

COBALT-CATALYZED CARBONYLATION OF OPTICALLY ACTIVE AND α -DEUTERATED PHENETHYL HALIDES

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Summary

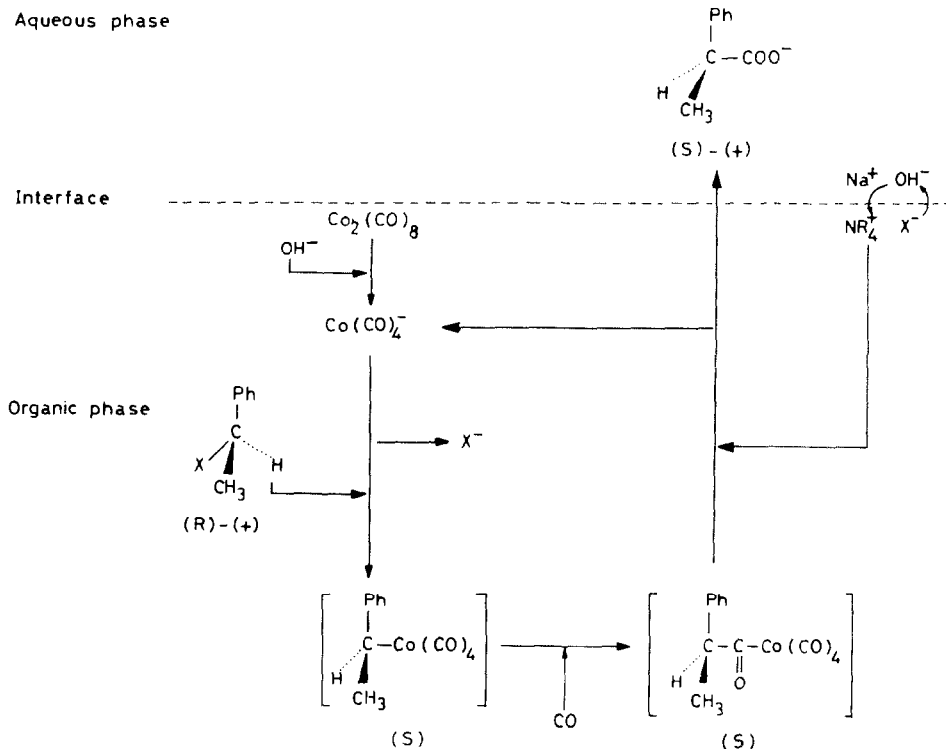
Carbonylation of optically active α -phenethyl halides under phase transfer conditions gives hydratropic acid of the opposite absolute configuration. The inversion of configuration is accompanied by extensive racemization. The latter appears to originate from equilibria between keto and enol forms of acylcobalt-carbonyl complexes and between branched and linear alkyl complexes. Double carbonylation of α -phenethyl bromide is strongly inhibited when the benzylic hydrogen is replaced by deuterium. This large isotope effect provides the first experimental support for the proposed intermediacy of an enolic species in the double carbon monoxide insertion.

Introduction

Cobalt-catalyzed mono and double carbonylation of secondary benzyl halides under phase transfer conditions were recently described [1]. Since various mechanisms could be postulated for these reactions, we decided to study the stereochemistry of catalytic monocarbonylation of optically active α -phenethyl halides in order to obtain more information about the course of the reaction. We also devised appropriate deuterium-exchange experiments to clarify the origin of the double carbonylation.

Results and discussion

Monocarbonylation of optically active α -phenethyl bromide and chloride under phase transfer conditions led to hydratropic acid of opposite absolute configuration. The results obtained on carrying out the carbonylation in various organic phases are shown in Table 1. A stereospecific reaction is likely to occur with inversion of configuration at the benzylic carbon in the first step, leading to formation of the alkylcobalt carbonyl intermediate, and with retention in the second step, involving CO insertion and formation of the acylcobalt carbonyl complex (Scheme 1). Inver-



