SYNTHESIS OF DI-, TETRA-, AND HEXADEUTERATED 11-OCTADECENOATES

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Received February 21, 1978

SUMMARY

Methyl esters of 11-octadecenoic-15,16-d_2, -15,15,16,16-d_4, and -10,10,15,15,16,16-d_6 acids were prepared by Wittig synthesis from intermediates derived from 11-bromoundecanoic acid and 7-chloro-3-heptyne. The dideuterated acid was prepared by partial hydrogenation of the heptyne followed by saturation with deuterium to 1-chloroheptane-4,5-d_2 for Wittig synthesis. Saturation of the heptyne with deuterium provided the Wittig intermediate for tetradeuterated acids. The hexadeuterated acids were prepared from tetradeuterated alkyl halide and 10-formyldecanoate-10,10-d_2.

Key words: Methyl *cis*-11-octadecenoate-15,16-d_2, Methyl *trans*-11-octadecenoate-15,15,16,16-d_4, Methyl *cis*-11-octadecenoate-10,10,15,15,16,16-d_6, Deuterated Fatty Acids, Deuterium.

INTRODUCTION

For studies of the metabolism in humans of *cis*- and *trans*-octadecenoic acids, a series of deuterium-labelled geometrical and positional isomers was required. One of these metabolic studies (1) involved pulsed simultaneous feeding of oleate-d_4 and elaidate-d_2 to a young male adult and subsequent periodic removal of blood samples over 48 hr. The blood samples were first fractionated into plasma and red blood cells and then further fractionated. The subfractions were analyzed for deuterium-labeled fatty acids to determine their distribution. Thus, the human metabolism of two fatty acid isomers has been simultaneously compared for the first time. Further studies involving simultaneous feeding of three labeled octadecenoates are in progress.

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0362-4803/78/0015-0451$01.00

Other reports from this laboratory described the preparation of 9-octadecenoates-d_4 and d_6 (2), 12-octadecenoates-d_2, -d_4, and -d_6 (3), and 8- and 13-octadecenoates-d_2 and -d_4 (4). The present report describes syntheses of deuterated 11-octadecenoates.

DISCUSSION

11-Octadecenoic acid was first prepared by Ahmad, Bumpus, and Strong (5) from 11-octadecynoic acid. Catalytic hydrogenation provided the *cis*-isomer, whereas the *trans*-isomer was obtained from the *cis*-isomer by isomerization. The same acetylenic intermediate was used in later syntheses by Huber (6), Gunstone and Ismail (7) and Barve and Gunstone (8). The acid was also synthesized by a Wittig procedure (9) such as was used here.

The preparation of methyl 11-octadecenoate-15,16-d_2, *1*, is outlined in Figure 1. Lindlar reduction of 7-chloro-3-heptyne, *2*, gave 7-chloro-

Figure 1

$$Cl(CH_2)_3C{\equiv}CCH_2CH_3 \xrightarrow[\text{Lindlar}]{H_2} Cl(CH_2)_3CH{=}CHCH_2CH_3 \xrightarrow[RhCl(Ph_3P)_3]{D_2}$$

2 3

$$Cl(CH_2)_3(CHD)_2CH_2CH_3 \xrightarrow[\text{b. } Ph_3P]{\text{a. NaI}} Ph_3P^+(CH_2)_3(CHD)_2CH_2CH_3I^-$$

4 5

$$\xrightarrow[\text{b. } OHC(CH_2)_9CO_2CH_3]{\text{a. } NaOCH_3} CH_3CH_2(CHD)_2(CH_2)_2CH{=}CH(CH_2)_9CO_2CH_3$$

1

cis-3-heptene, *3*, which was saturated with deuterium using Wilkinson's catalyst (10) to furnish 1-chloroheptane-4,5-d_2, *4*. Without isolation of the intermediate iodide, *4* was converted to the corresponding triphenylphosphonium iodide, *5*. *Cis/trans*-1 was prepared from *5* by Wittig reaction with methyl 10-formyldecanoate, *6*. Pure *cis*-1 was separated by silver-ion column chromatography (11) in a yield of 34% with isotopic purity of 97.5%. Table 1 shows the deuterium distribution.

