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The Preparation of Optically Pure 3-Hydeoxybutanoic Acid and Its Homologues as the Dibenzylammonium Salt

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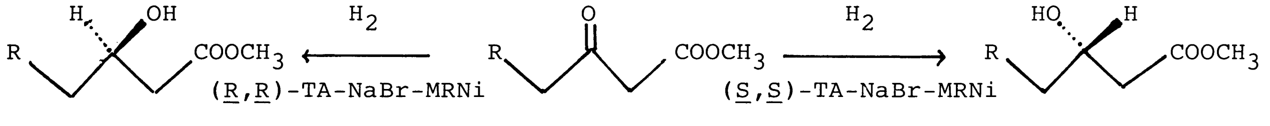
Optically pure (R)- and (S)-3-hydroxybutanoic acid and its homologues are prepared by the method consisting of the enantioface differentiating hydrogenation of methyl 3-oxoalkanoate to methyl 3-hydroxyalkanoate(80-90% e.e.) over asymmetrically modified nickel catalyst and the preferential crystallization of optically pure 3-hydroxyalkanoic acids from the hydrogenation products as the dibenzylammonium salts.

Optically active 3-hydroxyalkanoic acids (**1**) are key intermediates of the biosynthesis and metabolism of fatty acids and exist widely in biological systems. A series of optically pure **1**, especially the lower homologues such as 3-hydroxybutanoic acid (**1a**) are also useful chiral reagents for the asymmetric reaction as well as the starting materials of natural products. For these reasons, much attention has been paid on the development of facile and simple preparation of optically pure **1**. The biological reduction of 3-oxoalkanoic acids and their derivatives is one of the well documented methods.1) However, this method suffers a serious disadvantage that the products are limited to only one sort of enantiomers and no arbitrary choice of the enantiomer to be produced is possible. Thus, an efficient chemical method enables us to produce both (R)- and (S)-enantiomers has been greatly desired. In the previous communication, we have reported an effective chemical method for the preparation of optically pure **1** of carbon number 10 through 16.2) The method consists of the enantioface differentiating hydrogenation of methyl 3-oxoalkanoate (**2**) over asymmetrically modified Raney nickel and the preferential crystallization of optically pure **1** from the hydrogenation product as the dicyclohexylammonium salt.

The enantioface differentiating hydrogenation of **2** to (R)- or (S)-methyl 3-hydroxyalkanoate (**3**) over Raney nickel catalyst modified with (R,R)- or (S,S)-tartaric acid and NaBr(TA-NaBr-MRNi) is a well established process (Scheme 1) and gave the product in a 90-98% chemical yield and 80-85% optical yield.3)

As to the optical purification of higher homologues **1**, the recrystallization of their dicyclohexylammonium salts from acetonitrile was highly effective.2) The optical enrichment of lower homologues such as 3-hydroxybutanoic acid (**1a**) has been

