The Preparation of Optically Pure 3-Hydroxyalkanoic Acid. The Enantioface-differentiating Hydrogenation of the C=O Double Bond with Modified Raney Nickel. XXXVII.

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The enantioface-differentiating hydrogenation of methyl 3-oxoalkanoate ($CH_3(CH_2)_nCOCH_2COOCH_3$, n=0, 6, 8, 10, 12) over the (*R,R*)-tartaric acid–NaBr–modified Raney nickel catalyst ((*R,R*)-TA–NaBr–MRNi) gave methyl (*R*)-3-hydroxyalkanoate ($CH_3(CH_2)_nCH(OH)CH_2COOCH_3$, n=0, 6, 8, 10, 12) in an average optical yield of 85%. After the methyl ester had been converted to dicyclohexylammonium salt of 3-hydroxyalkanoic acid, the salt was recrystallized three times from acetonitrile and then treated with acid to give optically pure (*R*)-3-hydroxyalkanoic acid ($CH_3(CH_2)_nCH(OH)CH_2COOH$, n=0, 6, 8, 10, 12) in a reasonable yield. From the hydrogenation product with (*S,S*)-TA–NaBr–MRNi, optically pure (*S*)-3-hydroxyalkanoic acid was obtained by the same process as above.

Optically active 3-hydroxyalkanoic acids (**1**) and their derivatives exist widely in the biological system. For example, 3-hydroxydecanoic acid is a sprouting regulatory substance secreted by the leaf-cutting ant (*A sexdens*)[1] and is also a component of depsipeptide "Serataniolide,"[2] 3-hydroxytetradecanoic acid is a major fatty acid comprising "lipid-A in endotoxin,"[3] the choline ester of 3-acetoxyhexadecanoic acid is a fish toxin "pahutoxine,"[4] and 3-hydroxyoctadecanoic acid is a component of emposatilin, an antitumor reagent.[5]

Although various methods of synthesizing these important 3-hydroxyalkanoic acids have been proposed,[6–8] no practical ways for the preparation of these optically pure compounds have been reported. As has been briefly reported in a preliminary communication,[9] the present method consists of the enantioface-differentiating hydrogenation of the methyl 3-oxoalkanoate over an asymmetrically modified nickel and the preferential crystallization of an optically pure substance from the hydrogenation products. In this paper, the preparations of optically pure acids of carbon numbers from 10 to 16 in the practical scale will be reported.

Results and Discussion

The preparation of optically pure 3-hydroxyalkanoic acid (**1**) was carried out by the process outlined in Scheme 1.

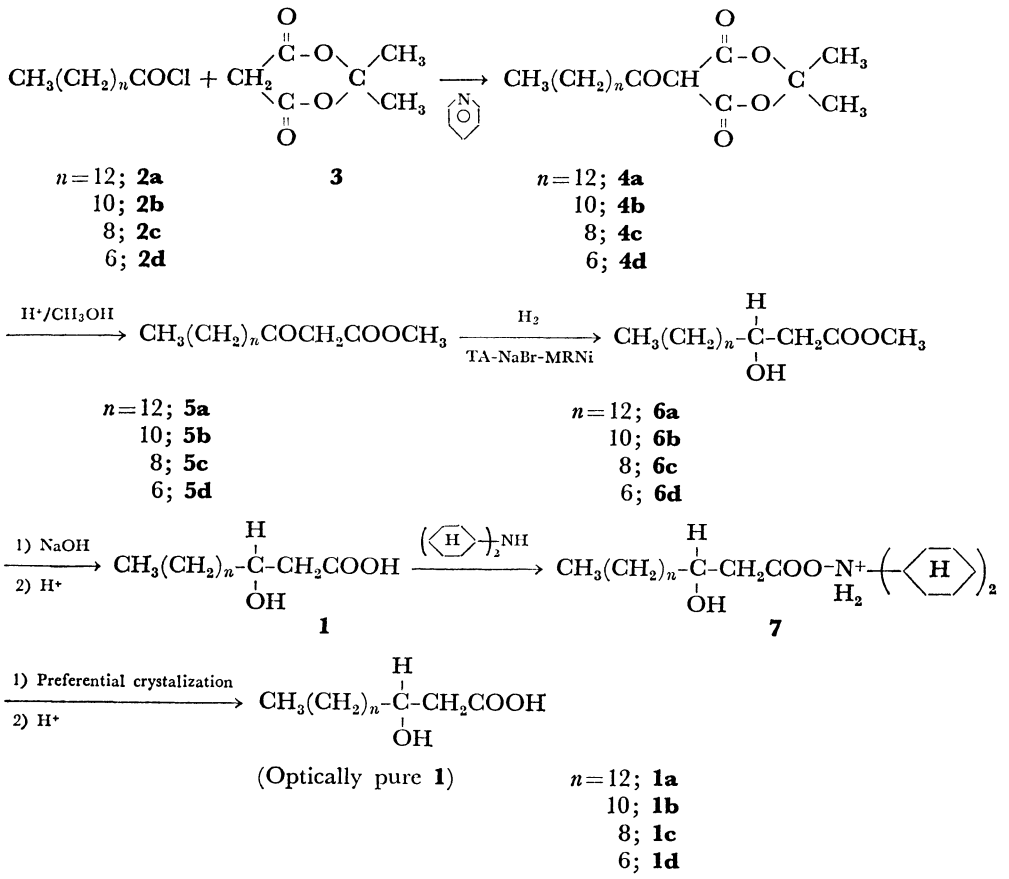
Since the catalytic hydrogenation with the nickel catalyst is sensitive to the impurities of the substrate, one of the essential factors in the present process is the development of a suitable method to synthesize methyl 3-oxoalkanoate (**5**). Among the previously reported methods[10–13] here examined, a modification of the method of Oikawa and his co-workers[10] (Scheme 1) gave the best results with respect to the practical-scale preparation of chemically pure **5**. The isolation and purification of the intermediate (**4**) before the decarboxylation was necessary to obtain long-chain methyl 3-oxoalkanoate (**5**) in a high purity. The average yield of **4** was 70%, based on **3**.