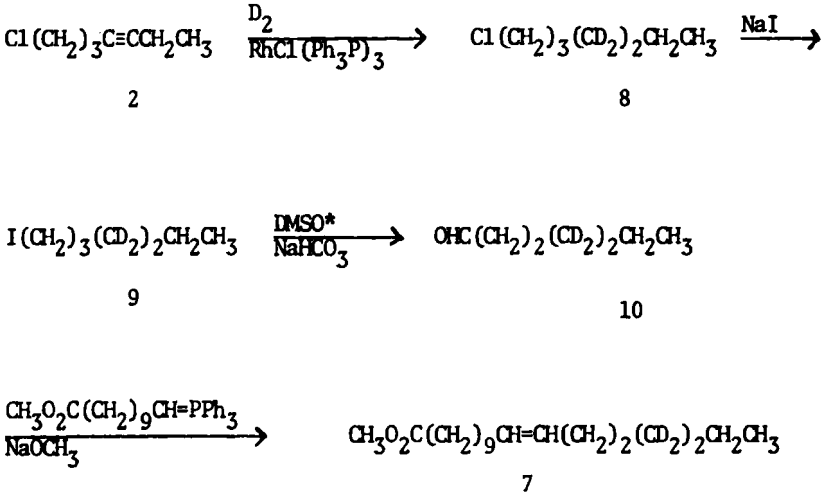
TABLE I: Deuterium Analyses of 11-Octadecenoates

	Number of Deuterium Atoms[1]									
Substance	0	1	2	3	4	5	6	7	8	Avg. per molecule
Methyl *cis*-11-octadecenoate-d_2	2.6	4.3	89.3	3.2	0.3	0.2				1.95
Methyl *trans*-11-octadecenoate-d_4	4.3	1.5	2.9	4.4	82.7	3.5	0.6			3.7
Methyl *cis*-11-octadecenoate-d_6	0.7	0.9	2.2	2.4	3.2	16.1	70.7	3.3	0.5	5.6

[1] Figures in table below number of deuteriums 0-8 are in percent.

Methyl 11-octadecenoate-15,15,16,16-d_4, *7*, was prepared as indicated in Figure 2. Saturation of *2* with deuterium using Wilkinson's catalyst gave 1-chloroheptane-4,4,5,5-d_4, *8*, which, refluxed with NaI, yielded the corresponding iodide, *9*. Oxidation of *9* according to Johnson and Pelter (12) gave *10*, heptanal-4,4,5,5-d_4. Wittig reaction of *10* with 10-carbomethoxydecanylidene triphenylphosphorane gave *7* in 63% yield as a mixture containing 91% *cis* and 9% *trans*. *Cis*-7 was isomerized by standard procedure (13) and the *trans*-isomer was separated by silver-ion column chromatography.

Figure 2



2 8 9 10 7

* DMSO = Dimethyl sulfoxide

Synthesis of methyl 11-octadecenoate-10,10,15,15,16,16-d_6, *11*, was accomplished by Wittig condensation of methyl 10-formyldecanoate-10,10-d_2, *12*, with the triphenylphosphonium iodide from *9*. Yield of *11* was 63%, with 93% isotopic purity. The *cis*-isomer was isolated by silver-ion column chromatography.

The procedure of introducing deuterium by reduction of an alkynyl or alkenyl chloride using Wilkinson's catalyst is a convenient means of labeling a Wittig intermediate. This was used to prepare all of the deuterated 11-octadecenoates reported here. Some deuterium scattering does occur as is evident in the first two octadecenoates in Table 1. For a discussion of deuterium scattering and its relation to isomerization with this catalyst, see the chapter in McQuillin's book (14). The deuterium scattering we have encountered upon deuteration of unsaturated chlorides, such as were used here and previously (2), was minor. Mass analysis for deuterium in alkyl halides has not proved reliable, so we

have only the analyses of the deuterated octadecenoates to determine the scatter. Deuterium exchange in the Wittig reaction is inconsequential when the aldehyde moiety does not contain α-deuterium and may be avoided even then by use of t-butyllithium and tetrahydrofuran solvent.

The scatter of the hexadeuterated octadecenoate (Table 1) is greater than that of the other octadecenoates because it has the product scatter of two deuterated components to the Wittig reaction. Mass analysis of *12*, the deuterated aldehyde, proved unreliable due to memory effect; but NMR showed a singlet for the aldehyde proton rather than a triplet expected for an aldehyde with α-protons. Deuterium exchange of aldehydes is a low-yield, slow process and is wasteful of deuterium (15).

