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Synthesis and ^{1}H-NMR spectra of 1,1-dideutero- and 2,2-dideutero-4-phenylbutane

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SUMMARY

The specifically deuterated bromides $PhCH_2CH_2CD_2CH_2Br$ and $PhCH_2CH_2CH_2CD_2Br$ have been prepared in good yields and high isotopic purity. The halides have been used to prepare the corresponding organomagnesium halides and then the solvated tri-organochromium compounds. The NMR spectra and C-D stretching frequencies of the deuterated alkyl halides and of all the intermediates involved in their syntheses are recorded.

INTRODUCTION.

The fragmentation of alkyl-chromium compounds has been shown to result in the formation of alkane, alkenes and a hydridochromium species [1, 2]. In order to obtain chemical evidence for the origins of the hydrogen required for the formation of the hydridochromium species and the alkane experiments on the fragmentation of deuterated alkyl-chromium compounds were undertaken. For these, significant quantities of specifically deuterated alkyl halides of high isotopic purity were required. The present paper describes the preparation of 2,2-dideutero- and 1,1-dideutero-4-phenylbutyl bromides of high isotopic purity.

DATA AND DISCUSSION.

2,2-Dideutero-4-phenylbutyl bromide.

The route chosen for the synthesis of 2,2-dideutero-4-phenylbutyl bromide is based upon that described for the synthesis of 2,2-dideutero-octyl bromide [3]. Thus, ethyl dihydrocinnamate was reduced with $LiAlD_4$ and the resulting specifically labelled

$$PhCH_2CH_2C(=O)OEt \xrightarrow{LiAlD_4} PhCH_2CH_2CD_2OH \xrightarrow{PBr_3} PhCH_2CH_2CD_2Br \quad (1)$$

(1) (2)

deutero-alcohol (1) converted to the bromide (2) by interaction with PBr_3 under controlled conditions [4] (equation 1). The bromo-compound can, in principle, be transformed into the homologous alcohol (4) either directly by the reaction of the deuterophenylpropylmagnesium bromide with formaldehyde or indirectly by carbonation of the organomagnesium compound and subsequent reduction of the acid (3) (equations 2 and 3).

$$PhCH_2CH_2CD_2MgBr \xrightarrow{HCHO} PhCH_2CH_2CD_2CH_2OH \quad (2)$$

(4)

$$PhCH_2CH_2CD_2MgBr \xrightarrow{CO_2} PhCH_2CH_2CD_2COOH \xrightarrow{LiAlH_4} PhCH_2CH_2CD_2CH_2OH \quad (3)$$

(3) (4)

Experiments with undeuterated 3-phenylpropylmagnesium bromide showed that the former reaction (equation 2) gave a mediocre yield of an impure product [5]. Carbonation of the organomagnesium halide could, on the other hand, be effected in quantitative yield by carrying out the reaction in tetrahydrofuran, at low temperatures and in the presence of excess of carbon dioxide.

In order to avoid side reactions, (i.e. cyclization, dehydration, etc.) the alcohol (4) was converted to the corresponding bromide (5) by interaction with PBr_3 under controlled conditions.

The purity of the 2,2-dideutero-4-phenylbutylbromide (5) was established by converting it to the corresponding organomagnesium halide and hydrolyzing the latter (equation 4). The hydrocarbon thus formed (6) was shown by NMR spectroscopy and mass spectrometry [6] to consist essentially of 2,2-dideutero-4-phenylbutane (see Experimental).

$$PhCH_2CH_2CD_2CH_2OH \xrightarrow{PBr_3} PhCH_2CH_2CD_2CH_2Br \xrightarrow[2)\ H_2O]{1)\ Mg/THF} PhCH_2CH_2CD_2CH_3 \quad (4)$$

(5) (6)

1,1-Dideutero-4-phenylbutyl bromide.

