_2O (Found: C, 74·72; H, 13·95. $C_9H_{20}O$ requires: C, 74·93; H, 13·98%).

2-d_1-5,5-Dimethyl-2-heptanol (**1D**) was obtained by oxidation of **1H** with Jones reagent[12b] followed by reduction of the so formed 5,5-dimethyl-2-heptanone (**4H**) with LAD (Fluka, 99% D) in the usual way, and purification by gas chromatography as above. NMR (CCl_4): as for **1H** (see above), except that the signal at 1·13 δ (3H, 1-Me) is now a broad singlet and the signal for the carbinol C-2 proton at 3·62 δ has disappeared.

Lead tetraacetate reactions. The thermal LTA oxidations in benzene were carried out according to the general procedure described previously [4, 5]

Alcohol **1H** (1·40 g, 0·01 mole) was oxidized with 0·01 mole (+5% excess) LTA in 50 ml refluxing dry benzene in the presence of 0·01 mole (+10% excess) anh $CaCO_3$, until disappearance of tetravalent lead (22 hr). After the usual work up[4, 5] and removal of solvents (under normal pressure), the residue was subjected to preparative gas chromatography (20% Carbowax 20M on Chromosorb W, 2 m × 0·6 cm, 110°), whereby products **2H**, **4H**, **5H** and **6H** (Scheme 2) were isolated. The reaction mixture was also analysed by combining gas chromatography and mass spectrometry, and the yields of products obtained by analytical gas chromatography (3% Carbowax 20M on Chromosorb W, 80–100 mesh, 2 m × 0·3 cm, t = 40–200°, Δ = 6°/min) are given in Scheme 2 (reaction **a**).*

Alcohol **1D** (0·5 g, $3\cdot5 \times 10^{-3}$ mole) was oxidized with $3\cdot5 \times 10^{-3}$ mole (+5% excess) LTA in 20 ml refluxing benzene in the presence of $3\cdot5 \times 10^{-3}$ mole (+10% excess) anh $CaCO_3$, as above (23 hr), and the resulting mixture was analysed by gas chromatography and mass spectrometry. Products and their yields are given in Scheme 2 (reaction **b**).*

Reaction products†

2,3,3,6-Tetramethyltetrahydro-2H-pyran (**2H**). IR (CCl_4), ν_{max}: 1382 and 1365 (*gem*-diMe), 1377 (Me), 1110 and 1090 (C—O) cm^{-1}; NMR (CCl_4), δ: 0·81 (s, 3H) and 0·96 (s, 3H) correspond to 3-CMe_2, 1·04 (d, $J = 6\cdot7$, 3H, 2-CMe), 1·09 (d, $J = 6\cdot4$, 3H, 6-CMe), 3·48 (q, $J = 6\cdot7$, 1H, 2-CH), 3·80 (m, 1H, 6-CH); MS, *m*/*e*: 142 (M)*, 127 (M—CH_3)*, 109 [(M—CH_3)—H_2O]*, 98 (M—C_2H_4O)*, 85 (M—C_4H_9), 83 [(M—CH_3)—C_2H_4O] and [(M—C_2H_4O)—CH_3]**, 73 (M—C_5H_9)*.

2-d_1-2,3,3,6-Tetramethyltetrahydro-2H-pyran (**2D**). NMR (CCl_4), as for **2H**, except that the signal at 1·09 δ (3H, 6-CMe) is now a broad singlet and the signal at 3·80 δ (for the proton at C-6) has disappeared; MS: as above for **2H**, except that the peaks marked with (*) have a value greater by +1 and peak (**) consists of *m*/*e* 83 and 84.

5-Ethyl-2,5-dimethyltetrahydro-2H-pyran (**3H**). MS, *m*/*e*: 142 (M),* 127 (M—CH_3),* 109 [(M—CH_3)—H_2O],* 95 [(M—H_2O)—C_2H_5],* 91 (?), 83 (C_6H_{11}), 70 (C_5H_{10}), 69 (C_5H_9).

2-d_1-5-Ethyl-2,5-dimethyltetrahydro-2H-pyran (**3D**). Ms: as above for **3H**, except that peaks marked with (*) have a value greater by +1.

Both compounds **3H** and **3D** represent a mixture of *cis*- and *trans*-isomers with very close gas-chromatographic retention times.

