THE SYNTHESIS OF FOUR SPECIFICALLY DEUTERATED *trans*-4-OCTENES

G. John Shaw
Applied Biochemistry Division, Department of Scientific and Industrial Research, Palmerston North, New Zealand.

SUMMARY

trans-4-Octene-1,1,1-$^2H_3$; -2,2-$^2H_2$; -3,3-$^2H_2$ and -4-$^2H_1$ have been synthesised. The electron impact mass spectra and isotopic enrichment of these compounds have been measured and are reported.

Key Words: *trans*-4-octene-1,1,1-$^2H_3$, *trans*-4-octene-2,2-$^2H_2$, *trans*-4-octene-3,3-$^2H_2$, *trans*-4-octene-4-$^2H_1$, deuterium, mass spectra.

INTRODUCTION

The mass spectra of isomeric alkenes exhibit many similar features[1]. Under electron impact ionization conditions it has been assumed that facile migration of the radical site with accompanying hydrogen rearrangement in the molecular ion species leads to an equilibrium between the various double bond isomers[2]. Recently[3] it has been shown that molecular ion species of 1-, 2-, 3- and 4-octene undergo complete and facile isomerisation to a mixture of interconverting structures prior to decomposition. While the exact mode of such rearrangements still remains obscure the possibility of 1,3 hydrogen shifts has been advanced to explain these observations. However other hydrogen transfer mechanisms can not be ruled out at this time.

In an attempt to rationalise the mass spectrometric behaviour of this class of compounds in more detail the convenient synthesis of four specifically deuterated *trans*-4-octenes was undertaken and is reported here.

RESULTS AND DISCUSSION

Recent work[4] on the facile decarboxylation of geminal diesters via nucleo-

0362-4803/81/111641-08$01.00

Received October 28, 1980
Revised January 28, 1981

philic attack formed the basis of the synthetic route (Scheme 1) leading to *trans*-4-octene-1,1,1-$^2H_3$ (6). Thus the allylic chloride, 2, was prepared from the allylic alcohol (1) under mild conditions using triphenylphosphine in CCl_4[5]. A malonate chain extension of 2 with sodium dimethylmalonate via an S_N2 reaction gave dimethyl *trans*-2-hexenylmalonate (3). Decarboxylation of the geminal diester with NaCl in wet DMSO gave methyl *trans*-4-octenoate (4) in good yield. Reduction using lithium aluminium deuteride (LAD) in refluxing ether afforded 5. Treatment of dideutero alcohol with tosyl chloride in pyridine at 0°C provided the corresponding toxylate which, without purification, was converted to 6 by reduction with LAD in ether.

$$\underset{1}{RCH{=}CH_2OH} \xrightarrow{i} \underset{2}{RCH{=}CH_2Cl} \xrightarrow{ii} \underset{3}{RCH{=}CHCH_2CH(COOCH_3)_2} \xrightarrow{iii}$$

$$\underset{4}{RCH{=}CH(CH_2)_2COOCH_3} \xrightarrow{iv} \underset{5}{RCH{=}CH(CH_2)_2C^2H_2OH} \xrightarrow{v}$$

$$\underset{6}{RCH{=}CH(CH_2)_2C^2H_3}$$

Scheme 1. R=-$(CH_2)_2CH_3$. (*i*) $\emptyset_3P/CCl_4$ (*ii*) $Na^{+-}CH(COOMe)_2$ (*iii*) NaCl/DMSO (*iv*) LAD (*v*)(a) TsCl (b) LAD

The trans configuration of 6 as with all other products was confirmed by a strong absorption band at 965 cm^{-1} in the IR spectrum. In the 70eV electron impact mass spectrum of 6 the molecular ion was observed at m/z 115 with minor ions at m/z 100 ($M-CH_3$) and m/z 97 ($M-C^2H_3$). The more common allylic cleavage gave rise to prominent ions at m/z 86 and m/z 83 while McLafferty rearrangement ions were discernable at m/z 87 and m/z 85. Isotopic enrichment analysis (see experimental) revealed that 96.3% of the product was trideuterated.

