65. Homogeneous and Heterogeneous Asymmetric Reactions

Part 5[1])

Diastereoselective and Enantioselective Hydrogenation of Cyclic β-Keto Esters on Modified *Raney*-Nickel Catalysts

by **Gyula Wittmann, György Göndös,** and **Mihály Bartók***

Department of Organic Chemistry, József Attila University, H-6720 Szeged, Dóm tér 8., Hungary

(29.I.90)

The hydrogenations of methyl 2-oxocyclopentanecarboxylate (**1**), ethyl 2-oxocyclohexanecarboxylate (**3**), and 2-methylcyclohexanone (**5**) on unmodified *Raney*-Ni catalyst lead predominately to the formation of the *cis*-hydroxy diastereoisomers of **2**, **4**, and **6**, respectively *(Scheme 2)*. In the asymmetric hydrogenations on catalysts modified with chiral tartaric acid ((*R,R*)-$C_4H_6O_6$/*Raney*-Ni and (*R,R*)-$C_4H_6O_6$/NaBr/*Raney*-Ni), the predominance of the *cis*-isomer increases significantly. The hydrogenations of β-keto esters **1** and **3** proceed with an enantioselectivity of 10–15% on the modified catalysts, while the similar hydrogenation of **5** yields optically inactive **6**. The (1*S*,2*R*)-enantiomers of the *cis*-isomers of **2** and **4** are formed in larger quantity, whereas the (1*R*,2*R*)-enantiomers of the corresponding *trans*-isomers predominate *(Scheme 1)*. The enantioselective formation of *trans*-**2** and *trans*-**4** can be interpreted mainly in terms of the asymmetric hydrogenation of cyclic β-keto esters through the keto form, while that of the corresponding *cis*-hydroxy esters proceeds through the enol form.

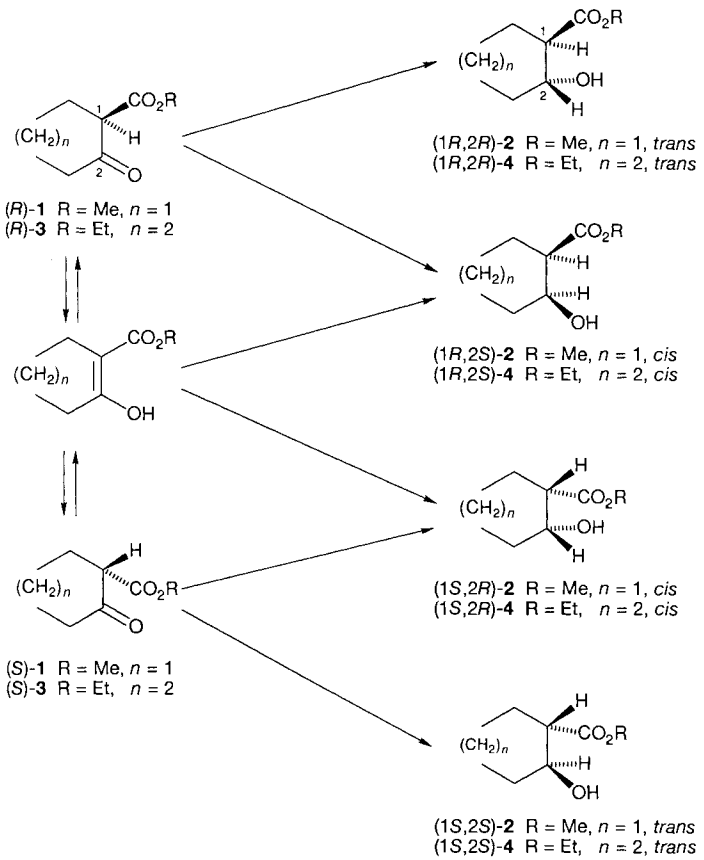
1. Introduction. – The asymmetric hydrogenation of β-ketocarboxylates by different methods has been studied widely. Different microbiological and biochemical methods [2] have made the highest diastereoselectivity and enantioselectivity attainable. As for chemical methods, homogeneous catalytic asymmetric hydrogenation [3] and hydrosilylation [4] have resulted in high enantioselectivity. Concerning heterogeneous catalytic reactions, mainly modified *Raney*-Ni catalysts [5] have been used with great success. The asymmetric hydrogenation of cyclic β-ketocarboxylates has so far been studied exclusively by biological methods [6] [7].

