Asymmetric Synthesis with Sugar Derivatives. IV. Catalytic Hydrogenations of Phenylglyoxylic Esters of Sugar Derivatives

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In connection with the studies[1] of asymmetric synthesis with sugar derivatives, the present work was undertaken to examine the effects of the sugars on the stereochemical course of the hydrogenations of phenylglyoxylic sugar-esters over the metal catalysts. The following sugar esters were employed: 1, 2; 5, 6-di-*O*-cyclohexylidene-3-*O*-phenylglyoxyl-α-D-glucofuranose (I), its isopropylidene derivative (II), 5-*O*-ethyl-1, 2-*O*-isopropylidene-3-*O*-phenylglyoxyl-α-D-xylofuranose (III), and its 5-deoxy derivative (IV). These esters were hydrogenated over Raney nickel or palladium in ethanol to the diastereomeric sugar mandelates, which were rapidly hydrolyzed under alkaline conditions[2] at room temperature to produce mandelic acid in 44.6% (maximum) optical yield (Table 1).

The easy removal of the sugar parts is of great advantage to asymmetric synthesis of optically unstable substances.

Mitsui *et al.*[3a] reported that (−)-menthyl phenylglyoxylate (V) was hydrogenated in the presence of various catalysts to diastereomeric (−)-menthyl mandelates, which gave either enatiomer of mandelic acid in excess after partial hydrolysis[4] with acid (Table 1). The direction of the asymmetric induction dependend on the natures of the catalysts used: 5% palladium on charcoal (Pd-C) prepared by the reduction of palladium chloride with hydrogen, or with formaldehyde in an alkaline solution contains extremely small quantities of acid (A) or base (B), respectively, and Raney nickel (Ni) has also trace amounts of alkali. They found that the acid or the base in the catalysts exerted influence on an equilibrium between (−)-menthyl ester (V) and its hemiketal in ethanol, and explained the steric course of the asymmetric hydrogenation according to Prelog's rule[5] as described below.[3a−d]

In the presence of Pd-C-A, *s*-cis (–COCO–) conformer of (−)-menthyl ester (V) will exist predominantly over *s*-trans one since the hemiketal of the former is more stabilized than that of the latter by the formation of intramolecular hydrogen bonding between the hydroxyl and the ester

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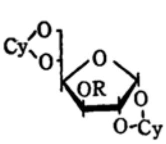
[1] Part III: M. Kawana and S. Emoto, This Bulletin, **40**, 2168 (1967).

[2] A. McKenzie, *J. Chem. Soc.*, **85**, 1249 (1904); M. Kawana and S. Emoto, This Bulletin, **40**, 618 (1967).

[3] a) S. Mitsui, T. Kamaishi, M. Imaizumi and K. Takamura, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **83**, 1115 (1962); *Chem. Abstr.*, **59**, 11569 (1963); b) T. Kamaishi and S. Mitsui, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **86**, 623 (1965); *Chem. Abstr.*, **65**, 2326 (1966); c) S. Mitsui and A. Kanai, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **87**, 179 (1966); *Chem. Abstr.*, **65**, 17006 (1966); d) S. Mitsui and Y. Imai, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **88**, 86 (1967).

[4] It was verified that (—)-menthyl (±)-mandelate was hydrolyzed with acid at equal rate.

[5] V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953); V. Prelog and H. Scherrer, *ibid.*, **42**, 2227 (1959).



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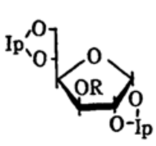

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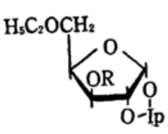

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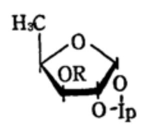

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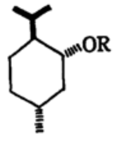

V

R = -$COCOC_6H_5$, Cy = Cyclohexylidene, Ip = Isopropylidene

TABLE 1. ASYMMETRIC SYNTHESIS OF MANDELIC ACID

Ester[a]	Catalyst,[b]	mg	Reduction time, hr	Yield %	$[\alpha]_D$ (c, H_2O),	°C	Optical[c] yield, %
I	Raney Ni	300 (wet)	2.5	72.4	−70.5° (0.44)	25	44.6
	5% Pd-C-B	50	8.0	71.1	−36.1° (0.44)	21	22.8
	5% Pd-C-A	50	2.0	70.4	+38.1° (0.42)	20	24.1
II	Raney Ni	500 (wet)	1.0	76.3	−58.0° (0.46)	25	36.7
	5% Pd-C-B	50	4.5	80.3	−24.4° (0.45)	26	15.4
	5% Pd-C-A	50	1.5	83.6	+32.0° (0.41)	20	20.3
III	Raney Ni	250 (wet)	1.5	72.3	−31.4° (0.43)	25	19.9
	5% Pd-C-B	33	3.0	82.2	+ 2.3° (0.44)	26	1.5
	5% Pd-C-A	33	4.0	89.1	+14.9° (0.41)	26	9.4
IV	Raney Ni	350 (wet)	2.0	72.4	−22.1° (0.48)	26	14.0
	5% Pd-C-B	50	5.3	78.9	−20.0° (0.40)	21	12.7
	5% Pd-C-A	50	1.5	77.0	+20.2° (0.45)	25	12.8
V[d]	Raney Ni	1000 (wet)	1	—	−25.4° (4.6)	4	16.1
	5% Pd-C-B	500	10	—	−15.8° (3.2)	28	10.0
	5% Pd-C-A	100	5	—	+21.2° (5.1)	12	13.4