trans-3-Heptenoic acid (7) a convenient starting point leading to *trans*-4-octene-2,2-$^2H_2$ (10) was prepared via a Knoevenagel condensation of pentanal and malonic acid in the presence of triethanolamine[7] (Scheme 2). Reduction of 7 with LAD gave *trans*-hept-3-en-1-ol-1,1-$^2H_2$ (8) which was subsequently transformed into the corresponding alkenyl iodide (9) with triphenylphosphite methiodide. Treatment of 9 with excess lithium dimethylcuprate afforded *trans*-4-octene-2,2-$^2H_2$ (10) in good yield.

$$RCH_2CHO + CH_2(COOH)_2 \xrightarrow{vi} \underset{\underline{7}}{RCH{=}CHCH_2COOH} \xrightarrow{vii}$$

$$\underset{\underline{8}}{RCH{=}CHCH_2C^2H_2OH} \xrightarrow{viii} \underset{\underline{9}}{RCH{=}CHCH_2C^2H_2I} \xrightarrow{ix} \underset{\underline{10}}{RCH{=}CHCH_2C^2H_2CH_3}$$

Scheme 2. R=-$(CH_2)_2CH_3$. (*vi*) Et_3N (*vii*) LAD (*viii*) $\emptyset_3P$(MeI) (*ix*) Me_2LiCu

The mass spectrum revealed a molecular ion at m/z 114. Other diagnostic ions were observed at m/z 85 ($M-C_2H_5$), m/z 83 ($M-CH_3C^2H_2$), m/z 86 ($M-C_2H_4$) and m/z 84 ($M-CH_2C^2H_2$). This fragmentation pattern is consistent with two deuterium atoms on carbon 2 of *trans*-4-octene. Isotopic analysis showed that 97.6% of the product was dideuterated.

Synthesis of *trans*-4-octene-3,3^2H_2 (12) was undertaken via a carefully controlled Wittig reaction (Scheme 3). Accordingly n-butyltriphenylphosphonium bromide (11), prepared from butyl bromide and triphenylphosphine, was converted to the corresponding phosphorus ylide with n-butyllithium. Condensation with butyraldehyde-2,2-$^2H_2$ yielded 12. The mass spectrum which showed a molecular

$$RCH_2Br \xrightarrow{x} \underset{\underline{11}}{RCH_2P^+(C_6H_5)_3Br^-} \xrightarrow{xi} \underset{\underline{12}}{RCH{=}CHC^2H_2CH_2CH_3}$$

Scheme 3. R=-$(CH_2)_2CH_3$. (*x*) $\emptyset_3P$ (*xi*) $CH_3CH_2C^2H_2CHO$

ion at m/z 114, consistent with the introduction of two deuterium atoms. However unlike the mass spectrum for 10, neither the allylic cleavage ion at m/z 85 nor the McLafferty rearrangement ion at m/z 86 is accompanied by loss of deuterium. Isotopic analysis gave 96% of the product as being dideuterated.

trans-4-Octene-4-$^2H_1$ (14) was readily prepared (Scheme 4) by reduction of 4-octyne (13) with LAD in THF-diglyme under nitrogen[8]. The purified product gave a mass spectrum with a molecular ion at m/z 113. The product proved to be 98.8% monodeuterated.

$$\underset{\underline{13}}{CH_3(CH_2)_2CH{\equiv}CH(CH_2)_2CH_3} \xrightarrow{xii} \underset{\underline{14}}{CH_3(CH_2)_2CH{=}C^2H_1(CH_2)_2CH_3}$$

Scheme 4. (*xii*) LAD.

EXPERIMENTAL APPROACH

Low resolution and high resolution electron impact mass spectra were recorded using AEI MS30 and AEI MS9 mass spectrometers, respectively.