The title compound was prepared by the steps outlined in equation 5. The isotopic purity of this bromo-compound was

$$PhCH_2CH_2CH_2COOEt \xrightarrow{LiAlD_4} \underset{(7)}{PhCH_2CH_2CH_2CD_2OH} \xrightarrow{PBr_3} \underset{(8)}{PhCH_2CH_2CH_2CD_2Br} \quad (5)$$

established by converting it *via* the organomagnesium bromide to the deutero-alkane (9) (equation 6).

$$\underset{(8)}{PhCH_2CH_2CH_2CD_2Br} \xrightarrow[2)\ H_2O]{1)\ Mg/THF} \underset{(9)}{PhCH_2CH_2CH_2CD_2H} \quad (6)$$

This hydrocarbon was shown by NMR spectroscopy and mass spectrometry [6] to consist essentially of 1,1-dideutero-4-phenylbutane (see Experimental).

The relevant infra-red C-D stretching frequencies of the deutero-compounds 1 to 9 are given, together with some literature values, in table I. The NMR spectra * of the deutero-compounds 1 to 9, together with those of the undeuterated species are presented in figures 1 to 4.

TABLE I. C-D stretching frequencies of Deuterocompounds 1-9[a]

Compound	Frequency in cm^{-1}	Intensity[b]
(1) $PhCH_2CH_2CD_2OH$	2083, 2105 (sh), 2198, 2210 (sh)	equal, 3
(2) $PhCH_2CH_2CD_2Br$	2160	
(3) $PhCH_2CH_2CD_2COOH$	2105 2140	1, 3
(4) $PhCH_2CH_2CD_2CH_2OH$	2105 2185	equal, 3
(5) $PhCH_2CH_2CD_2CH_2Br$	2105 2139 2196	2, 1, 3
(6) $PhCH_2CH_2CD_2CH_3$	2112 2174 2220	3, 3, 1
(7) $PhCH_2CH_2CH_2CD_2OH$	2083 2186	equal, 3
(8) $PhCH_2CH_2CH_2CD_2Br$	2160	
(9) $PhCH_2CH_2CH_2CD_2H$	2120 2220	2, 3
(10)[7] $C_5H_{11}CD_2H$	2140 2220	2, 3
(11)[8] $Ph_3CCD_2OCH_3$	2075 2180	not given
(12)[8] Ph_2CD_2	2100 2130 2220	not given
(13)[8] $PhCD_3$	2060 2130 2220	not given
(14)[8] Ph_3CCD_3	2215	not given

[a] It is of interest to note the variations in the *number of bands*, their *position* and their *intensity*, in these compounds. Thus in the alkanes the CD_2 group of the β,β-dideutero compound (6) shows three bands (two intense and one medium) whilst those of the α,α-dideutero-compounds 9 and 10 show only two bands (at a different frequency) the one intense the other medium.

[b] Intensity 1 is the weakest and 3 the strongest signal.

* For convenience in drawing the aromatic protons at $\delta_{TMS} = 7.07$ in all the compounds and the acidic proton at $\delta_{TMS} = 12.1$ in the acid (3) have been omitted.