a) One mmol of the ester was hydrogenated except III and V, which were 0.67 and 10 mmol, respectively.
b) 5% Pd-C-B or -A means 5% palladium on charcoal contained base or acid, respectively; see Ref. 6. The catalysts from the same batch were used throughout the present experiments.
c) Calculated on the base of $[\alpha]_D$ 158° for optically pure mandelic acid.
d) Mitsui's data, see Ref. 3a.

carbonyl group. As a result of the reduction of the dominant *s*-cis conformer, L(+)-mandelic acid was produced in excess after the hydrolysis. In the presence of Pd-C-B or Ni, however, the *s*-trans conformer will be dominant since the formation of the hydrogen bonding of the hemiketal is prevented by the base contained in the catalyst. Therefore, preponderance of D(−)-mandelic acid was brougt about.

The data for the sign of rotation of mandelic acid from the sugar esters were in agreement with Mitsui's results except for 5-*O*-ethyl derivative (III), which afforded L(+)-acid in slightly excess by the reduction over Pd-C-B; such a specific property of Pd-C-B was observed in the asymmetric hydrogenation of (−)-menthyl α-naphtylglyoxylate.[3d] It seemed likely that the exposure of oxygen of the ethoxyl group in 5-*O*-ethyl derivative (III) played an important role for III being absorbed on Pd-C-B.

Regarding to the optical yields of mandelic acid, nickel gave better results than palladium did, and this trend appeared in the hydrogenation of (−)-menthyl ester (V). In the case of 5-deoxy derivative (IV), however, the difference of the optical yield between Ni and Pd was very small.

From these experiments it is concluded that in the asymmetric hydrogenation as well as the asymmetric Grignard addition[1] the sugar derivatives in the esters behaved like (−)-menthol in regard to determining the stereochemical course, one exception being included.

Experimental

Optical rotations were measured with a Perkin-Elmer Model 141 photoelectric polarimeter in a 1 dm tube.

Starting materials were prepared according to the procedure described earlier.[1]

Asymmetric Synthesis of Mandelic Acid. A solution of the sugar ester (1.0 mmol) in absolute ethanol (15 m*l*) was hydrogenated over 5% palladium on charcoal⁶⁾ or Raney nickel (W-7)⁷⁾ catalyst at room temperature and ordinary pressure. Hydrogen absorption stopped or nearly stopped after the consumption of 1.0—1.2 mmol of hydrogen. The catalyst was removed by filtration and washed with ethanol. Evaporation of ethanol at 25°C and reduced pressure gave the crude sugar mandelate whose infrared spectrum did not showed the absorption of the keto carbonyl group. The reduction products were hydrolyzed without purification with a mixture of sodium hydroxide (80 mg) in water (3 m*l*) and methanol (10 m*l*) at room temperature for 30 min. After water (7 m*l*) had been added under cooling, the mixture was concentrated to about 10 m*l* at 25°C and reduced pressure, diluted with water (5 m*l*) and extracted several times with chloroform (70—140 m*l*, total volume) until the sugar in the last extract could not be detected by thin-layer chromatography of silica gel G (E. Merck, Darmstadt, Germaney) with ether-petroleum ether (3 : 7, v/v) solvent system.⁸⁾

From the extract the crude sugar derivative was recovered in 84—99% yield. The complete hydrolysis of the reduction products was ascertained by the measurement of infrared spectrum of the extract.

The water layer was acidified with 6 N hydrochloric acid (1 m*l*) and extracted with ether (100 m*l*). The extract was washed twice with a small quantities of water and dried over sodium sulfate. Evaporation of ether afforded the crude acid, which, on treatment with charcoal (20 mg) in water (5 m*l*), gave mandelic acid. The infrared spectrum of the acid was identical with that of the commercially available one.

The results and other experimental conditions are summarized in Table 1.

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6) R. Mozingo, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, p. 685 (1955); 5% Pd-C-B and Pd-C-A were prepared by the procedures B and C, respectively. Pd-C-A was used for the hydrogenation without washing with ethanol.

7) H. R. Billica and H. Adkins, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, p. 176 (1955); The catalyst was sufficiently washed with water.

8) The developed layer was visualized by spraying with a mixture of methanol, sulfuric acid, and *p*-anisaldehyde (17 : 2 : 1, v/v) and then heating.