Precise isotopic enrichments were calculated from the electron impact ionization mass spectra using the "LAB" option of the Mass Spectral Search System, a component of the Chemical Information System[9].

trans-1-Chloro-2-hexene (2) -- To a solution of triphenylphosphine (26.2g) in carbon tetrachloride (40 ml) was added 1 (9.5g). After stirring at r.t. for 64 hr the mixture was filtered and concentrated to an oil *in vacuo*[5]. Distillation gave 2 (10.4g), b.p. 128-129°C, lit.[10] 131-133°C. MS m/z (rel. abundance) : 118 (M^+; 18), 91 (3), 83 (28), 82 (28), 69 (37), 67 (37), 56 (37), 55 (71), 54 (26), 53 (41), 43 (25), 42 (71), 41 (100).

Dimethyl *trans*-2-Hexenylmalonate (3) -- To a stirred solution of freshly prepared sodium methoxide (1 equiv.) and dimethylmalonate (2.55g) in methanol (50 ml) was added 2 (2.25g). The reaction mixture was refluxed for 2 hr, filtered and concentrated *in vacuo*. Vacuum distillation of the oil gave 3 (3g), b.p. 67-69°C (20 mm Hg). MS m/z 214.1237 (M^+; calculated for $C_{11}H_{18}O_4$, 214.1205). MS m/z (rel. abundance) : 214 (4), 154 (34), 151 (34), 132 (99), 110 (100), 100 (40), 95 (48), 82 (41), 81 (29), 67 (47), 59 (43), 55 (57), 41 (60).

Methyl *trans*-4-Octenoate (4) -- To a stirred mixture of sodium chloride (7.75mg) in water (0.74 ml) and dimethyl sulfoxide (8 ml) was added 3 (2.3g). The reaction mixture was slowly heated to 155°C over 45 min and held at that temperature until all carbon dioxide evolution had ceased (2.5 hr)[4]. The product was extracted two times with 50 ml portions of ether. The ether extracts were washed with water, dried (Na_2SO_4) and filtered. Evaporation of the ether and vacuum distillation of the oil afforded 4 (1.5g), b.p. 37°C (1.2 mm Hg). Mass spectrum m/z (rel. abundance) : 156 (M^+; 14), 125 (21), 124 (36), 96 (40), 85 (30), 83 (32), 82 (64), 74 (100), 67 (47), 55 (77), 54 (28), 43 (49), 41 (59).

trans-4-Octen-1-ol-1,1-$^2H_2$ (5) -- A solution of 4 (10g) in 30 ml ether was added dropwise to LAD (3.6g, 98 atom %D) in ether (50 ml) and refluxed for 5 hr. Excess reagent was destroyed with water and the ether layer was separated. Distillation gave 6.9 g of 5, b.p. 93-95°C (17 mm Hg), lit.[11] 95°C (17 mm Hg). Mass spectrum m/z (rel. abundance) : 130 (M^+; 2), 113 (22), 97 (16), 83 (100),

70 (58), 69 (50), 56 (40), 55 (95), 41 (84).

trans-4-Octene-1,1,1-$^2H_3$ (6) -- To a solution of 5 (1g) in dry pyridine (40 ml) at 0°C was added tosyl chloride (8g) and then stirred for 12 hr. The reaction was poured onto ice and extracted twice with cold chloroform. The chloroform extracts were washed with water, dried (Na_2SO_4) and evaporated to dryness. The crude tosylate (2g) was added to a stirred suspension of LAD (0.45 g) 99 atom %D) in dry ether (30 ml) and gently refluxed for 24 hr. The excess LAD was hydrolysed with water and the product extracted with ether. Distillation of the resulting oil afforded 6 (0.6 g), b.p. 120-122°C, lit.[21] 121.4°C (739 mm Hg). ν_{max}^{film} cm^{-1} : 965. Mass spectrum m/z (rel. abundance) : 115 (M^+; 43), 86 (22), 83 (23), 73 (39), 72 (28), 70 (39), 69 (30), 59 (37), 58 (39), 57 (45), 56 (60), 55 (94), 43 (41), 42 (42), 41 (100). Isotopically labelled species (mole percent) : $^2H_3$ = 96.4%, $^2H_2$ = 3.6%.