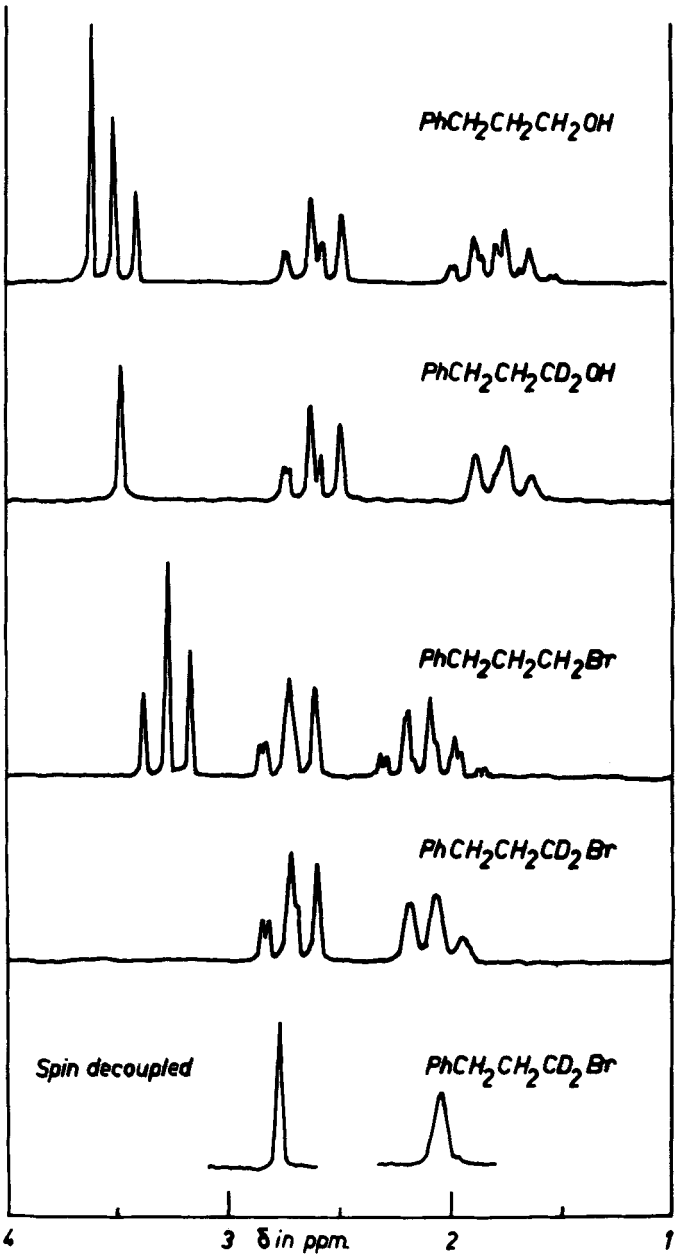
PhCH2CH2CH2OH
PhCH2CH2CD2OH
PhCH2CH2CH2Br
PhCH2CH2CD2Br
Spin decoupled
PhCH2CH2CD2Br
4
3
δ in ppm
2
1

FIG. 1

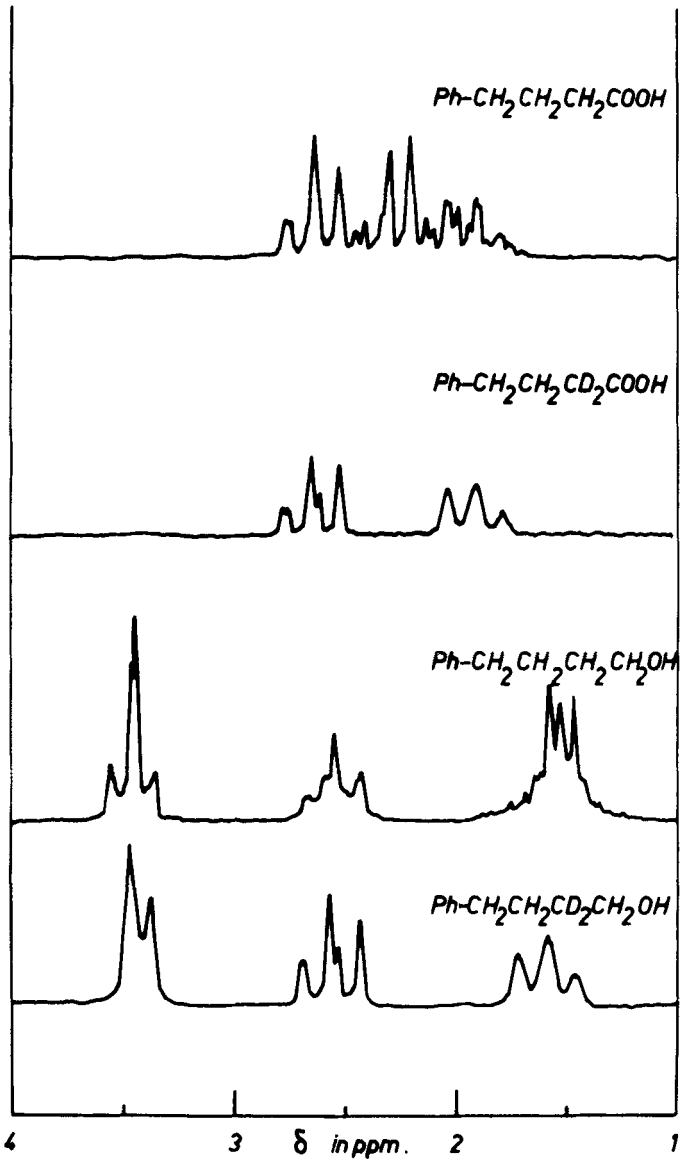
Ph-CH2CH2CH2COOH
Ph-CH2CH2CD2COOH
Ph-CH2CH2CH2CH2OH
Ph-CH2CH2CD2CH2OH
4
3
δ in ppm.
2
1