The catalyst (TA–NaBr–MRNi) employed for the enantioface-differentiating hydrogenation of **5** to methyl 3-hydroxyalkanoate (**6**) was prepared by soaking the Raney nickel catalyst in an aqueous solution of tartaric acid (TA) and NaBr at 100 °C.[14]

Table 1. Enantioface-differentiating hydrogenation of methyl 3-oxoalkanoate over TA-NaBr-MRNi

No.	Substrate $CH_3(CH_2)_nCOCH_2COOCH_3$ (n)	Catalyst modifying reagent	Reaction products: $CH_3(CH_2)_nCHOHCH_2COOCH_3$ Configuration	e. e. (%)[a]	$CH_3(CH_2)_nCHOHCH_2COOH$ Isolated yield[b]
1	12 (**5a**)	(*R,R*)-TA	(*R*)	87.0	82.1
2		(*S,S*)-TA	(*S*)	84.4	81.2
3	10 (**5b**)	(*R,R*)-TA	(*R*)	85.5	79.7
4		(*S,S*)-TA	(*S*)	84.5	81.5
5	8 (**5c**)	(*R,R*)-TA	(*R*)	86.7	80.1
6		(*S,S*)-TA	(*S*)	84.8	79.8
7	6 (**5d**)	(*R,R*)-TA	(*R*)	83.3	79.0
8		(*S,S*)-TA	(*S*)	87.5	75.8
9	0	(*R,R*)-TA	(*R*)	83[c]	70
10		(*S,S*)-TA	(*S*)	83[c]	70

a) Determined by means of ^{1}H-NMR with a chiral shift reagent. b) Isolation yield based on **5**. c) Taken from our published data.



Scheme 1.

Table 2. The efficiencies of the preferential recrystallizations of various ammonium salts of 3-hydroxyhexadecanoic acid from acetonitrile[a)]

No.	Amine employed	Amount of solvent used for recrystallization per g salt (ml)	Recovery after three recrystallization (%)	Optical rotation of free acid recovered $[\alpha]_D^{20}$/° (*c* 1, $CHCl_3$)
1	Cyclohexylamine	73	36.8	−11.6
2	Benzylamine	45	76.1	−12.5
3	Aniline	7.7	58.5	−12.5
4	Dicyclohexylamine	27	90.7	−13.8 (e. e.>98%)
5	*n*-Hexylamine	>164[b)]	—	—

a) 3-Hydroxyhexadecanoic acid ($[\alpha]_D^{20}$ −10.7° (*c* 1, $CHCl_3$), 85% e. e.) was used as the starting material. b) The solubility of salt was too small for it to be used for recrystallization.

