PREPARATION OF CYCLOHEPTANOLS SYMMETRICALLY LABELLED WITH DEUTERIUM

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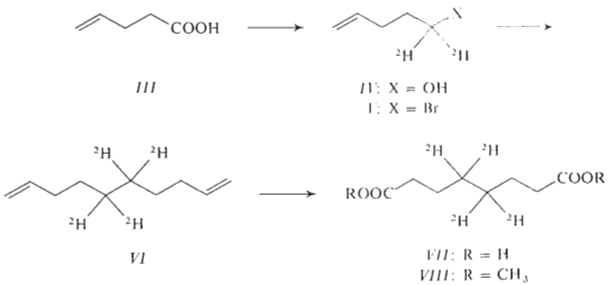
Cycloheptanols labelled symmetrically with deuterium in "inaccessible" positions were prepared by multistep syntheses. The key intermediates of the syntheses were the corresponding labelled octanedioic acids. The method of two-phase oxidation of olefins to carboxylic acids was modified so that it would be utilizable for the preparation of dicarboxylic acids.

For the study of the mechanism of the loss of water from molecular ions of cycloheptanol we needed derivatives labelled with deuterium in the positions symmetrical to $C_{(1)}$. While (1-^{2}H) and (2,2,7,7-$^2H_4$)cycloheptanol are easily accessible from cycloheptanone, the preparation of (4,4,5,5-$^2H_4$) and (3,3,6,6-$^2H_4$)cycloheptanol is no trivial matter. Asymmetrically labelled (6,6-$^2H_2$)-2,2-dimethylcycloheptanone was prepared[1] from 2,2-dimethylcyclohexanone by exchange of labile hydrogens for deuterium and subsequent expansion of the ring: however, this method does not lead to any symmetrically labelled derivative. The difficulties with a specific introduction of deuterium into equivalent positions of a monosubstituted cycloheptane derivative follow from the symmetry of the seven-membered ring. Commonly used methods of labelling (isotopic exchange or reduction with a metal deuteride[2]) lead to compounds with a geminal or 1,3-arrangement of deuterium atoms on the skeleton. Such labelling requires a single suitable functional group, which is finally removed. However, the preparation of labelled derivatives with 1,2- or 1,4-arrangement of deuterium atoms (as in *I* or *II*) requires the presence of at least two auxiliary functional groups suitably located on the skeleton. Such cycloheptane derivatives are not easily accessible, however. In addition to this the transannular reactions[3] taking place in seven-membered ring compounds can distribute deuterium into undesirable positions and so decrease the regiospecificity of the labelling. Therefore it would be advantageous to find such a precursor which contains deuterium in inactive positions and which is convertible to cycloheptanol in a minimum number of steps. One of the possible precursors is octanedioic acid and, therefore, efforts were focussed on the preparation of specifically deuterated octanedioic acids.

The synthesis of alcohol *I* (Scheme 1) was started from 4-pentenoic acid (*III*) (ref.[4]) which was reduced with lithium aluminum deuteride to (1,1-$^2H_2$)-4-penten-1-ol (*IV*) (ref.[5]). Alcohol *IV* was converted to (1,1-$^2H_2$)-1-bromo-4-pentene (*V*) on reaction with phosphorus tribromide[6]. The coupling of the Grignard reagent prepared from *V* with the bromide *V* under catalysis with lithium chlorocuprate[7] gave (5,5,6,6-$^2H_4$)--1,9-decadiene (*VI*). Two-phase oxidation of diene *VI* with potassium permanganate[8] afforded (4,4,5,5-$^2H_4$)octanedioic acid (*VII*). The oxidation method had to be modified, since the original Stark's procedure[8] led to oily products only. The increase in pH during this oxidation probably causes hydrolysis of the intermediary manganese ester and the potassium salt of the diol acid formed is no longer oxidized under the given reaction conditions. The buffering of the reaction mixture with acetic acid led to a complete oxidation of the diene and acid *VII* was obtained in a good yield.



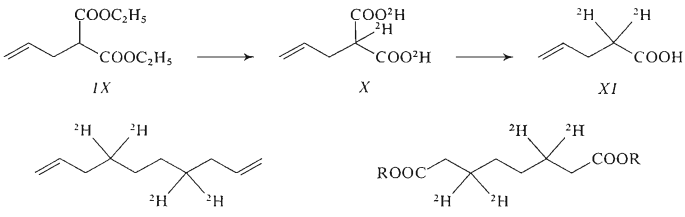
SCHEME 1

For the preparation of (3,3,6,6-$^2H_4$)octanedioic acid (*XV*) two procedures were used. In the first (Scheme 2) (2,2-$^2H_2$)-4-pentenoic acid (*XI*) was prepared from diethyl allylmalonate (*IX*) and then converted in four steps to acid *XV*. However, it proved difficult to maintain the high degree of deuteration in the intermediate – allylmalonic acid *X* – so that acid *XI* contained 85% of the $^2H_2$-species only, corresponding to maximum 72% of the $^2H_4$ species in *XIV* and *XV*. Therefore an alternative route was used for the preparation of acid *XV* (Scheme 3).