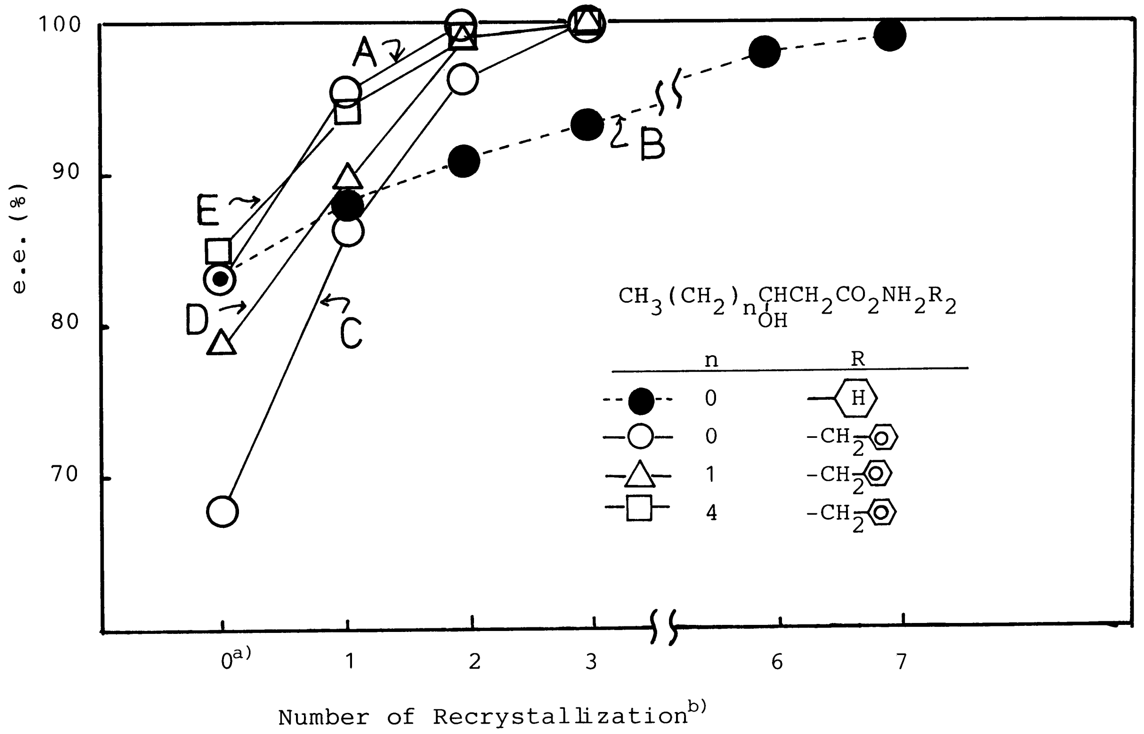


R; -H, and $-(CH_2)_nCH_3$

Scheme 1. Mode of enatioface differentiating hydrogenation over TA-NaBr-MRNi.

effected also by this method, with less satisfactory result.

The intensive investigation of the recrystallization process led us to the present finding that the use of dibenzylamine instead of dicyclohexylaminine outstandingly increased the efficiency of the optical enrichment of lower homologues of **1** as illustrated in Fig. 1. By only twice recrystallizations of the dibenzylammonium salt (**4a**), **1a** of 85% e.e. was purified to the optically pure state(Fig. 1, **A**), while in the case of dicyclohexylammoniun salt, more than seven recrystallizations were required to complete the enrichment(Fig. 1, **B**). The sample of fairly low optical purity (70% e.e.), which was hard to be purified as the dicyclohexylammonium salt, was also easily purified(Fig. 1, **C**). This method was also successfully applied to the purification of 3-hydroxypentanoic acid (**1b**) (Fig. 1, **D**) and 3-hydroxyoctanoic acid (**1c**)(Fig. 1, **E**).



a) Starting materials.

b) The yield of each recrystallization was adjusted to 88-90%.

Fig. 1. The efficiencies of the optical enrichment by the recrystallization of dibenzyl- and dicyclohexylammonium 3-hydroxyalkanoates.

A typical procedure for the preparation of optically pure (R)-**1a** is as follows: The enantioface differentiating hydrogenation of methyl acetoacetate (**2a**)(100 g) over (R,R)-TA-NaBr-MRNi was carried out by the reported method.3) The resulting (R)-methyl 3-hydroxybutanoate (**3a**) of 83% e.e.(99 g) was saponified with NaOH(37 g) dissolved in a mixture of methanol(100 ml) and water(200 ml). The resulting sodium salt of **1a** was loaded on a column of Amberite IR-120(H^+ type, 1000 ml) and eluted with a mixture of methanol(300 ml) and water(600 ml). To this eluate dibenzylamine(166 g) was added slowly under vigorous stirring, then the mixture was kept for 1 h at 50 °C. After the evaporation of the solvent from the mixture under reduced pressure, the residue was completely dried over anhydrous $CaCl_2$ to give 245 g of crude dibenzylammonium 3-hydroxybutanoate (**4a-0**). The recrystallization of a 244 g portion of **4a-0** from 14.64 l of acetonitrile (the ratio of the salt and solvent is 1 g to 60 ml) gave 218 g of the first crystals (**4a-1**), $[\alpha]_D$ -21.6° (c 1.2, $CHCl_3$). A 215 g portion of **4a-1** was again recrystalized by the same way as above to give 192 g of the second crystals (**4a-2**), mp 135.1 °C, $[\alpha]_D$ -22.45° (c 1.1, $CHCl_3$), Found: C,71.67; H,7.55; N,4.57%. Calcd for $C_{18}H_{23}NO_3$: C,71.73; H,7.69; N,4.65%. Further recrystallization of **4a-2** to **4a-3**($[\alpha]_D$ -22.44° (c 1.1, $CHCl_3$)), resulted in no significant increment of the optical rotation. The ^{1}HNMR spectrum of **3a** derived from **4a-2** showed no detectable signals of the antipode in the presence of chiral shift reagent (Eu[hfmc]$_3$).4) Thus, the **4a-2** was confirmed to be an optically pure state. The yield of **4a-2** from **3a** was calculated to be 77%.

