NOTES

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Asymmetric Hydrogenation of C=O Double Bond with Modified Raney Nickel. XXVI. Asymmetric Hydrogenation of β-Keto Esters

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It was found that the Raney nickel catalyst modified with the α-amino or α-hydroxy acid catalyzed the hydrogenations of β-keto esters to the corresponding β-hydroxyesters in good asymmetric yields, and that the alkoxy moiety of the ester of acetoacetic acid influenced the asymmetric yields.1) For the elucidation of the enantiotopic selection2) mechanism of the modified Raney nickel catalyst, the effect of the bulk of the acyl group on the asymmetric yield of the product has been studied with various methyl acylacetates.

Experimental

Preparation of the Substrate. The methyl acylacetates were prepared by the ester-interchange of the ethyl acylacetates with sodium methoxide in methanol. The ethyl acylacetates were synthesized by the decomposition of the acylated malonic esters, which had been prepared from magnesium malonate and acyl chloride by the method of Riegel *et al.*3) Ethyl oxalacetate was prepared by the condensation of ethyl acetate and ethyl oxalate with sodium.4)

Optical Resolution of DL-*3-Hydroxy*-n-*valeric Acid.* One hundred grams of ethyl propionylacetate2) was reduced with 2.4 g of a Raney nickel catalyst1); the product was hydrolyzed with a slightly excess 50% sodium hydroxide solution and acidified with concd hydrochloric acid equivalent to the alkali used. After concentration *in vacuo*, the acid was extracted with acetone and the acetone was removed by distillation under reduced pressure. Seventy grams of the acid was thus obtained.

Quinine monohydrate (152 g) in 1 l of water was neutralized with 50 g of DL-3-hydroxy-*n*-valeric acid at 100°C. Then the solution was cooled to room temperature. The quinine salts were collected by filtration and recrystallized once from water. Yield, 90 g; mp 112°C.

Found: C, 65.33; H, 8.19; N, 5.91%. Calcd for $C_{25}H_{36}O_6N_2$: C, 65.19; H, 7.88; N, 6.08%.

$[\alpha]^{20}_{D}$ $-119°$ (c 1, ethanol).

Ninety grams of the quinine salt was suspended in 1.5 l of water and decomposed with 90 ml of a 10% sodium hydroxide solution. The mixture was then let stand overnight, after which the quinine was removed by filtration. The solution was washed with 150 ml of chloroform five times, neutralized with N hydrochloric acid, and concentrated to dryness. The sodium salt was extracted with ethanol, and the ethanol solution was cooled to room temperature. The sodium salts were filtered off and dried in a vacuum desiccator at 60°C. Yield, 26 g; mp 116 °C. $[\alpha]^{20}_{D}$ $+8.48°$ (c 4, water).

Found: C, 41.65; H, 6.95%. Calcd for $C_5H_9O_3Na \cdot 1/4H_2O$: C, 41.52; H, 6.62%.

Preparation of Methyl L$_{s}$5)*-(+)-3-Hydroxy*-n-*valerate.* Five grams of the sodium salt was dissolved in 50 ml of water; the solution was then acidified with 3.2 ml of concd hydrochloric acid and concentrated to dryness under reduced pressure. The acid was extracted with 100 ml of ether and esterified with diazomethane.6) After the removal of the ether, the ester was distilled under reduced pressure. Yield, 3.6 g; bp 81°C/17 mmHg.

Found: C, 53.80; H, 9.33%. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15%.

α^{20}_{D} $+18.60$ (without dilution).

Preparation of the Modified Raney Nickel Catalyst and Measurement of the Asymmetric Activity of the Catalyst. The procedures for the preparation of the modified Raney nickel catalyst and the measurement of the asymmetric activity were the same as have been described in a previous paper.7)

Results and Discussion

In order to elucidate the effect of the bulk of the acyl group of the β-keto ester on the asymmetric activity of the catalyst, various methyl acylacetates and diethyl oxalacetate were hydrogenated with catalysts modified with L-glutamic acid and D-tartaric acid. The acyl groups used were propionyl, *n*-butyryl, isobutyryl, and octanoyl groups. The results are compared in Table 1 with those of the hydrogenation of methyl acetoacetate.