FIG. 2

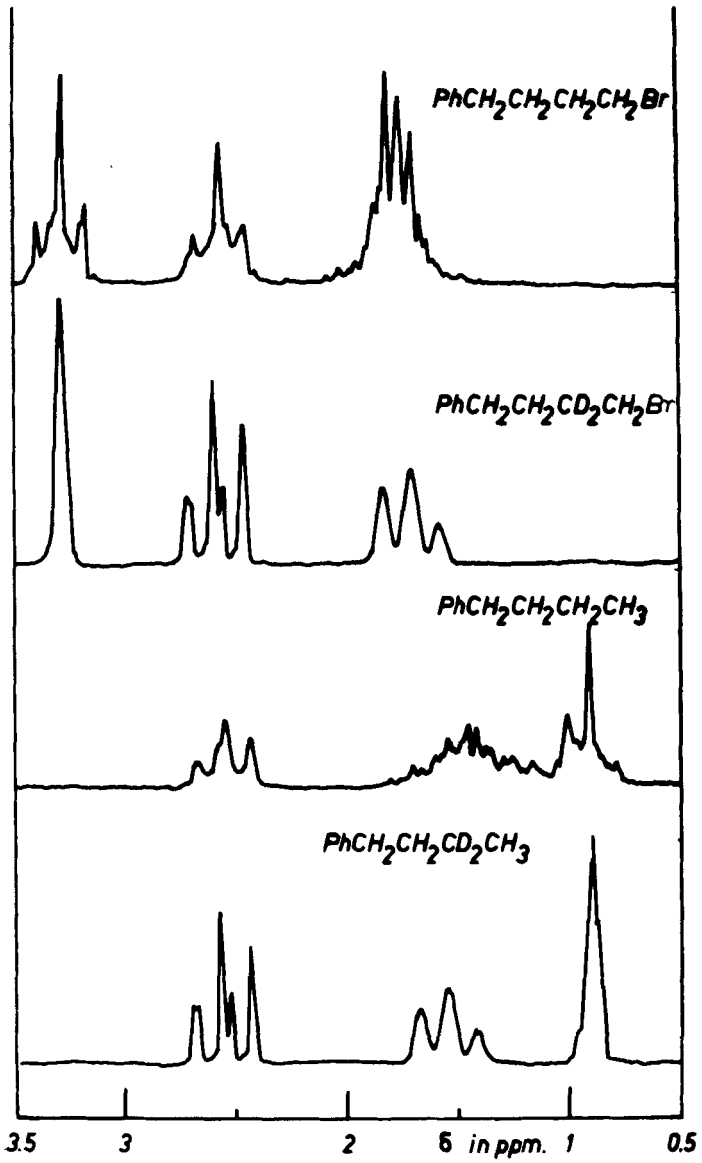
PhCH2CH2CH2CH2Br
PhCH2CH2CD2CH2Br
PhCH2CH2CH2CH3
PhCH2CH2CD2CH3
3.5
3
2
δ in ppm.
1
0.5