(2,2,5,5-$^2H_4$)Hexanedioic acid[9] (*XVI*) was esterified to dimethyl ester *XVII* and reduced with lithium aluminum hydride to (2,2,5,5-$^2H_4$)-1,6-hexanediol (*XVIII*). Tosylate *XIX*, prepared from diol *XVIII* was converted[10] to (3,3,6,6-$^2H_4$)octanedinitrile (*XX*) which was hydrolysed with alkali to acid *XV*.

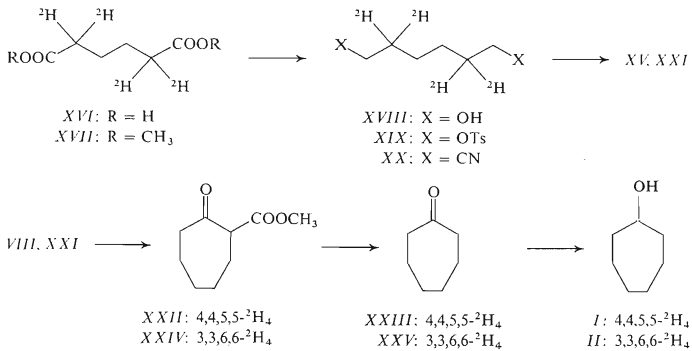
Further procedure of the synthesis of alcohols *I* and *II* comprised cyclization of dimethyl octanedioates *VIII* and *XXI* to the corresponding keto esters *XXII* and

XXIV, respectively. Dieckmann's cyclization of dimethyl octanedioate with potassium tert-butoxide in xylene in highly diluted solution has been described earlier[11,12]. However, this method is unsuitable for small amounts of substances, since it is difficult to separate the volatile cycloheptanone from the large excess of xylene.



SCHEME 2

Therefore the method of cyclization was modified by using the system potassium tert-butoxide – 18-crown-6-ether – potassium hydride (proton scavenger) in benzene under conditions of medium high dilution. Using this procedure keto esters *XXII* and *XXIV* were prepared in reasonable yields. On hydrolysis and decarboxylation of *XXII* under neutral conditions[13] (4,4,5,5-$^2H_4$)cycloheptanone *XXIII* was obtained,



SCHEME 3

which was reduced with lithium aluminum hydride to alcohol *I*. In the same manner keto ester *XXIV* was converted to alcohol *II*.

The content of deuterium in cycloheptanols *I* and *II* was determined from the mass spectra of cycloheptanones *XXIII* and *XXV*, respectively, since alcohols *I* and *II* afford molecular ions of low relative intensity, which are furthermore accompanied by the ions $(M-H)^+$ and $(M-{}^2H)^+$. The abundance of the $^2H_4$-species in *XXIII* (found 85·4%; theoretical value 88·5% and *XXV* (found 98·6%; theoretical value 99·1%) show that no substantial exchange of hydrogen in the labelled positions takes place, and, hence, the chosen procedures are suitable for the preparation of specifically labelled cycloheptane derivatives.

EXPERIMENTAL

The melting points were determined on a Boetius melting-point apparatus. The mass spectra were measured on a JEOL D-100 spectrometer, 14–75 eV. The samples were introduced by direct inlet using very thin glass capillaries or in GC/MS coupling (column GE-SE-30, 3% on Chromosorb W, 2 m/3 mm i.d.). The IR spectra were measured on a Zeiss UR 20 (Jena) spectrophotometer (liquid film). The purity of the compounds was checked by thin-layer chromatography on Merck Kieselguhr plates and by gas chromatography-mass spectrometry. The volatile labelled compounds (*I*, *II*, *V*, *VI*, *XII*, *XIII*, *XIV*, *XVII*, *XX*, *XXI*, *XXIII*, *XXV*) were identified on the basis of refractive indices and by comparison of their retention parameters with those of authentic non-labelled standards. The expression "worked up" means that the extract was dried over sodium sulfate and the solvent was distilled off through a 20 cm Vigreux column (compounds *I*, *II*, *V*, *VI*, *XII*, *XIII*, *XIV*, *XXII*–*XXV*) or on a rotatory evaporator (compounds *VIII*, *XVII*, *XVIII*, *XX*, *XXI*).