trans-3-Heptenoic Acid (7) -- A cooled mixture of pentanal (33.1g), malonic acid (46.4g) and triethanolamine (56.6g) was stirred until homogenous and then heated on a steam bath until CO_2 evolution ceased (2 hr). The reaction was cooled, acidified with dilute H_2SO_4 and extracted with ether. Distillation gave 22.6 g of 7, b.p. 71.5°C (0.9 mm Hg), lit.[12] 69.9°C (1 mm Hg). Mass spectrum m/z (rel. abundance) : 128 (M^+; 5), 110 (55), 69 (75), 68 (100), 57 (40), 55 (63), 43 (35), 41 (63).

trans-3-Hepten-1-ol-1,1-$^2H_2$ (8) -- A solution of 7 (10g) in 20 ml ether was added dropwise to LAD (3.45g, 98 atom %D) in ether (50 ml), and refluxed for 5 hr. Excess reagent was destroyed with water and the ether layer was separated. Distillation gave 8.25 g of 8, b.p. 79-81°C (19 mm Hg), lit.[13] 81-83°C (19 mm Hg). Mass spectrum m/z (rel. abundance) : 116 (M^+; 3), 98 (20), 83 (37), 69 (60), 60 (30), 59 (100), 41 (58).

Triphenylphosphite methiodide -- A solution of triphenylphosphite (31g) in methyl iodide (21g) was refluxed for 24 hr. The reaction was cooled and diluted with dry ether. The crystalline solid (40g) was filtered, washed with ether and stored under vacuum until required[14].

trans-1-Iodo-3-heptene-1,1-$^2H_2$ (9) -- A solution of 8 (7.5g) and triphenylphosphite methiodide (30g) was stirred at r.t. for 14 hr. Both 9 and the

by-product phenol, were distilled (40-50°C, 2.6 mm Hg) directly from the reaction, diluted with ether and washed with cold dilute NaOH[14]. Redistillation gave 9.1 g of 9, b.p. 45.5°C (2.7 mm Hg). Mass spectrum m/z (rel. abundance) : 226 (M^+; 2), 99 (100), 69 (14), 57 (56), 56 (48), 55 (38), 43 (14), 42 (10), 41 (16).

trans-4-Octene-2,2-$^2H_2$ (10) -- Lithium dimethylcuprate was prepared immediately prior to use by adding 2 equivalents of freshly prepared[15] MeLi (120 mmol[16]) to 1 equiv. Cu(I)I[17] (10.5g) in ether at 0°C according to the procedure of Whitesides *et al.*[18]. To this stirred pale tan suspension was immediately added 4.2 g of 9. The reaction was allowed to rise to r.t. and after 4 hr was quenched with a saturated solution of NH_4Cl. After the ethereal solution had been washed with aqueous NaCl, dried and concentrated, distillation of the residual liquid gave 10 (1.8g), b.p. 120-122°C, lit.[21] 121.4°C (739 mm Hg). ν_{max}^{film} cm^{-1} : 965. Mass spectrum m/z (rel. abundance) : 114 (M^+; 64), 85 (34), 83 (18), 72 (19), 71 (31), 70 (21), 69 (25), 57 (77), 56 (100), 55 (43), 43 (72), 42 (80), 41 (90). Isotopically labelled species (mole percent) : $^2H_2$ = 97.6%, $^2H_1$ = 2.4%.

n-Butyltriphenylphosphonium Bromide (11) -- A mixture of butyl bromide (5.3g) and triphenylphosphine (19g) in 25 ml of toluene was refluxed for 10 hr, cooled, filtered and dried to give 13.5 g of 11, m.p. 238-240°C, lit.[20] 240-241°C.

trans-4-Octene-3,3-$^2H_2$ (12) -- To a stirred suspension of 11, (4.5g) in 50 ml benzene was added 11.4 mmoles of n-butyllithium in hexane under nitrogen. After 20 min butyraldehyde-2,2-$^2H_2$ (1.0g, 98 atom %D)[19] was added dropwise. After stirring for a further 12 hr the mixture was filtered and concentrated *in vacuo*. Distillation of the resulting oil gave 0.83 g of 12, b.p. 120-122°C, lit.[21] 121.4°C (739 mm Hg). ν_{max}^{film} cm^{-1} : 965. Mass spectrum m/z (rel. abundance) : 114 (M^+; 43), 85 (40), 72 (33), 71 (42), 70 (26), 69 (22), 58 (38), 57 (87), 56 (100), 55 (39), 43 (55), 42 (72), 41 (51). Isotopically labelled species (mole percent) : $^2H_2$ = 96%, $^2H_1$ = 4%.