FIG. 3

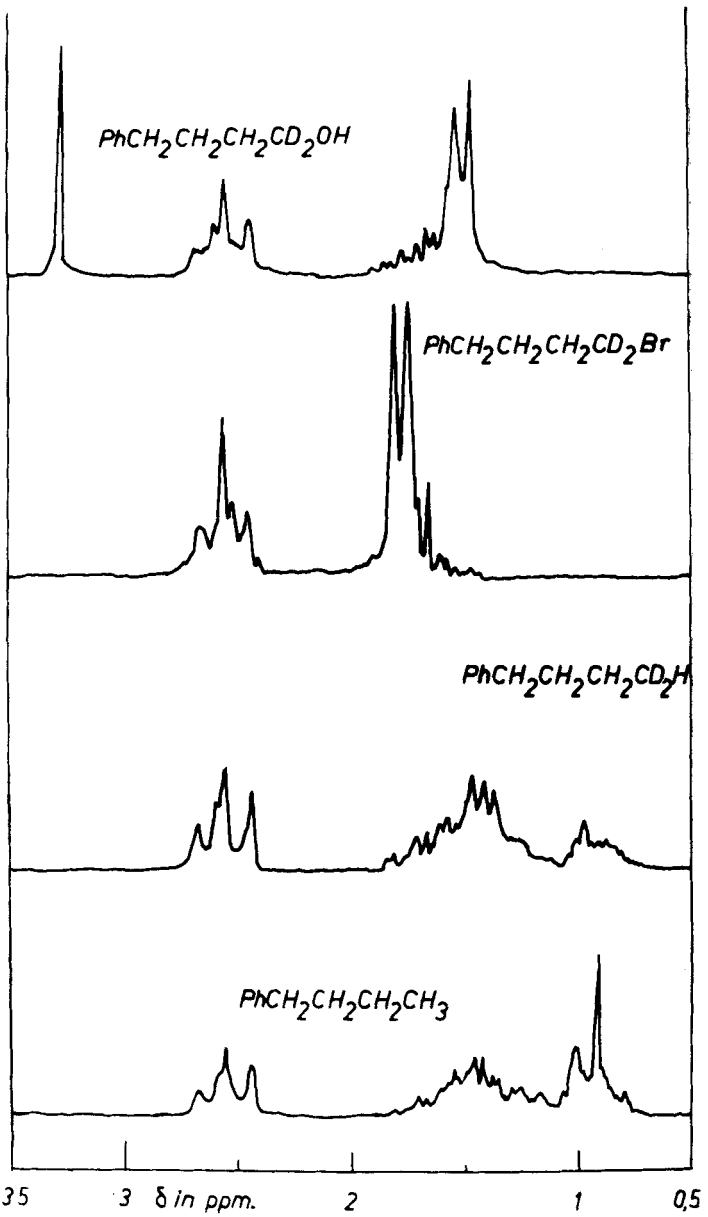
PhCH2CH2CH2CD2OH
PhCH2CH2CH2CD2Br
PhCH2CH2CH2CD2H
PhCH2CH2CH2CH3
3.5
3
δ in ppm.
2
1
0.5

FIG. 4

The proton count (from the integrals) and the NMR spectra establish that no hydrogen/deuterium exchange occurred at any stage in either synthesis. The isotopic purity, and NMR spectra of the final hydrocarbons (obtained by hydrolysis of the derived organomagnesium halides) prove not only that no H/D exchange took place either during the formation or the hydrolysis of the respective organomagnesium halides, but also that no H/D exchange took place during gas-chromatographic isolation of the respective hydrocarbons.

Solvated tris-2,2-dideutero- and 1,1-dideutero-4-phenylbutyl chromium.

Interaction of the specifically deuterated alkylmagnesium bromides with $CrCl_3(THF)_3$, ratio 3 : 1, in tetrahydrofuran at −70 to −40 °C gave the corresponding solvated trialkylchromium compounds (equation 7, R = $PhCH_2CH_2CD_2CH_2$- and $PhCH_2CH_2CH_2CD_2$- respectively). These red solutions are moderately stable at −40 °C undergoing methanolysis at −40 °C to give essentially pure 2,2-dideutero- and

$$3\ RMgX + CrCl_3(THF)_3 \xrightarrow[-70^{\circ}\ \text{to}\ -40^{\circ}]{\text{THF}} R_3Cr(THF)_n \qquad (7)$$

1,1-dideutero-4-phenylbutane (see Experimental). It is thus evident that the *formation* and *methanolysis* of these trialkylchromium compounds take place without H/D exchange.