In spite of the fact that the asymmetric hydrogenation of β-keto esters on modified *Raney*-Ni catalysts has been investigated by numerous authors [5], it is still not clear, whether the substrate is hydrogenated in its keto or in its enol form. The reduction of cyclic β-keto esters promised to be a convenient way to establish this. As shown in *Scheme 1*, the *cis*-hydroxy ester can be derived from both the keto and the enol form, whereas the *trans*-isomer is formed mainly from the keto form.

Accordingly, we have made a study of the asymmetric hydrogenations of the racemic methyl 2-oxocyclopentanecarboxylate (**1**) and ethyl 2-oxocyclohexanecarboxylate (**3**) on tartaric acid modified and tartaric acid/NaBr modified *Raney*-Ni catalysts. The diastereoselectivity and enantioselectivity of the reactions were also investigated. The hydrogenations were carried out on unmodified catalysts, too. For comparison, the hydrogenations of 2-methylcyclohexanone (**5**) and ethyl acetylacetate (**7**) were also performed.

[1]) Part 4, see [1].

Scheme 1. *Stereochemical Relationship between Substrate and Products in the Hydrogenation of* **1** *and* **3**



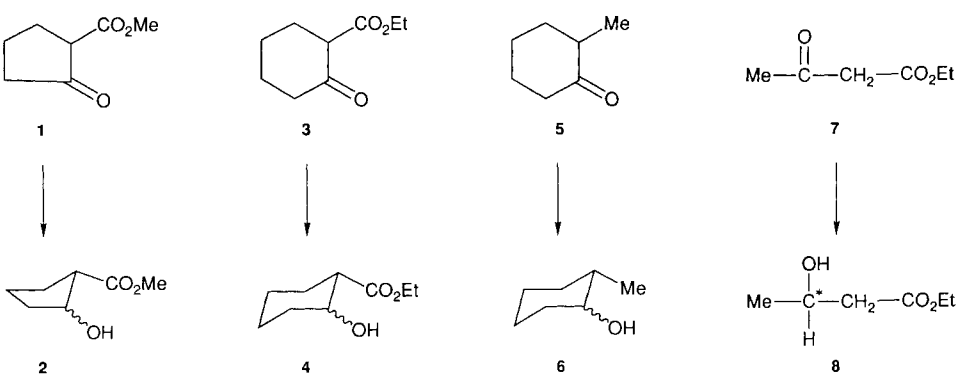
2. Results and Discussion. – The results of the hydrogenation of **1**, **3**, **5**, and **7** on various modified or unmodified Ni catalysts are summarized in the *Table*. On *Raney*-Ni, (*Entries 1, 4,* and *6*) under atmospheric H_2 pressure, larger amounts of *cis*-**2**, *cis*-**4**, and *cis*-**6** are formed than of the corresponding *trans*-isomers *(Scheme 2)*. Our earlier investigations gave similar results when the cyclic β-keto esters **1** and **3** were reduced at 60° under an initial H_2 pressure of 120 atm (*cis*/*trans*-**2** 87:14 and *cis*/*trans*-**4** 85:15) [8]. The *Table* also shows that greater quantities of *cis*-**2**, *cis*-**4**, and *cis*-**6** are formed on modified catalysts (*Entries 2, 3, 5,* and *7*) than on unmodified ones (*Entries 1, 4,* and *6*). In our opinion, the further increase of the *cis*/*trans* ratio in hydrogenations over the modified catalysts can be attributed to the fact that the modification favors enolization of the substrate. In a tautomeric equilibrium system, the enol concentration continues to increase, and H_2 addition results mainly in formation of the *cis*-isomer (see *Scheme 1*). This hypothesis is supported by our experience that for **5** *(Entry 7)*, where the possibility of enolization is smaller, the *cis*/*trans* ratio is 64:36, *i.e.* the amount of *cis*-isomer increases to only a small degree on the modified catalyst.