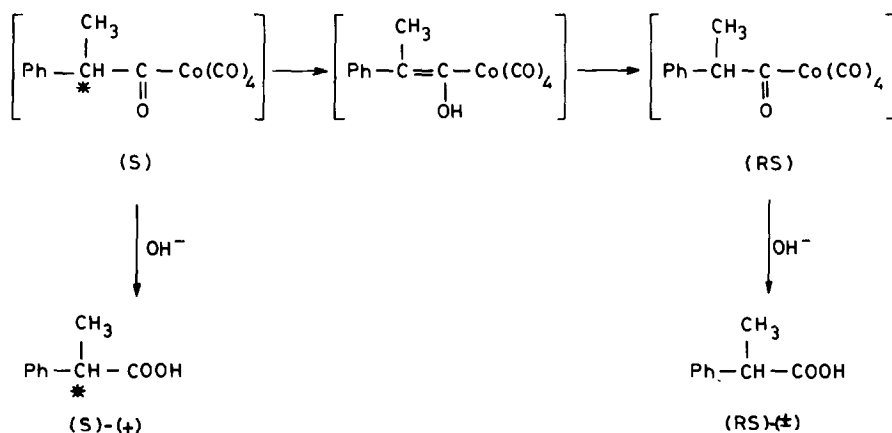
SCHEME 1

sion of configuration in the reaction between α -phenethyl halides and tetracarbonyl cobaltate is in agreement with the S_N2 mechanism proposed for this reaction [1] and with published information on the reaction of this carbonyl at chiral centres [2]. Moreover the results reported so far about the stereochemistry at carbon in alkyl-acyl migratory insertion are consistent with retention of configuration at the migrating chiral center [3]. Although such reactions at chiral centres are generally highly stereospecific [2, 3], the observed degree of stereospecificity in catalytic carbonylation was not high. It varied between 28 and 58% depending mainly on the polarity of the organic phase and the nature of the leaving group. Under the conditions used, after 15 h optically active hydratropic acid and α -phenethyl chloride suffered 10–15% loss of optical activity. (Analogous measurements for optically active α -phenethyl bromide could not be carried out owing to its high reactivity). This racemization is too slow to account for the loss of stereochemistry in carbonylation. While there is no reason to believe that the alkyl-acyl migratory insertion is not completely stereospecific in this case also, loss of stereochemistry could occur during the formation of the alkylcobalt carbonyl complex if concomitant ionic and radical pathways [4] or mixed S_N2 and S_N1 mechanisms [5] were operating. The opposite effect of solvent polarity on the degree of stereospecificity should be expected, however, if racemization were due to a radical mechanism. On the other hand, if a S_N1 -like mechanism caused the racemization, it is not easy to understand why a larger loss of stereochemistry was observed in carbonylation of α -phenethyl chloride.

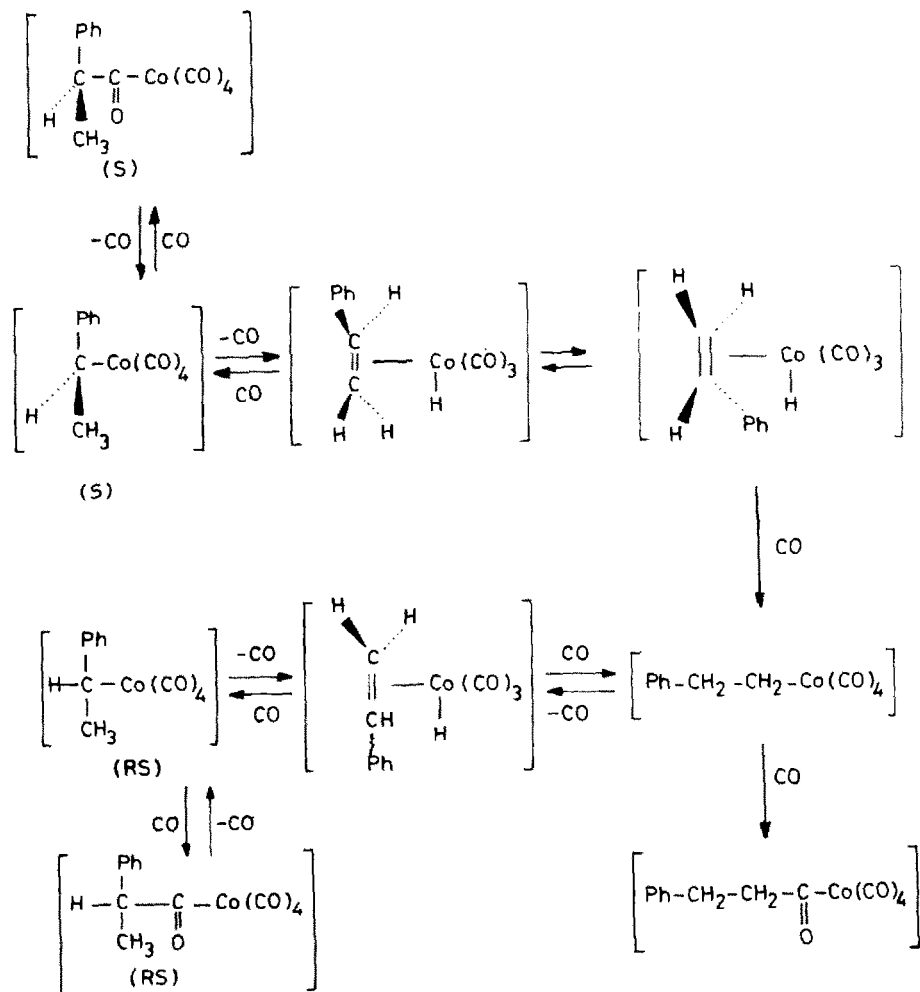
This type of mechanism should be more favoured in the case of α -phenethyl bromide [6].