With the catalysts modified by D-tartaric acid, and by L-glutamic acid, the methyl acylacetates were hydrogenated to the products of the levorotatory optical rotation.8)

Upon modification with tartaric acid, the asymmetric yield was higher in methyl propionylacetate than in methyl acetoacetate and a product with a large op-

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1) Y. Izumi, M. Imaida, T. Harada, T. Tanabe, S. Yajima, and T. Ninomiya, This Bulletin, **42**, 241 (1969).

2) The definition was proposed in *Angew. Chem., Int. Ed. Engl.*, **10**, 871 (1971).

3) B. Riegel and W. M. Lilienfeld, *J. Amer. Chem. Soc.*, **67**, 1273 (1945).

4) W. Wislicenus, *Ann.*, **246**, 315 (1888).

5) P. A. Levene and H. L. Haller, *J. Biol. Chem.*, **76**, 415 (1928).

6) H. Pechman, *Ber.*, **27**, 1888 (1894).

7) Y. Izumi, T. Harada, T. Tanabe, and K. Okuda, This Bulletin, **44**, 1418 (1971).

8) The optical rotations of the methyl esters of optically-active 3-hydroxycaproic acid, 3-hydroxy-4-methyl-*n*-valeric acid, and 3-hydroxycapric acid have not been obtained successfully. However, the optical rotations of optically-pure methyl 3-hydroxybutyrate and methyl 3-hydroxy-*n*-valerate were 23.8 and 18.6° respectively and the elongation of the carbon chain in the 3-hydroxy-*n*-aliphatic acid seems to be accompanied by a decrease in the optical rotation.

Table 1. Relation between asymmetric yield and bulk of acyl group of β-keto ester $R-CO-CH_2-COOCH_3$

Substrate R in $RCOCH_2COOCH_3$	Modifying[b)] reagent	Optical rotation of product, α_D^{20}	Asymmetric yield P %
CH_3-	L-Glutamic acid	−5.03	21[a)]
CH_3CH_2-	L-Glutamic acid	−3.13	17
$CH_3(CH_2)_2-$	L-Glutamic acid	−1.29	—
$(CH_3)_2CH-$	L-Glutamic acid	−4.06	—
$CH_3(CH_2)_6-$	L-Glutamic acid	−0.28	—
CH_3-	D-Tartaric acid	−7.73	33[a)]
CH_3CH_2-	D-Tartaric acid	−10.19	55
$CH_3(CH_2)_2-$	D-Tartaric acid	−4.23	—
$(CH_3)_2CH-$	D-Tartaric acid	−15.95	—
$CH_3(CH_2)_6-$	D-Tartaric acid	−0.61	—
CH_3CH_2-	D-Tartaric acid[c)]	−12.25	66
C_2H_5OCO-[d)]	D-Tartaric acid	0	0

a) Part XXV of this series: T. Tanabe, K. Okuda, and Y. Izumi, to be reported in this Bulletin.
b) Modifying condition: pH 5.0, 0 °C.
c) Modified at pH 5.0, 100 °C.
d) Diethyl oxalacetate.

tical rotation was obtained in the hydrogenation of methyl isobutyrylacetate. These facts suggest that the bulk of the acyl group contributed to the enantiotopic selection of the substrate by D-tartaric acid on the catalyst surface. Upon modification at 100°C, a higher asymmetric yield (66%) was obtained in the hydrogenation of methyl propionylacetate.

The catalyst modified with L-glutamic acid was found to have a different asymmetric activity than the one modified with D-tartaric acid. Though the asymmetric directions of the products were levorotatory, it seemed that the asymmetric yields of the products were not much affected by the bulk of the acyl group. Accordingly, a high asymmetric yield would not be obtained by the modification of the acyl group of the methyl acylacetate.

Diethyl oxalacetate was not asymmetrically hydrogenated with the catalyst modified with tartaric acid, as may be seen in Table 1. This result suggests that the smaller defference in the groups around the carbonyl group to be reduced may result in the difficulty of the enantiotopic selection by the modifying reagent.

The results presented above show that the sorts of the substituents and the steric requirement around the carbonyl group of the substrate are very important for the enantiotopic selection by the modifying reagent, especially in the asymmetric hydrogenation by the catalyst modified with tartaric acid.

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