The optically pure (S)-**4a**($[\alpha]_D$ +22.5° (c 1.1, $CHCl_3$)) was obtained from the hydrogenation product of **2a** over (S,S)-TA-NaBr-MRNi by the exactly same process as mentioned above.

The optically pure dibenzylammonium salts of (R)-3-hydroxypentanoic acid (**4b**)(mp 130.0 °C, $[\alpha]_D$ -17.76° (c 1.2 , $CHCl_3$), Found: C,72.44; H,7.90; N,4.42%. Calcd for $C_{19}H_{25}NO_3$: C,72.35; H,7.99; N,4.44%) and (S)-**4b**(mp 130.0 °C, $[\alpha]_D$ +17.80° (c 1.0 , $CHCl_3$)) were also obtained from methyl 3-oxopentanoate by the same process as mentioned above.

As to the purification of 3-hydroxyoctanoic acid (**1c**), the same process as above could not be employed owing to the hydrophobic nature of **1c**. Thus, the methyl 3-hydroxyoctanoate (**2c**) was derived to dibenzylammonium salt of **1c** (**4c**) as follows. A 90 g portion of (R)-**3c**(bp 68 °C/133 Pa, 91% e.e.) obtained by the hydrogenation of methyl 3-oxooctanoate (**2c**)(100 g) over (R,R)-TA-NaBr-MRNi was saponified with 20.7 g of NaOH dissolved in a mixture of water(80 ml) and methanol(500 ml). The reaction product was treated with 52.5 ml of concd HCl and concentrated under reduced pressure. The extraction of the condensate with 450 ml of chloroform and evaporation of the solvent gave 71.6 g of crude **1c**, which was converted to **4c** by the treatment with 94.0 g of dibenzylamine dissolved in 10.54 l of acetonitrile. The resulting crude salt (**4c-0**) in acetonitrile was heated until all solid matter was dissolved. The first crystals (**4c-1**) were precipitated on cooling the solution in a refrigerator. Twice recrystallizations of the resulting **4c** gave optically pure product, (R)-**4c-3**, mp 114.0 °C, $[\alpha]_D$ -14.08° (c 1.4, $CHCl_3$), Found: C,73.87; H,8.80; N,3.89%. Calcd for $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74; N,3.92%.

By the same method as above, optically pure (S)-**4c-3** was obtained from (S)-**3c** of 89% e.e. in a yield 65% based on **2a**, mp 115.5 $^{\circ}$C, $[\alpha]_D$ +14.08° (c,1.2, $CHCl_3$), Found: C,73.70; H, 8.90; N,3.90%.

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4) ^{1}HNMR spectra were measured with a JEOL-GX-400 spectrometer. A solution of **2**(5 mg) and Eu[hfmc]$_3$(3-5 mg) in $CDCl_3$(0.4 ml) was subjected to analysis. The difference in chemical shift for methyl proton of methoxycarbonyl group(singlet) of (R)- and (S)-**2** was 12-22 Hz.

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