In our opinion the observed racemization can be accounted for in terms of the existence under the conditions used of equilibria between keto and enol forms of the acyl complex and between branched and linear alkyl complexes (Scheme 2 and 3). In order to obtain experimental evidence for this hypothesis, α -D-phenethyl bromide was carbonylated under phase transfer conditions using n-butanol or t-amyl alcohol as organic phases. The acid mixtures thus obtained were carefully analyzed by ^1H - and ^{13}C -NMR and by mass spectrometry. The results are summarized in Table 2. When n-butanol was used, about 22% of hydratropic acid did not contain deuterium. This isotope exchange supports the presence of a keto-enol equilibrium as indicated in Scheme 2. (We can rule out the occurrence of a deuterium-hydrogen exchange in α -D-hydratropic acid itself, because no isotope exchange was observed upon heating the acid at 35°C for several hours in the two phase n-butanol-50% aqueous KOH system.) In contrast, when the carbonylation was carried out in the two phase t-amyl alcohol/50% aqueous KOH system, no deuterium-hydrogen exchange occurred. The effect of the lower polarity of this solvent, added to the deuterium isotope effect, probably makes enolization of the acyl complex more difficult. The concentration of base present in t-amyl alcohol was determined by titration and was shown to be much lower than in n-butanol ($4.4 \times 10^{-2} \text{ M}$ instead of 1.13 M). Thus nucleophilic attack on the branched acyl complex becomes slower, and a competitive isomerization of the alkyl complex in equilibrium with the acyl complex can occur in t-amyl alcohol [1]. If this secondary to primary alkyl group isomerization is a reversible process, it could cause racemization, as indicated in Scheme 3.

The presence, among the reaction products, of $\text{C}_6\text{H}_5\text{CH}(\text{CH}_2\text{D})\text{COOH}$ (about 25% of hydratropic acid) and of $\text{C}_6\text{H}_5\text{CH}_2\text{CHD}\text{COOH}$ (about 40% of β -phenylpropionic acid) supports this hypothesis. The incorporation of deuterium in both the benzylic and methyl positions can be readily accounted for if the equilibrium between the two forms of the alkylcobalt intermediate is reached by successive β -hydrogen elimination and α -hydrogen addition to the coordinated olefin, as indicated in Scheme 3 [7].



SCHEME 2



SCHEME 3

Variation of stereospecificity in carbonylation with the nature of the organic phase can be explained in terms of the relative importance of the two racemization routes. The large loss of stereochemistry in carbonylation of α -phenethyl chloride can be attributed to the higher reaction temperature and/or longer reaction time.

Easy enolization of the acyl complex intermediate, related to the mobility of the benzylic hydrogen, has been postulated as a requisite for carbon monoxide insertion into the phenylacetyl-cobalt bond [8, 9]. The previously reported double carbonylation of α -phenethyl bromide under phase transfer conditions is consistent with this hypothesis [1]. The results of the double carbonylation of α -D-phenethyl bromide (Table 3) provide the first experimental support for the proposed relationship between enolization of the acyl complex and double carbon monoxide insertion. In fact the presence of deuterium on the benzylic carbon makes double carbonylation so difficult that it is no longer the major reaction under the conditions used. The large deuterium isotope effect [10] in the keto-enol equilibrium can easily account for

this phenomenon. The absence of deuterium in the α -ketoacid provides additional support, although it is not conclusive in itself because of the possibility of deuterium-hydrogen exchange in this acid.