(1,1-$^2H_2$)-1-*Bromo*-4-*pentene* (V): Phosphorus tribromide (3·9 g) in pentane (5 ml) was added dropwise to a solution of alcohol *IV* (ref.[5]) (3 g) and pyridine (800 mg) in pentane (5 ml) at −40°C. The mixture was stirred at −20°C for 1 h, pentane and bromide *V* were distilled off gradually and the distillate was diluted with pentane (20 ml), washed with 5% $NaHCO_3$ and worked up. Distillation gave 3·8 g (74%) of bromide *V*, n_D^{20} 1·4648 (lit.[6] gives n_D^{28} 1·4610 for 1-bromo-4-pentene).

(5,5,6,6-$^2H_4$)-1,9-*Decadiene* (VI): Bromide *V* (1·9 g) in tetrahydrofuran (5 ml) was added dropwise over 30 min under argon to magnesium shavings (305 mg) in refluxing tetrahydrofuran (5 ml). After the magnesium had dissolved the solution was cooled to 0°C and bromide *V* (1·85 g) and 1·2 ml of 0·1M-Li_2CuCl_4 in tetrahydrofuran[7] were added. The mixture was allowed to stand at 0°C for 5 h, then poured into water and the product extracted with pentane and worked up. Distillation gave 1·52 g (86%) of diene *VI*, n_D^{20} 1·4316 (ref.[14] gives 1·4325 for 1,9-decadiene).

(4,4,5,5-$^2H_4$)-*Octanedioic acid* (VII): Diene *VI* (1·50 g) and Aliquat 336 (200 mg) in benzene (10 ml) were added at 30°C to a vigorously stirred solution of potassium permanganate (14 g) and acetic acid (5 ml) in 120 ml of water. After 5 h stirring sodium hydroxide (6 g) was added, the manganese dioxide filtered off, washed with 0·5M-NaOH, and the aqueous filtrate concentrated *in vacuo* to about 60 ml. The solution was acidified with hydrochloric acid, cooled to 0°C, the acid *VII* was filtered off under suction and recrystallized from water. Yield 1·22 g (65%) of *VII*, m.p. 139–141°C. The mixture melting point with an authentic sample of octanedioic acid was undepressed.

Dimethyl(4,4,5,5-$^2H_4$)*octanedioate* (VIII): Acid *VII* (1·2 g) was esterified with methanol (27 ml) under catalysis with *p*-toluenesulfonic acid (200 mg). After working up and distillation 1·25 g (90%) of ester *VIII* were obtained, n_D^{20} 1·4329.

(2,2-$^2H_2$)-4-*Pentenoic acid* (XI): Diethyl allylmalonate (11·5 g) in tetrahydrofuran (10 ml) was added dropwise and under argon to a suspension of sodium hydride (3·45 g) in tetrahydrofuran (10 ml) at 0°C. After 30 min deuterium oxide (20 ml) was added dropwise, then triethylbenzylammonium chloride (400 mg) was added and the mixture was refluxed for 8 h. After cooling a solution of phosphoric acid ($^2H_3$) (144 mmol) in deuterium oxide was added, the solvents were evaporated under reduced pressure, the residue extracted with tetrahydrofuran which was then distilled off. The residue was crystallized twice from deuterium oxide (8 ml), dried and decomposed at 180–190°C and 6·7 kPa. The acid *XI* obtained contained 85·2% $^2H_0$; 12·7% $^2H_1$ and 2·1% $^2H_0$ (determined by mass spectrometry).

(2,2-$^2H_2$)-4-*Penten*-1-*ol* (XII) was prepared in a 90% yield as described earlier[5].

(2,2-$^2H_2$)-1-*Bromo*-4-*pentene* (XIII) was prepared from alcohol *XII* as described for *V*. Yield, 76%, n_D^{20} 1·4630.

(4,4,7,7-$^2H_4$)-1,9 *decadiene* (XIV) was prepared from bromide *XIII* as described for *VI*. Yield, 78%, n_D^{20} 1·4309.

Dimethyl (2,2,5,5-$^2H_4$)*hexanedioate* (XVII) was prepared by esterification of acid[9] *XVI*, using the procedure described for *VIII*. Yield, 92%, n_D^{20} 1·4262.

(2,2,5,5-$^2H_4$)-1,6-*Hexanediol* (XVIII) was prepared on reduction of ester *XVII* with lithium aluminum hydride using the standard procedure. Yield, 95%. The product was purified by distillation (b.p. 115°C at 67 Pa), m.p. 40–42°C.