Table 3. Preferential recrystallization of dicyclohexylammonium salt of 3-hydroxyalkanoic acid from acetonitrile

No.	3-Hydroxyalkanoic acid $CH_3(CH_2)_nCH(OH)CH_2CO_2H$ (*n*)	Starting material: Configuration	Starting material: e. e. (%)	Amount of solvent used fore ach crystallization per g salt (ml)	Recovery after three recrystallization (%)	Product e. e. (%)
1	12 (**1a**)	(*R*)	87	24.5	75.9	>98
		(*S*)	85		74.5	>97
2	10 (**1b**)	(*R*)	85	19.0	72.1	100
		(*S*)	86		73.0	100
3	8 (**1c**)	(*R*)	88	18.0	73.5	100
		(*S*)	85		72.5	100
4	6 (**1d**)	(*R*)	87	11.5	50.5	>98
		(*S*)	85		51.5	>98
5	0 (**1e**)	(*R*)	86	7.0	52[a)]	>98
		(*S*)	86		55[a)]	>98

a) Recovery after 6 recrystallizations.

The hydrogenations of **5** to **6** proceeded smoothly under an initial hydrogen pressure of 100 kg/cm² at 100 °C; they produced quantitative chemical yields and an optical yield of more than 83%. The saponification of **6** gave **1** in an averaged isolation yield of 95%, based on **5**. The results are listed in Table 1. In all cases, the use of (*R*,*R*)-TA–NaBr–MRNi gave (*R*)-**1** in excess. It is advantageous that the natural type of (*R*)-**1** can, incidentally, be obtained by the use of common (*R*,*R*)-TA as a modifying reagent.

The isolation of optically pure **1** from the reaction product (85% e.e.) was achieved by the preferential crystallization method.

To ascertain the most effective derivatives of **1** for the preferential crystallization, various ammonium salts of **1a** (C_{16} acid) were prepared and the efficiencies of resolution were examined. The results are listed in Table 2. Among the ammonium salts of **1** examined, the dicyclohexylammonium salt (**7**) gave the best result. An optically pure substance was obtained in a yield of 70% by three successive recrystallizations from acetonitrile.

The method was also effectively applicable to the resolution of **1b** to **1e** as is shown in Table 3.

The advantage of the present procedure is that optically pure 3-hydroxyalkanoic acid with various alkyl chain lengths is easily obtained by a simple unit process: catalytic hydrogenation and recrystallization. Furthermore, the preparation of TA–NaBr–MRNi is very simple, and the cost of the catalyst is negligible.

Experimental

The ^{1}H-NMR and IR spectra were taken with a JEOL FX-100 spectrometer and a Shimadzu IR 27G spectrometer respectively. The optical rotation was measured with a Perkin Elmer 241 Polarimeter. The GLC was carried out with a Shimadzu 6A-PF Gas Chromatography, using a 3 m-5 mm o.d. glass column packed with 2% Silicone OV-17 on Chromosorb W (OV-17).

All the chemicals except those described below were obtained from commercial sources and were used without further purification.

*Substrate. Methyl 3-Oxohexadecanoate (**5a**)*: Tetradecanoyl chloride (**2a**) (217 g, 0.88 mol) was added, drop by drop, into a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (**3**) (115 g, 0.8 mol) and pyridine (128 g) in 1000 ml of CH_2Cl_2 at 5 °C. The reaction mixture was then stirred for 1 h at room temperature. The mixture was washed with three 200-ml portions of 10% HCl and a 200-ml portion of water successively, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in 200 ml of methanol and kept overnight at −20 °C. The crystalline intermediate, **4**, precipitated was collected by filtration and washed with a small portion of cold methanol. The resulting substance was dissolved in 1000 ml of methanol and subjected to decarboxylation under reflux for 5 h. After the evaporation of the solvent from the reaction product, the residue was crystallized from 100 ml of methanol at −20 °C. The separation of the crystals by filtration at −20 °C gave 170 g of **5a** in a yield of 75% based on **3**; mp 41 °C. Calcd for $C_{17}H_{32}O_3$: C, 71.78; H, 11.34%. Found C, 71.50; H, 11.57%. IR, (KBr disk) 2950, 1735, 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$); δ 0.89 (t, 3H, $-C\underline{H}_3$), 1.25 (m, 22H, $-(C\underline{H}_2)_n$), 2.55 (t, 2H, $-C\underline{H}_2-\overset{\overset{O}{\|}}{C}-$), 3.42 (s, 2H, $-CO-C\underline{H}_2-CO$), 3.72 (s, 3H, $-OC\underline{H}_3$).