Experimental

NMR spectra were run in CDCl_3 with a Bruker WH-90 spectrometer. ^{13}C spectra were recorded by Proton Broad Band Decoupling. Mass spectra were run at 70 eV and a trap current of 300 μA , on a Varian MAT CH5-DF mass spectrometer connected to a Spectro-System MAT 200.

Materials

(*R*)-(+)-Phenethyl bromide [11] (optical purity 76.9%) and (*R*)-(+)-phenethyl chloride [12] (optical purity 78.7%) were made by published methods. α -D-Phenethyl bromide was prepared from α -D-phenethyl alcohol [13] by reaction with 48% HBr. ^1H NMR: $\delta(\text{CH}_3)$ 2.0(s); $\delta(\text{C}_6\text{H}_5)$ 7.5–7.2 (m).

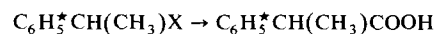
Mono and double carbonylation

These reactions were carried out under the phase transfer conditions previously described [1]. The ratio between α - and β -phenylpropionic acid was determined by GLC analysis of methyl esters (column: 10% SP2100 on 80/100 Supelcoport)

Monocarbonylation of optically active α -phenethyl halides. The optical purity of the hydratropic acid obtained from carbonylations under the conditions shown in Table I was calculated by comparing the corresponding specific rotation with that of the pure compound: $[\alpha]_{\text{D}}^{25}$ 75.8° (CHCl_3) [14, 15].

TABLE I

MONOCARBONYLATION OF OPTICALLY ACTIVE PHENETHYL HALIDES ^{a,b}



X	Organic phase	(<i>R</i>)-(+)	(<i>S</i>)-(+)	$\begin{array}{c} \text{CH}_3 \\ \\ \text{C}_6\text{H}_5\text{CHCOOH} \end{array}$	Optical purity (%)	Degree of stereospecificity
		<i>T</i> (°C)	<i>t</i> (h)			
Br	n-butanol	35	2	> 99	25	32.5
Br	t-amyl alcohol	35	4	93	35	45.5
Br	t-butyl methyl ether	35	4	73	45	58.5
Cl	n-butanol	45	16	97	22	28.5
Cl	t-amyl alcohol ^d	35	16	91	29.7	37.8
Cl	t-amyl alcohol ^e	45	5	83.2	29.6	37.6
Cl	t-butyl methyl ether ^f	45	48	93	27	34.5

^a All the experiments were run under one atmosphere of CO, using aqueous 50% KOH, $\text{Co}_2(\text{CO})_8$ as catalyst, and $\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_3\text{Br}$ as phase transfer catalyst. ^b $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{Br}$: optical purity 76.9%; $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{Cl}$: optical purity 78.7%. ^c The percentage composition of the mixture of acids was determined by GLC of methyl esters. ^d The recovered α -phenethyl chloride showed 10% loss of stereochemistry. ^e The reaction was over after 48 h. ^f The reaction was very slow and the conversion was only 12%.

TABLE 2

MONOCARBONYLATION OF α -D-PHENETHYL BROMIDE ^a

Organic phase	Total acid fraction ^b (%)	$\begin{array}{c} \text{CH}_3 \\ \\ \text{C}_6\text{H}_5\text{CDCOOH} \end{array}$	$\begin{array}{c} \text{CH}_3 \\ \\ \text{C}_6\text{H}_5\text{CHCOOH} \end{array}$	$\begin{array}{c} \text{CH}_2\text{D} \\ \\ \text{C}_6\text{H}_5\text{CHCOOH} \end{array}$	$\text{C}_6\text{H}_5\text{CHDCH}_2\text{COOH}$	$\text{C}_6\text{H}_5\text{CH}_2\text{CHDCOOH}$
		(%)	(%)	(%)	(%)	(%)
n-butanol	54	78.5	21.5	–	traces	–
t-amyl alcohol	55.2	68.3	–	22.8	5.2	3.6

^a All the experiments were run at 35°C for 4 h, using aqueous 50% KOH, $\text{Co}_2(\text{CO})_8$ as catalyst and $\text{C}_6\text{H}_5\text{N}(\text{CH}_3)_3\text{Br}$ as phase transfer catalyst. ^b Yields are based on the α -phenethyl bromide taken. The product distribution was determined by ¹H- and ¹³C-NMR and mass spectrometry (see Experimental). Styrene, phenethyl alcohol and 2,3-diphenylbutane were the main components in the neutral fraction.