Table. *Hydrogenation of β-Keto Esters* **1**, **3**, **7**, *and* **5** *over Modified* Raney-*Ni Catalysts*

Entry	Catalyst	Sub-strate	Products				Rate [mmol H_2/(g catalyst × min)]
			Yield [%]	Diastereo-isomer ratio	Optical purity [%]		
				cis/*trans*	*cis*	*trans*	
1	*Raney*-Ni	**1**	38[a]) (**2**)	56:44	–	–	–
2	(*R*,*R*)-$C_4H_6O_6$/*Raney*-Ni	**1**	80 (**2**)	97:3	11.2 (1*S*,2*R*)	15.0 (1*R*,2*R*)	$2.38 \cdot 10^{-3}$
3	(*R*,*R*)-$C_4H_6O_6$/NaBr/*Raney*-Ni	**1**	80 (**2**)	97:3	14.0 (1*S*,2*R*)	10.0 (1*R*,2*R*)	$2.01 \cdot 10^{-3}$
4	*Raney*-Ni	**3**	52 (**4**)	58:42	–	–	$7.57 \cdot 10^{-4}$
5	(*R*,*R*)-$C_4H_6O_6$/NaBr/*Raney*-Ni	**3**	70 (**4**)	92:8	10.0 (1*S*,2*R*)	9.0 (1*R*,2*R*)	$1.38 \cdot 10^{-3}$
6	*Raney*-Ni	**5**	86 (**6**)	59:41	–	–	–
7	(*R*,*R*)-$C_4H_6O_6$/NaBr/*Raney*-Ni	**5**	93 (**6**)	64:36	–	–	$1.45 \cdot 10^{-3}$
8	(*R*,*R*)-$C_4H_6O_6$/NaBr/*Raney*-Ni	**7**	99 (**8**)		44.0 (*R*)		$9.32 \cdot 10^{-3}$

[a]) The low yield of **2** can be attributed to hydrogenolysis of COOR. The β-keto acid thus formed is insoluble in EtOH and precipitates onto the catalyst surface leading to decreased catalyst activity. The ratio of diastereoisomers was determined after converting the product of hydrogenation to methyl esters with diazomethane.

Scheme 2



The earlier indirect conformation analysis [9a] of the *cis*- and *trans*-isomer of **2** and **4**, (*cis*: COOR equatorial, OH axial; *trans*: COOR and OH both equatorial), is confirmed by their 400-MHz ^{1}H-NMR spectra (see [9b, c]).

As the *Table* shows, the hydrogenation of both **1** and **3** *(Entries 2, 3,* and *5)* takes place with 10–15% enantioselectivity on the modified catalysts, the (1*S*,2*R*)-enantiomer of *cis*-**2** and *cis*-**4** being preferred to the (1*R*,2*S*)-enantiomer, while for *trans*-**2** and *trans*-**4**, formation of the (1*R*,2*R*)-enantiomer is preferred under the given conditions. For both the *cis*- and *trans*-diastereoisomers, the new asymmetric centre at C(2) has decisively (*R*)-configuration. It should be noted that, under similar conditions, the (*R*)-enantiomer is likewise formed preferentially from the comparable β-keto ester **7** *(Entry 8)*. Hydrogenation on (*R*,*R*)-$C_4H_6O_6$/NaBr/*Raney*-Ni catalyst for substrate **5** *(Entry 7)* results in formation of an optically inactive hydroxy derivative **6**.

The data in the *Table* also show that in the case of cyclic β-keto esters, the enantioselectivity is not significantly influenced by addition of NaBr to the (*R*,*R*)-$C_6H_4O_6$/

Raney-Ni catalyst. This is in contrast with the literature data concerning the hydrogenation of methyl acetylacetate [10].

As *Scheme 1* shows, the *cis*-product can originate from either the keto or the enol tautomeric form, but the *trans*-product is derived mainly from the keto form. It is unambiguously proved by the formation of *trans*-hydroxy esters that the asymmetric hydrogenation of cyclic β-keto esters also proceeds through the keto form. Although it is not proved by literature evidence, our results strongly suggest that the enantioselective hydrogenation of β-keto esters can also take place from the keto tautomers. Consequently, the reductions of (*R*)-**1** and (*R*)-**3** occur with higher rate than the reductions of (*S*)-**1** and (*S*)-**3** on *Raney*-Ni modified with (*R*,*R*)-$C_4H_6O_6$. The *cis*-isomers (1*S*,2*R*)-**2** and (1*S*,2*R*)-**4** can originate either from the enol form or from (1*S*)-**1** or (1*S*)-**3**. The enantiomeric ratio of the *trans*-products ((1*R*,2*R*) > (1*S*,2*S*)), however, indicates that the enantiomers (1*S*,2*R*)-**2** and (1*S*,2*R*)-**4** more probably originate from the enol form. Nevertheless, on the basis of the experimental results, it remains an open question as to whether the enantiodifferentiating step can be assigned to the keto or the enol form.