EXPERIMENTAL

Instruments--Determinations were made using the following equipment as indicated: mass spectra on a Nuclide 12-90G spectrometer with 70 eV impact ionization inlet at 200°C, infrared (IR) spectra on a Perkin-Elmer model 621, gas-liquid chromatography (GLC) on an Aerograph 600B or a Packard Model 7400 equipped with dual flame detectors and temperature programming, and nuclear magnetic resonance (NMR) on a Varian HA 100 spectrometer at 100 MHz.

Preparations--Methyl 11-iodoundecanoate, *14*: Technical 11-bromoundecanoic acid (Aldrich Chemical Co.) was esterified by refluxing with methanol and *p*-toluenesulfonic acid. Distillation of the product gave an 84% yield of 83% pure (GLC) methyl ester. Crude methyl 11-bromoundecanoate (239 g, 0.856 mole) was refluxed in an N_2 atm. with a solution of 192.6 g (1.28 mole) NaI in acetone. Conversion was completed in 3 hr (GLC). The acetone was removed on a rotary evaporator. The residue was filtered, poured into 1 liter of water, and taken up in three 100-ml portions of dichloromethane. The dichloromethane solution was washed with dilute

sodium thiosulfate and water, dried over magnesium sulfate, and filtered. The filtrate after removal of the dichloromethane on the rotary evaporator yielded 276 g yellow solid *14* (ca. 87% pure by GLC). Two recrystallizations from petroleum ether (PE, bp 35-60°) yielded 234.7 g (81%) *14* (96% pure by GLC). NMR: 1.29-1.82δ methylene complex, 2.03δ triplet-CH_2CH_2CO-, 3.18δ triplet CH_2-CH_2-I.

Methyl 10-formyldecanoate, *6*: Oxidation of *14* with dimethyl sulfoxide (DMSO) according to Johnson and Pelter (12) gave *6* in yields of 57-67% and 98-100% purity (GLC) after purification by bisulfite adduct. NMR: 1.3-1.9δ methylene complex, 2.2-2.5δ triplet -CH_2CH_2CO-, 3.66 singlet -CO_2CH_3, 9.76δ triplet-CH_2CHO.

7-Chloro-*cis*-3-heptene, *3*: In a 500-ml round-bottomed flask, magnetically stirred, were placed 6.0 g Lindlar's catalyst (16), 0.6 g quinoline, and 250 ml pentane. The flask was twice flushed with H_2 and a solution of *2* (30 g, 0.23 mole) in 50 ml pentane was added. The mixture was stirred under 1 atm. H_2 while the rate of hydrogenation was monitored periodically (17). When the reduction had virtually stopped, GLC analysis indicated complete conversion to *3*. The mixture was filtered through Celite, and the filtrate was washed with 300 ml 1.5 N HCl and twice with 300-ml portions H_2O. The solution was dried ($MgSO_4$) and filtered, and the pentane was distilled from it through a 2 ft X 0.5 in. HeliPak column. The residue was distilled through a 6-in. Vigreux column to yield 29.1 g (95%) of pure *cis*-3, bp 158-160°/745 mm, n_D^{20}1.4464. *Trans*-3 had bp 158°/760 mm and n_D^{20} 1.4430 (18). GLC on 20 ft X 0.25 in. 15% OV 275 showed less than 0.5% *trans*-3 to be present. NMR: 0.95δ triplet CH_3CH_2-, 1.7-2.2δ methylene complex, 3.5δ triplet $ClCH_2CH_2$-, 5.1-5.6δ olefin complex. IR showed only trace absorption at 950-1000 cm^{-1}.

1-Chloroheptane-4,5-d_2, *4*: Reduction of *cis*-3 with D_2 and *tris*(triphenylphosphine)chlororhodium (I) (Wilkinson's catalyst) according to a standard procedure (2) gave a 95% yield of *4* which had n_D^{20} 1.4232 [n_D^{20} 1.4251 (19)]. NMR showed triplet 0.8-0.95δ CH_2CH_3, complex 1.15-1.5δ methylenes, 1.6-1.9δ complex $-CH_2-CH_2Cl$; triplet at 3.5δ $ClCH_2CH_2$.