TABLE 3

COMPARISON BETWEEN DOUBLE CARBOXYLATION OF $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{Br}$ AND $\text{C}_6\text{H}_5\text{CD}(\text{CH}_3)\text{Br}$ ^a

Substrate	Total acid fraction (%) ^b	$\begin{array}{c} \text{CH}_3 \\ \\ \text{C}_6\text{H}_5\text{CHCOCOOH} \end{array}$	$\begin{array}{c} \text{CH}_3 \\ \\ \text{C}_6\text{H}_5\text{CHCOOH} \end{array}$	$\begin{array}{c} \text{CH}_3 \\ \\ \text{C}_6\text{H}_5\text{CDCOOH} \end{array}$	$\text{C}_6\text{H}_5(\text{CH}_2)_2\text{COOH}$	$\text{C}_6\text{H}_5\text{CHDCH}_2\text{COOH}$
		(%)	(%)	(%)	(%)	(%)
$\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{Br}$ [1]	66.3	82.9	15.1	–	2	–
$\text{C}_6\text{H}_5\text{CD}(\text{CH}_3)\text{Br}$	39.3 ^c	22.6	2 ^d	71 ^e	1 ^d	3.3 ^f

^a The reactions were carried out in the two phase t-amyl alcohol/20% aqueous NaOH system using $\text{Co}_2(\text{CO})_8$ as catalyst ($\text{RX}/\text{Co}_2(\text{CO})_8 = 20-40$) and $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{N}(\text{CH}_3)_3\text{I}$ as phase transfer catalyst. ^b Yields are based on the α -phenethyl bromide taken. Styrene, phenethyl alcohol and 2,3-diphenylbutane were the main products in the neutral fraction. ^c The lower yield was accounted for by the formation of larger amount of styrene. ^d The formation of these compounds is partly due to carbonylation of the ammonium salt [16]. ^e $\text{C}_6\text{H}_5\text{CH}(\text{CH}_2\text{D})\text{COOH}$ was also present in very small amounts. ^f $\text{C}_6\text{H}_5\text{CH}_2\text{CHDCOOH}$ was also present in very small amounts.

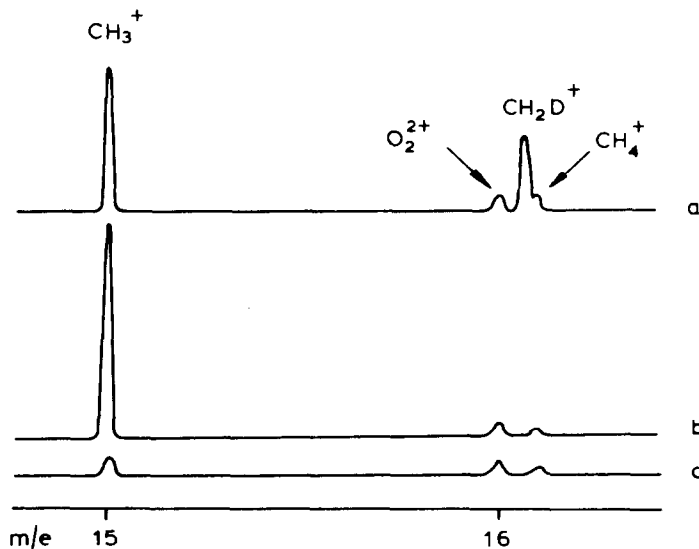


Fig. 1. Partial mass spectra of: (a) deuterated acid mixture; (b) α -phenyl propionic acid; (c) β -phenyl propionic acid.

Monocarbonylation of α -D-phenethyl bromide in the two phase n-butanol (50%) KOH aqueous solution system. A mixture of $C_6H_5CH(CH_3)COOH$ and $C_6H_5CD(CH_3)COOH$ was obtained (Table 2). The nature of the products was determined from the 1H -, ^{13}C -NMR and GC/MS of the corresponding methyl esters.