*Methyl 3-Oxotetradecanoate (**5b**) and Methyl 3-Oxododecanoate (**5c**)*: These substances were prepared by the same procedure as that used for **5a**, except for the use of dodecanoyl chloride (**2b**) and decanoyl chloride (**2c**) respectively, instead of tetradecanoyl chloride (**2a**), as starting materials.

From 193 g (0.88 mol) of **2b** and 115 g of **3** (0.8 mol), 147 g of **5b** were obtained. (Yield 72% based on **3**). Mp 30 °C. Calcd for $C_{15}H_{18}O_3$: C, 70.27; H, 11.01%. Found: C, 70.20; H, 11.21%.

From 167.6 g (0.88 mol) of **2c** and 115 g of **3**, 123 g of **5c** was obtained. The final purification was performed by vacuum distillation instead of crystallization. Bp 127 °C/3 mmHg.** Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59%. Found: C, 67.80; H, 10.66%. The IR and ^{1}H-NMR spectra of these samples consisted of structures of **5b** and **5c**.

*Methyl 3-Oxodecanoate (**5d**)*: Octanoyl chloride (**2d**) (162 g, 0.88 mol) and **3** (115 g, 0.8 mol) were subjected to the reaction under the same conditions as those described before. The resulting crude intermediate (**4**) in CH_2Cl_2 was washed three 200-ml portions of 10% HCl and three 200-ml portions of water, and then concentrated under reduced pressure. The residue was dissolved in 800 ml of methanol, and the mixture was refluxed for 5 h. After the evaporation of the methanol from the reaction mixture, the residue was dissolved in 400 ml of benzene, washed successively with two 100-ml portions of a 10% aqueous K_2CO_3 solution and two 100-ml portions of water, and dried over Na_2SO_4. The solvent was evaporated, and the residue was distilled under reduced pressure to give 83 g of **5d**. Bp 112 °C/3 mmHg, Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%. Found: C, 66.10; H, 10.07%. The ^{1}H-NMR and IR spectra of the sample consisted of the structure of **5d**.

Catalyst. (R,R)-TA–NaBr–MRNi: Into an alkaline solution (4.5 g of NaOH in 20 ml of H_2O) was added 1.9 g of the Raney nickel alloy (Ni:Al=42:58, Kawaken Fine Chemicals Co.) portion by portion. The resulting suspension was kept for 1 h at 100 °C, after which the supernatant was removed by decantation. The resulting Raney nickel catalyst (RNi) was washed 15 times with 30-ml portions of deionized water. (*R*,*R*)-TA (1 g) and NaBr (10 g) were dissolved in 100 ml of deionized water, and the pH of the solution was adjusted to 3.2 with 1 M NaOH solution. To the solution heated in a boiling-water bath was then added the Raney nickel previously prepared; the mixture was kept for 1 h with occasional stirring at 100 °C. After the removal of the supernatant by decantation, the residual catalyst was washed with a 10-ml portion of water, two 50-ml portions of methanol, and a 25-ml portion of methyl propionate, and then stored in 25-ml of methyl propionate. By the same process, (*S*,*S*)-TA–NaBr–MRNi was prepared by the use of (*S*,*S*)-TA.

*3-Hydroxyalkanoic Acid **1a** (or **1b**, **1c**, **1d**).* In an autoclave (100-ml capacity) were placed 10 g of **5a** (or **5b**, **5c**, **5d**), 30 ml of methyl propionate, 0.1 ml of acetic acid, and TA–NaBr–MRNi prepared from 1.9 g of the Raney alloy. Hydrogenation was carried out at an initial H_2-pressure of 100 kg/cm² at 100 °C until no more consumption of H_2 was observed. After the subsequent evacuation of H_2, the reaction product was dissolved in 50 ml of ether and filtered to separate the catalyst. The filtrate was washed with a 30-ml portion of 10% aqueous Na_2CO_3 and con-