1-Heptyl-4,5-d_2 triphenylphosphonium iodide, *5*: In a 2-liter, 3-necked flask fitted with an N_2-inlet, thermometer, mechanical stirrer, and reflux condenser with drying tube were placed 90 g (0.6 mole) of NaI and 450 ml acetonitrile. The mixture was stirred briefly under N_2 until solution occurred, and then 76.6 g (0.563 mole) of *4* in 50 ml acetonitrile was added. Some solid separated at once. The mixture was stirred and refluxed (84°C) for 9 hr. After 9 hr, a sample analyzed by GLC showed 97% conversion to 1-iodoheptane-4,5-d_2. The mixture was cooled and 157.2 g (0.6 mole) triphenylphosphine with 200 ml acetonitrile were added. After 2 hr of further refluxing, GLC analysis showed approximately 97% conversion of the iodide to the phosphonium salt, *5*. The mixture was cooled and filtered. The acetonitrile was removed from the filtrate on the rotary evaporator. The residue stirred with 600 ml ether gave crystals that were washed by stirring for 15 min with two successive 600-ml portions of ether. Filtration gave 228.2 g (83%) of *5* mp 86-87°.

Methyl 11-octadecenoate-15,16-d_2, *1*: Wittig synthesis between *5* and *6* was carried out by the general method (2). Distillation gave a 55% yield of *1*. The *cis*-isomer was separated on a 5 X 300 cm silver-resin column (2) in 34% yield overall yield. See Table 1 for deuterium analysis.

1-Chloroheptane-4,4,5,5-d_4, *8*: Reduction of *2* with Wilkinson's catalyst as described for preparation of *4* gave *8* in 91% yield (ca. 92% pure by GLC). This purity was sufficient for further synthesis.

1-Iodoheptane-4,4,5,5-d_4, *9*: Refluxing *8* (80 g, 0.58 mole) overnight with NaI (225 g, 1.50 mole) in acetone (1 liter) gave 118.9 g (89%) *9* (93% pure by GLC).

1-Heptanal-4,4,5,5-d_4, *10*: Oxidation of *9* by dimethyl sulfoxide according to a reported method (12), followed by purification by bisulfite adduct, furnished pure aldehyde in 25% yield.

10-Carbomethoxydecyltriphenylphosphonium bromide, *13*: Methyl 11-bromoundecanoate (82.8 g, 0.3 mole) and 87.0 g (0.33 mole) in triphenylphosphine were heated at reflux in 350 ml dry acetonitrile under N_2 overnight. Compound *13* was obtained in 92% yield mp 120-121° following purification as for *5*.

Methyl 11-octadecenoate-15,15,16,16-d_4, *7*: Wittig reaction between *10* and *13* using $NaOCH_3$ and DMF (2) gave 70% of a mixture of 91% *cis*- and 9% *trans*-isomers. The isomers were separated by silver-resin column chromatography as previously described. Nitrous acid isomerization of *7* (13) followed by silver-resin column chromatography gave *trans*-compound *7* in 65% yield. The deuterium analysis is given in Table 1.

1-Heptyl-4,4,5,5-d_4-triphenylphosphonium iodide, *14*: Triphenylphosphine (118 g, 0.45 mole), *9* (90 g, 0.39 mole), and 250 ml acetonitrile were refluxed overnight. The product, *14*, was isolated as for *5*. The yield was 177.52 g (92%) mp 123-125°.

Methyl 10-formyldecanoate-10,10-d_2, *12*: Compound *6* was subjected to deuterium exchange with heavy water-pyridine by a previous method (2,15) in 39% yield with 98% purity (GLC). Mass analysis was not reliable due to memory effect but NMR showed at δ9.3 a singlet for aldehydic proton, indicating absence of α-protons in the aldehyde.

Methyl 11-octadecenoate-10,10,15,15,16,16-d_6, *11*: Wittig reaction between *12* and *14* using t-butyllithium on tetrahydrofuran furnished *cis/trans*-compound *11* in 63% yield as previously described (2). *Cis*-isomer was separated in 35% yield by silver-ion column chromatography. See Table 1 for deuterium analysis.

ACKNOWLEDGMENTS

W. K. Rohwedder and W. L. Everhart for mass analyses, D. Weisleder for NMR analysis.

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