1H NMR: $\delta(CDCH_3)$ 1.49(s), $\delta(CHCH_3)$ 1.49(d), $\delta(CHCH_3)$ 3.72(q); $J(CHCH_3)$ 7.2 Hz; ^{13}C NMR; $\delta(CHCH_3)$ 45.5(s), $\delta(CDCH_3)$ 45.1(t), $J(C,D)$ 19.8 Hz.

GC/MS of $C_6H_5CD(CH_3)COOCH_3$: $m/e = 165$ (M^+), 106 ($M^+ - COOCH_3$); $C_6H_5CH(CH_3)COOCH_3$: $m/e = 164$ (M^+), 105 ($M^+ - COOCH_3$).

The molar ratio between $C_6H_5CH(CH_3)COOH$ and $C_6H_5CD(CH_3)COOH$ was determined from the 1H NMR spectrum by comparison of the relative intensities of the CH quartet at 3.72 ppm and the methyl groups at 1.49 ppm, and confirmed mass spectrometrically by determining the relative intensities of the parent ions at m/e 164 and m/e 165.

Monocarbonylation of α -D-phenethyl bromide in the two-phase t-amyl alcohol / 50% KOH aqueous solution system. No deuterium-hydrogen exchange was found for α - and β -phenylpropionic acid, as shown by GC/MS analysis of methyl esters. (In both cases the parent ion M^+ at m/e 164 was absent). The presence of $C_6H_5CH(CH_2D)COOH$ was shown by 1H , ^{13}C NMR and mass spectrometry of the acid mixture. 1H NMR: $\delta(CH)$ 3.71(t), $\delta(CH_2D) = 1.48$, $J(CH,CH_2D)$ 7.19 Hz; upon irradiation at 1.48 ppm a singlet at 3.71 ppm was obtained;

^{13}C NMR: $\delta(CH_2D)$ 17.8(t), $J(C,D)$ 19.8 Hz.

In the mass spectrum of the mixture of acids, $C_6H_5CD(CH_3)COOH$ and $C_6H_5CH(CH_2D)COOH$ were distinguished by examining the ions at $m/e = 15$ (CH_3) and $m/e = 16$ (CH_2D) due to the characteristic fragmentation of α -phenylpropionic acid (see Fig. 1). Accurate mass measurements at high resolution (~ 3000)

and with a doubly-charged back-ground oxygen ion as reference mass, showed that the composition of the ion at $m/e - 16$ was in agreement only with CH_2D . The presence of $\text{C}_6\text{H}_5\text{CHDCH}_2\text{COOH}$ and $\text{C}_6\text{H}_5\text{CH}_2\text{CHDCOOH}$ in the acid mixture was shown by GC/MS with corresponding methyl esters, $\text{C}_6\text{H}_5\text{CHDCH}_2\text{COOCH}_3$; $m/e = 165$ (M^+), 106, 105, 92; $\text{C}_6\text{H}_5\text{CH}_2\text{CHDCOOCH}_3$; m/e 165 (M^+), 106, 105, 91 and then confirmed by ^{13}C NMR.

^{13}C NMR: $\delta(\text{CHDCH}_2) + \delta(\text{CH}_2\text{CHD})$ 35.3(t), 30.3(t); $J(\text{C},\text{D})$ 19.8 Hz. The molar ratio between the two deuterated β -phenylpropionic acids was calculated from the relative intensities of the ions at m/e 92 ($\text{C}_6\text{H}_5\text{CHD}$) and m/e 91 ($\text{C}_6\text{H}_5\text{CH}_2$).

Double carbonylation of α -D-phenethyl bromide in the two phase t-amyl alcohol (20%) NaOH aqueous solution system. The composition of the acid mixture was determined by GLC of trimethyl-silyl-esters, as previously reported [1] (Table 3). The formation of $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{COCOCH}_3$ was confirmed by the ^1H NMR spectrum of the acid mixture which showed a quartet at δ 4.51 [1]. By comparing the intensities of this quartet and of the methyl group, the molar ratio between α -keto- β -phenylbutyric acid and hydratropic acid was found to be very close to that derived by GLC. This confirms that no deuterium is present in the α -ketoacid. The ratio between $\text{C}_6\text{H}_5\text{CD}(\text{CH}_3)\text{COOH}$ and $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{COOH}$ and between $\text{C}_6\text{H}_5\text{CHDCH}_2\text{COOH}$ and $\text{C}_6\text{H}_5(\text{CH}_2)_2\text{COOH}$ was obtained by mass spectrometry (see above).

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