The deuterium transfer reactions associated with the fragmentation of these specifically deuterated trialkylchromium compounds will be reported later. [9]

EXPERIMENTAL. *

The diethyl ether and tetrahydrofuran used in the reactions with organomagnesium halides, $LiAlH_4$ and $LiAlD_4$ were freshly distilled, under argon, first from sodium and then from $LiAlH_4$. The reactions with $LiAlD_4$, $LiAlH_4$ and organo-magnesium and -chromium compounds were carried out in flame dried equipment, under argon. The $LiAlD_4$ used was purchased from CIBA, Basel, Switzerland, and guaranteed to have 99 atom % D. The PBr_3 used was freshly distilled and water white. The analytical and preparative scale gas chromatography were carried out respectively on an F and M model 5750 apparatus equipped with 9ft 1/4″ and 1/2″ 20 % Carbowax 20M columns. The microanalyses are by Mr. A Peisker, Brugg, Switzerland, and Mr. W. Manser of the Eidg. Technische Hochschule, Zürich, Switzerland.

* With the technical assistance of Miss. U. Feisst.

(1) *1,1-Dideutero-3-phenylpropanol* (1).

Ethyl dihydrocinnamate (b.p. 57-9 °C/0.05 mm; n_D^{20} 1.4943) (85 g, 0.5 mole) in diethyl ether (200 ml) was added slowly to a briskly stirred, cooled suspension of $LiAlD_4$ (10 g, 0.264 mole). After the addition, the resulting mixture was heated under reflux for 2 h., cooled, hydrolyzed and acidified. The ether solution was washed with NaOH (5 %) water and dried over $MgSO_4$ and subsequently concentrated on the rotary evaporator. In order to remove unreduced ester, the crude material was dissolved in a mixture of ethanol (200 ml) and water (100 ml) containing NaOH (20 g). The resulting homogeneous solution was heated under reflux in an argon atmosphere for 2 h. The cooled reaction mixture was diluted with water and subsequently extracted with ether. The ether extract after washing with NaOH (5 %) and water and drying ($MgSO_4$) was fractionally distilled. In this way 1,1-dideutero-3-phenylpropanol (53 g) was obtained as a colorless liquid b.p. 62-66 °C/0.05 mm; n_D^{20} 1.5260.

(2) *1,1-Dideutero-3-phenylpropylbromide* (2).

Phosphorous tribromide (14 ml, 0.142 moles) was added dropwise to the briskly stirred alcohol (1) (53 g, 0.384 moles) at −5 °C. The reaction mixture was kept between −5 and 0 °C during the addition and was afterwards allowed to warm to 20 °C. The homogeneous reaction mixture was now warmed gently in a hot water bath until such time (2 hr). as two separate layers were formed. The cooled reaction mixture was poured on to crushed ice and the organic halide isolated with the aid of hexane. The hexane extract was washed thoroughly with NaOH (5 %) water and finally dried ($MgSO_4$). Fractional distillation of the extract finally gave 1,1-dideutero-3-phenylpropylbromide (59 g) as a colorless liquid b.p. 47-49 °C/0.02 mm; n_D^{20} 1.5448.

(3) "*4-Phenylbutanol*[4]".

A slow stream of argon and formaldehyde (from the pyrolysis of paraformaldehyde 20 g) was bubbled through a stirred solution of 3-phenylbutylmagnesium bromide (0.276 moles) in tetrahydrofuran (150 ml). The temperature of the reaction was controlled by water-cooling. When all the paraformaldehyde had been added the reaction mixture was stirred for a further 2 h. (Gilman color test No. 1 for RMgX, negative) and then heated under reflux for 1/2 h. The cooled reaction mixture was poured into water and extracted with ether. The ether extract was washed with water, sodium bisulfite solution and water. Fractional distillation of the dried extract gave crude 4-phenylbutanol (17 g) b.p. 80-81 °C/0.3 mm; n_D^{20} 1.5078. This material contained considerable quantities of impurities as evidenced by the *extra* signals in the NMR spectrum at $\delta_{TMS} = 4.1, 7.9$ (H-C(=O)-O ?) and in the infrared at V_{max}

1712 and 1163 cm^{-1} (COOR ?). Steam distillation of the crude material from acid solution [4], removed some of the impurities but still did not furnish pure carbinol.