** 1 mmHg ≈ 133.322 Pa.

Table 4. Analytical data of optically pure 3-hydroxyalkanoic acid

Compound	$[\alpha]_D^{20}$/°(c 1, $CHCl_3$)	Mp θ_m/°C	Calcd(Found)(%)	
			$C_{16}H_{32}O_3$	C, 70.54; H, 11.84
(*R*)-**1a**	−13.8	76.8		(70.90) (12.06)
(*S*)-**1a**	13.9	77.0		(70.84) (11.97)
			$C_{14}H_{28}O_3$	C, 68.81; H, 11.55
(*R*)-**1b**	−16.2 lit,[9] −16	72.0		(68.55) (11.88)
(*S*)-**1b**	16.1 (c 1, $CHCl_3$)	71.8		(68.61) (11.89)
			$C_{12}H_{24}O_3$	C, 66.63; H, 11.18
(*R*)-**1c**	−17.5	56.5		(66.43) (11.42)
(*S*)-**1c**	17.4	56.8		(66.31) (11.29)
			$C_{10}H_{20}O_3$	C, 63.79; H, 10.71
(*R*)-**1d**	−20.6 lit,[10] −20.8	bp 129—131 °C		(63.48) (10.80)
(*S*)-**1d**	19.8 (c 1, $CHCl_3$)	(1 mmHg)		(63.51) (10.82)

centrated under reduced pressure to give crude **6a** (or **6b**, **6c**, **6d**). A 100-mg portion of crude **6a** (or **6b**, **6c**, **6d**) was purified on preparative TLC as the sample for NMR and IR analysis. The GLC (OV-17) of each purified sample showed a single peak. The retention times of the samples were 31.2 min (**6a**, 160 °C), 11.4 min (**6b**, 160 °C), 12.0 min (**6c**, 110 °C), and 4.2 min (**6d**, 100 °C). The IR and ^{1}H-NMR spectra of **6a** were as follows: IR (KBr disk), 3390, 2950, 1739, 1700; NMR ($CDCl_3$) δ 0.90 (t, 3H, $-C\underline{H}_3$), 1.30 (m, 24H, $-(C\underline{H}_2)_n-$), 2.50 (m, 2H, $-C\underline{H}(OH)-C\underline{H}_2-C(=O)-$), 3.72 (s, 3H, $-OC\underline{H}_3$), 4.00 (m, 1H, $-C\underline{H}(OH)-$). The spectra of **6b**, **6c**, **6d** were almost the same as those of **6a** and were consistent with their structures.

The optical purity of each sample as determined by ^{1}H-NMR in the presence of Eu(hfmc)$_3$, is listed in Table 1. The difference in the chemical shift for the methyl proton of $-C(=O)-OC\underline{H}_3$ (singlet) of (*S*)- and (*R*)-**6** was 6—10 Hz when the spectra were measured with a solution of **6** (10 mg) and Eu(hfmc)$_3$ (15 mg) in 400 μl of $CDCl_3$. The saponification of the major part of crude **6a** (or **6b**, **6c**, **6d**) with NaOH and subsequent acid treatment gave crude **1a** (or **1b**, **1c**, **1d**). The yields are listed in Table 1.

Preferential Crystallizations of Various Ammonium Salts of 1a. Cyclohexyl-, benzyl-, phenyl-, dicyclohexyl-, and hexylammonium salts of **1a** (85% e.e., $[\alpha]_D^{20}$ −10.7 (c=1, $CHCl_3$)) were prepared from 5.5 g of **1a** and a 1.1-mol equivalent of the amine. Each ammonium salt was dissolved in a minimum amount of boiling acetonitrile and crystallized at room temperature. The amounts of acetonitrile used are listed in Table 2. After three recrystallizations, the salt was acidified with 10% aqueous HCl and the liberated **1a** was extracted with ether. After drying over Na_2SO_4, the extract was concentrated to the crystals. The optical rotation of **1a** liberated from each recrystallized salt is listed in Table 2.

Optically Pure 3-Hydroxyalkanoic Acid 1a (or 1b, 1c, 1d). Crude **1a** (or **1b**, **1c**, **1d**) obtained by the hydrogenation was converted to dicyclohexylammonium salt. Three recrystallizations of the salt from a minimum amount of acetonitrile gave the optically pure salt of **1a** (or **1b**, **1c**, **1d**). The optical purity of the starting material, the amount of acetonitrile used for recrystallization, and the recovery of optically active salt as crystals are listed in Table 3.

Optically active **1a** (or **1b**, **1c**, **1d**) was obtained by the acid treatment of the salt as described above. The analytical data of the products are listed in Table 4.

A 100-mg portion of each acid was converted to the methyl ester with diazomethane and purified by preparative TLC. The optical purity of each purified sample as determined by ^{1}H-NMR, is listed in Table 3.

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