5,5-Dimethyl-2-heptanone (**4H**). IR (film), ν_{max}: 1715 (C=O), 1380 and 1360 (*gem*-diMe), 1350 (Me) cm^{-1}; NMR (CCl_4), δ: 0·83 (s, 6H, 5-CMe_2), ~0·83 (m, 3H, 7-Me), ~1·23 (m, 2H, 6-CH_2), ~1·47 (m, 2H, 4-CH_2), 2·07 (s, 3H, 1-Me), ~2·30 (m, 2H, 3-CH_2). MS, *m*/*e*: 142 (8·8, M), 127 (7·4, M—CH_3), 113 (16, M—C_2H_5), 109 [6·6, (M—CH_3)—H_2O], 97 (1·1, 71% C_7H_{13} + 29% C_6H_9O), 95 [9·4, (M—C_2H_5)—H_2O], 84 (3·6, C_6H_{12}), 83 (1·1, C_6H_{11}), 72 (22·6, C_4H_7O), 71 (34·2, 80% C_5H_{11} + 20% C_4H_7O), 70 (9·4, C_5H_{10}), 69 (9·6, C_5H_9), 57 (6·4, 55% C_3H_5O + 45% C_4H_7), 55 (12·4, C_4H_7), 44 (3·3), *43* (*100*, 75% CH_3CO + 25% C_3H_7), 42 (3·3, 33% C_2H_2O + 67% C_3H_6), 41 (17·4, C_3H_5), 39 (6·9, C_3H_3).

5,5-Dimethyl-2-heptanone mixture (**4H + 4De + 4Dm**). IR (film) as for **4H** + a weak maximum at 2120 cm^{-1} (C—D); NMR (CCl_4): as for **4H** with small differences at 0·83 δ (narrower signal) and 1·23 δ (signal of weaker intensity), discussed on p. 5; MS, *m*/*e*: 143 (3·2), 142 (3·4), 128 (2·5), 127 (2·9), 114 (2·0), 113 (11·9), 110 (3·4), 109 (6·5), 98 (0·5), 97 (0·8), 96 (2·1), 95 (12·8), 85 (1·9), 84 (2·5), 83 (0·9), 73 (7·8), 72 (36·9), 71 (26·1), 70 (7·7), 69 (7·4), 68 (2·3), 58 (2·0), 57 (7·1), 56 (3·2), 55 (7·8), 53 (1·4), 45 (1·0), 44 (10·1), *43* (*100*), 42 (3·4), 41 (10·7), 40 (1·1), 39 (3·0). (The peaks corresponding to

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*Products **3H** (from **1H**), **3D** and **5D** (from **1D**) were only characterized by gas chromatography-mass spectrometry combination.

†Except for ketones **4H** and (**4H + 4De + 4Dm**), only selected MS fragment peaks are given for the reaction products.

those in the MS of **4H**, given above, are due to the same fragments, and those with a + 1 value to the respective deuterium containing fragments; see also Fig 1).

5,5-*Dimethyl-2-heptyl acetate* (**5H**). IR (CCl_4), ν_{max}: 1730 (acetate C=O), 1360 (Me), 1237 (acetate C—O) cm^{-1}; NMR (CCl_4), δ: 0 85 (s, 6H, 5-CMe_2), ~0·85 (m, 3H, 7-Me), 1·18 (d, $J = 6·3$, 3H, 1-Me), 1·97 (s, 3H, AcO), 4·78 (sext, $J = 6·3$, 1H, 2-CH—O); MS, *m/e*: 157 ($M—C_2H_5$),* 127 ($M—CH_3COO$),* 126 ($M—CH_3COOH$),* 116 ($M—C_5H_{10}$),* 115 ($M—C_5H_{11}$),* 111 [($M—CH_3COOH$)—CH_3],* 97 [($M—CH_3COOH$)—C_2H_5],* 87 ($C_4H_7O_2$),* 84 (C_6H_{12}), 83 (C_6H_{11}), 71 (C_5H_{11}), 70 (C_5H_{10}), 69 (C_5H_9).

In the mass spectrum of 2-d_1-5,5-*dimethyl-2-heptyl acetate* (**5D**) the peaks of **5H** marked with (*) have a value greater by + 1.

3,3-*Dimethyl*-1-*phenylpentane* (**6H**). IR (CCl_4), ν_{max}: 3075, 3055, 3020, 1592, 1480, 1450, 714 and 698 (all due to the benzene ring), 1378 and 1370 (*gem*-diMe), 1358 (Me) cm^{-1}; NMR (CCl_4), δ: ~0·87, (m, 3H, 5-Me), 0·90 (s, 6H, 3-CMe_2), 2 51 (m, 2H, 1-CH_2 benzylic), 7 11 (s, 5H, C_6H_5), 1·1–1·7 (complex signals for two CH_2); MS, *m/e*: 176 (M), 161 ($M—CH_3$), 147 ($M—C_2H_5$), 105 ($M—C_5H_{11}$), 91 (C_7H_7), 65 ($C_7H_7—C_2H_2$).

Acknowledgement—The authors are grateful to the Serbian Republic Research Fund for financial support.

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