(3,3,6,6-$^2H_4$)*Octanedinitrile* (XX): A mixture of diol *XVIII* (5·3 g), *p*-toluenesulfonyl chloride (18·5 g) and pyridine (30 ml) was allowed to stand at −5°C for 48 h. The mixture was then poured into water–ice mixture, the crystalline tosylate *XIX* was filtered off under suction, and dried *in vacuo*. Without further purification it was added to a solution of sodium cyanide (7·3 g) in dimethyl sulfoxide (30 ml) at 100°C. After 2 h stirring at this temperature the mixture was poured into water, nitrile *XX* was extracted with chloroform (5 . 20 ml), the solvent and the contaminating dimethyl sulfoxide were distilled off, and the product distilled *in vacuo*. B.p. 140–150°C/67 Pa. Yield, 4·8 g (79%, calculated per alcohol *XVIII*) of nitrile *XX*, n_D^{20} 1·4435.

(3,3,6,6-$^2H_4$)*Octanedioic acid* (XV): *A*) Nitrile *XX* (4·7 g) was refluxed with sodium hydroxide (4 g) and triethylbenzylammonium chloride (100 mg) in 30ml of water for 24 h. After cooling the solution was acidified with hydrochloric acid, acid *XV* was filtered off under suction and crystallized from water. Yield, 5·48 g (92%) of *XV*, m.p. 139–141°C. *B*) Diene *XIV* was oxidized with potassium permanganate as described for *VII*. Yield, 72%, m.p. 138–140°C.

Dimethyl (3,3,6,6-$^2H_4$)*octanedioate* (XXI) was prepared from acid *XV* as described for *VIII*. Yield, 94%, n_D^{20} 1·4315.

Methyl (5,5,6,6-$^2H_4$)-2-*oxocycloheptane*-1-*carboxylate* (XXII): Ester *VIII* (1 g) in 30 ml of benzene was added under argon over 12 h to a mixture of potassium hydride (430 mg), 18-crown-6-ether (125 mg) and tert-butyl alcohol (180 mg) in benzene (15 ml). After an additional 5 h of refluxing the mixture was neutralized with acetic acid, poured into a 5% $NaHCO_3$ solution and the product was extracted with pentane and worked up. Distillation at 150°C/2 kPa (bath temperature) gave 550 mg (65%) of keto ester *XXII*, n_D^{20} 1·4682. Mass spectrum (*m/z*): 174 ($M^{+\cdot}$), 146, 142, 116–113, 110, 101, 86, 75, 70, 57, 55.

Methyl (4,4,7,7-$^2H_4$)-2-*oxocycloheptane*-1-*carboxylate* (XXIV) was prepared from ester *XXI* as described for *XXII*. Yield 56%, n_D^{20} = 1·4686. IR: 2210, 2150, 2120, 1750, 1718, 1655, 1624, 1450, 1343, 1310, 1230, 1210, 1180 cm^{-1}: mass spectrum (*m/z*): 174 ($M^{+\bullet}$), 146, 142, 116, 101, 97, 86, 71, 57.

(4,4,5,5-$^2H_4$)*Cycloheptanone* (XXIII): Keto ester *XXII* (500 mg) was heated with water (200 mg) in dimethyl sulfoxide (5 ml) at 160°C for 3 h. After cooling the mixture was poured into water, the product extracted with pentane and worked up. Distillation gave 280 mg (85%) of ketone *XXIII*, n_D^{20} 1·4585. Mass spectrum (*m/z*): 116 ($M^{+\bullet}$), 101, 88, 70, 60–57, 55.

(3,3,6,6-$^2H_4$)*Cycloheptanone* (XXV) was prepared from keto ester *XXIV* as above (see the preparation of *XXIII*). Yield, 75%, n_D^{20} 1·4610. Mass spectrum (*m/z*): 116 ($M^{+\bullet}$), 86, 71, 57.

(4,4,5,5-$^2H_4$)*Cycloheptanol* (I): Ketone *XXIII* (220 mg) was reduced with lithium aluminum hydride (50 mg) in ether. After working up and distillation 190 mg (85%) of alcohol *I* were obtained, n_D^{20} 1·4735. Mass spectrum (*m/z*): 118 ($M^{+\bullet}$), 117, 100, 99, 85–82, 75–68, 57, 46–39.

(3,3,6,6-$^2H_4$)*Cycloheptanol* (II) was prepared from ketone *XXV* as described for *I*. Yield 80% n_D^{20} 1·4740. Mass spectrum (*m/z*): 118 ($M^{+\bullet}$), 117, 100–98, 88–82, 75–68, 59, 46–39.

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