trans-4-Octene-4-$^2H_1$ (14) -- To a filtered solution of approx. 1.4 g LAD (99 atom %D) in 50 ml THF and 50 ml diglyme was added 2.75 g of 4-octyne (13)[8]. The solution was refluxed for 10 hr and the excess LAD was hydrolysed with

water. The slurry was extracted with ether and the product was worked up in the usual manner. Distillation gave 2.6 g of 14, b.p.120-122°C, lit.[21] 121.4°C (739 mm Hg). Mass spectrum m/z (rel. abundance) : 113 (M^+; 39), 84 (35), 73 (13), 72 (14), 71 (40), 70 (37), 59 (22), 57 (39), 56 (100), 55 (57), 45 (30), 43 (22), 42 (74), 41 (48). Isotopically labelled species (mole percent) : $^2H_1$ = 98.8%, $^2H_0$ = 1.2%.

REFERENCES

1. Budzikiewics H., Djerassi C. and Williams D.H. - Mass Spectrometry of Organic Compounds, Holden-Day, San Francisco, California, 1967, p.55.
2. See for example, Millard B.J. and Shaw D.F. - J. Chem. Soc. B 664 (1966).
3. Borchers F., Levsen K., Schwarz H., Wesdemiotis C. and Winkler H.U. - J. Amer. Chem. Soc. 99: 6359 (1977).
4. Krapcho A.P. and Lovey A.J. - Tetrahedron Lett. 959 (1973).
5. (a) Downie I.M., Holmes B.J. and Lee J.B. - Chem. Ind. 900 (1966).
   (b) Lee J.B. - J. Amer. Chem. Soc. 88: 3440 (1966).
6. (a) Bellamy L.J. - Advances in Infrared Group Frequencies, Methnen, London, 1966.
   (b) Bellamy L.J. - Infrared Spectra of Complex Molecules (2nd Edition), Methnen, London, 1958.
   (c) Pouchert C.J. - The Aldrich Library of Infrared Spectra, Aldrich Chem. Co., 1970.
7. Boxer S.E. and Linstead R.P. - J. Chem. Soc. 740 (1931).
8. Magoon E.F. and Slaugh L.H. - Tetrahedron 23: 4509 (1967).
9. The CIS was accessed using the Telenet Global Computer Network. For further details contact G.W.A. Milne, Laboratory of Chemistry, National Heart, Lung, and Blood Institute, N.I.H., Bethesda, MD 20014, USA.
10. Smets G. - Chem. Abstr. 44: 8315 (1950).
11. Riobe R. - Compt. Rend 225: 334 (1947).
12. Morton A.A., Marsh F.D., Coombs R.D., Lyons A.L., Penner S.E., Ramsden H.E., Baker V.B., Little E.L. and Letsinger R.L. - J. Amer. Chem. Soc. 72: 3785 (1950).
13. Crombie L. - J. Chem. Soc. 4338 (1952).

14. Landauer S.R. and Rydon H.N. - J. Chem. Soc. 2224 (1953).

15. Schollkopf U., Paust J. and Patsch M.R. - Org. Syntheses Coll. Vol. 5: 859 (1973).

16. Voskuil W. and Arens J.F. - Org. Syntheses Coll. Vol. 5: 211 (1973).

17. Kirschner S. - Inorg. Syn. 6: 3 (1960).

18. Whitesides G.M., Fischer W.F., San Filippo J., Bashe R.W. and House H.O. - J. Amer. Chem. Soc. 91: 4871 (1969).

19. Merck Sharp and Dohme, Canada Ltd, Isotope Division, Pointe Claire, Quebec, Canada.

20. Schlosser M. - Chem. Ber. 97: 3219 (1964).

21. Pollock J.R.A. and Stevens R. - Dictionary of Organic Compounds, Eyre and Spottiswoode Publishers Ltd, London, 1965.