(4) *2,2-Dideutero-4-phenylbutyric acid* (3).

A solution of 1,1 dideutero-3-phenylmagnesium bromide (from the bromo-compound (2), (59 g) and magnesium (7.8 g) in tetrahydrofuran (300 ml) was added dropwise to a briskly stirred suspension of solid CO_2 (700 g) in tetrahydrofuran (1,000 ml) at −70 °C. When the addition was complete, the reaction mixture was allowed to warm to room temperature (Gilman color test No. 1, for RMgX, negative) and the majority of the tetrahydrofuran removed by distillation, under vacuum on the rotary evaporator. The residue was treated with crushed ice and acidified with HCl (10 %), and the organic material extracted with ether. The organic acids were extracted from this ether solution with cold aqueous NaOH (10 %); the alkaline extract acidified with ice cold HCl (10 %) and the organic acids isolated with the aid of ether. The crude 2,2-dideutero-4-phenylbutyric acid (40 g) m.p. 48-49 °C thus isolated was sufficiently pure (NMR spectrum) for the next stage of the synthesis.

(5) *2,2-Dideutero-4-phenylbutanol* (4).

A solution of the deuteroacid (3) (40 g, 0.24 moles) in diethyl ether (300 ml) was added dropwise to a briskly stirred suspension of $LiAlH_4$ (11.4 g, 0.3 moles) in diethyl ether (1,000 ml). When the addition was complete the reaction mixture was stirred and heated under reflux for 1/2 h. The cooled reaction mixture was treated *carefully* with water (50 ml) and acidified with HCl (10 %). The extract was washed with aqueous NaOH (5 %), with water and dried ($MgSO_4$). Fractional distillation of the extract gave 2,2-dideutero-4-phenylbutanol (36.8 g) b.p. 80-81 °C/0.3 mm, n_D^{20} 1.5199 as a colorless oil.

(6) *2.2-Dideutero-4-phenylbutyl bromide* (5).

In an experiment similar to that described under 2 (above) the deutero-alcohol (4) (36.8 g, 0.242 moles) was treated with PBr_3 (8 ml, 0.084 moles). The product, isolated as already described under 2 (above), consisted of 2,2-dideutero-4-phenylbutyl bromide (44 g) b.p. 58-60 °C/0.02 mm; n_D^{20} 1.5392 (Found : C, 55.8; "H", 6.8; Br, 36.9. $C_{10}H_{11}D_2Br$ Calcd. : C, 55.8; "H", 7.0; Br, 37.1 %).

(7) *2,2-Dideutero-4-phenylbutane* (6).

The bromo-compound (5) (21.5 g, 100 mmoles) was converted to 2,2-dideutero-4-phenylbutylmagnesium bromide in the conventional manner by interaction with magnesium (2.67 g) in tetrahydrofuran. An aliquot of the clear filtered solution of organomagnesium compound was hydrolyzed. The resulting hydrocarbons, isolated with the aid of ether, were shown by gas chromato-

graphic analysis to consist of a compound (99.2 %) with the same retention time as 4-phenylbutane and one (0.78 %) with the same retention time as 4-phenylbut-1-ene. The former was isolated by preparative scale gas chromatography and shown by NMR spectroscopy and by mass-spectrometry [6] to consist of 2,2-dideutero-4-phenylbutane (96.3 %) 2-deutero-4-phenylbutane (3.5 %) and a trideutero species (0.2 %). The total specimen had the composition Found : C, 88.5; "H", 10.9; $C_{10}H_{12}D_2$ Calcd. : C, 88.2; "H", 11.8 %.

(8) *1,1-Dideutero-4-phenylbutanol* (7).

Ethyl 4-phenylbutyrate (85 g) in diethyl ether (200 ml) was added to a briskly stirred suspension of $LiAlD_4$ (10 g) in diethyl ether (1.100 ml). The crude product was hydrolyzed as described under (1) (above). In this way 1,1-dideutero-4-phenylbutanol (50 g) b.p. 76 °C/0.07 mm, n_D^{20} 1.5210 was obtained as a colorless liquid. The NMR spectrum is given in figure 4.

(9) *1,1-Dideutero-4-phenylbutyl bromide* (8).

The alcohol prepared above (50 g) was treated with PBr_3 (10.9 g) as described under (6) (above). In this way 1,1-dideutero-4-phenylbutyl bromide (61,5 g) was obtained as a colorless liquid b.p. 86 °C/0.5 mm; n_D^{20} 1.5400. Found : C, 56.3; "H", 6.2; Br, 37.2. $C_{10}H_{11}D_2Br$ Calcd. : C, 55.8; "H", 7.0; Br, 37.1 %. The NMR spectrum is given in figure 4.

(10) *1,1-Dideutero-4-phenylbutane* (9).

The bromo-compound (8) (30 g, 139.5 mmole) was converted to 1,1-dideutero-4-phenylmagnesium bromide in the conventional manner by interaction with magnesium (3.8 g) in tetrahydrofuran (200 ml). An aliquot of the clear filtered solution of organomagnesium compound was hydrolyzed. The resulting hydrocarbons were shown by gas chromatographic analysis to consist of a compound (99.4 %) with the same retention time as 4-phenylbutane and traces of a compound (0.6 %), with the same retention time as 4-phenylbut-1-ene. The alkane was isolated by preparative scale gas chromatography and shown by NMR spectroscopy (Fig. 4) and mass-spectrometry [6] to consist of 1,1-dideutero-4-phenylbutane (97.2 %) and a monodeutero-4-phenylbutane (2.8 %).

(11) *Solvated tris-2-2-dideutero-4-phenylbutylchromium.*

A tetrahydrofuran solution of 2,2-dideutero-4-phenylbutylmagnesium bromide (50 ml, 31 mmoles) was added dropwise to a briskly stirred suspension of $CrCl_3(THF)_3$ (3.8 g, 10.2 mmoles) in tetrahydrofuran (50 ml) at −70 °C. The reaction mixture was allowed to warm slowly (1 h) to −40 °C and held at this temperature for 4 hours. The resulting red suspension was treated with oxygen-free methanol (10 ml) at −40 °C and allowed to stand overnight at this temperature. The clear green solution was allowed to warm to room

temperature then diluted with water. The organic products, isolated with ether, were shown by gas chromatographic analysis to consist of a compound (98.6 %) with the same retention time as 4-phenylbutane and one (1.4 %) with the same retention time as 4-phenylbut-1-ene. The alkane, isolated by preparative scale gas-chromatography, was shown by mass-spectrometry [6] and NMR-spectroscopy to consist of 2,2-dideutero-4-phenylbutane (96 %) and a monodeutero-compound (3 %); $\delta_{TMS} = 7.06$ (*m*, 5 protons, C_6H_5); 2.54 (*m*, 2 protons $PhCH_2$); 1.54 (*m*, 2 protons $-CH_2-$); 0.90 (*m*, 3 protons $-CH_3$).

(12) *Solvated tris-1,1-dideutero-4-phenylbutyl chromium.*

In a similar experiment, 1,1-dideutero-4-phenylbutyl magnesium bromide (50 ml, 31 mmole) was allowed to interact with $CrCl_3(THF)_3$ (3.8 g, 10.2mmoles) Methanolysis of the resulting red solution of the trialkylchromium compound, after 4 hrs at −40 °C, gave a compound (97.2 %) with the same gas chromatographic retention time as 4-phenylbutane, and another (2.8 %) with that of 4-phenylbut-1-ene. The alkane was shown by mass-spectrometry [6] and NMR spectroscopy to consist of 1,1-dideutero-4-phenylbutane (96.1 %) and a monodeutero-compound (3.1 %); $\delta_{TMS} = 7.05$ (*m*, 5 protons, C_6H_5); 2.54 (*m*, 1.97 protons, $PhCH_2$); 1.44 (*m* 3.97 protons CH_2CH_2); 0.9 (*m*, 1.00 protons $-CD_2H$).

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