Development of the (1*S*)-configuration from the enol form can be interpreted as follows. The *cis*-addition of H_2 and the interaction between the reacting agent and tartaric acid lead to the (2*R*)-configuration. As a result, the (1*S*)-configuration is produced on the other asymmetry centre.

3. Conclusions. – In the hydrogenations of the cyclic β-keto esters **1** and **3**, modification of the catalyst results in a significant increase in diastereoselectivity.

The enantioselective hydrogenations of these cyclic β-keto esters take place through both keto and enol forms. In the transformation of the enol form, formation of the (1*S*,2*R*)-products is preferred, whereas the keto form yields primarily the (1*R*,2*R*)-products. The reason for the preferred formation of the (1*S*,2*R*)-products is the *syn*-addition of H_2, while the predominant formation of the (1*R*,2*R*)-products is explained by fact that (1*R*)-**1** and (1*R*)-**3** are transformed more rapidly than (1*S*)-**1** and (1*S*)-**3**.

We presume that the lower enantioselectivity obtained in the asymmetric hydrogenation of cyclic β-keto esters as compared to acyclic ones can be attributed to the fixed position of the functional groups of these β-keto esters as a consequence of the cyclic structure. In contrast, in methyl and ethyl acetylacetate, free rotation occurs around the σ-bonds of the C-atoms attached to the two functional groups. We further assume that, for a cyclic β-keto esters, the formation of H-bonds between the tartaric acid adsorbed on the surface and the substrate is more ideal than for cyclic β-keto esters with rigid conformations.

The ester group in the β-position to the carbonyl group has a definite role in the formation of a H-bond between the adsorbed tartaric acid and the substrate, and hence in the enantioselectivity. This is suggested by the fact that the hydrogenation of 2-methylcyclohexanone (**5**) on a modified catalyst results in the formation of an optically inactive hydroxy derivative **6**.

Experimental Part

General. Distillation: *'Fischer-Spaltrohr-System'* apparatus. Prep. GLC: *Carlo-Erba-Mod-P* instrument; stainless steel column (4 m × 1 cm o.d.) packed with *PEG-20M* at 160°; detector temp. 200°. Anal. GLC: *Chrom-4* (Czechoslovak; flame ionization detector) gas chromatograph; glass column (2.4 or 3.6 m × 5 mm o.d.) packed with *PEG-20M*, at 160 or 180°. $[\alpha]_D$: *Carl Zeiss Polamat* polarimeter. ^{1}H-NMR spectra: *Varian-XL-400* spectrom-

eter; 10 mg of substrate in 0.6 ml of $CDCl_3$+tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium-(III); δ in ppm rel. to Me_4Si as internal reference, J in Hz.

Catalysts. Raney-Ni was prepared from NiAl alloy (*Fluka*; Ni/Al 1:1) as described earlier [10]. The preparation of the modified catalysts (*R,R*)-tartaric acid/*Raney*-Ni and (*R,R*)-tartaric acid/NaBr (*Raney*-Ni) used for the asymmetric hydrogenations is described in [11] [12]. The hydrogenation of ethyl acetylacetate was used to characterize the catalysts prepared.

Hydrogenations. In a hydrogenation vessel, the substrate **1**, **3**, **5**, or **7** (64.43 mmol) in 8 ml of abs. MeOH was hydrogenated over 504 mg of catalyst under 1 bar of H_2 at 50° until no more H_2 was consumed (volumetric monitoring). After removal of the catalyst, the product **2**, **4**, **6**, or **8** was distilled off under reduced pressure and then separated by prep. GLC for further purification. The enantiomeric compositions of the pure diastereoisomers were determined by ^{1}H-NMR in the presence of optically active shift reagent.

The distilled hydrogenation products consisted essentially of two isomers: *cis*-**2**, *cis*-**4**, or *cis*-**6** and *trans*-**2**, *trans*-**4**, or *trans*-**6**, accompanied by an unidentified impurity. The ratio *cis*/*trans*-isomer was determined from the anal. GLC peak areas. Anal GLC: t_R of **2**, 8.3 (*cis*) and 13.2 min (*trans*; 160°, 2.4-m column); t_R of **4**, 4.0 (*cis*) and 5.3 min (*trans*; 180° 2.4-m column); t_R of **6**, 38.0 (*cis*) and 40.0 min (*trans*; 160°, 3.6-m column).

cis-**2**: $[\alpha]_D^{20} = -3.46$ (1 dm, neat; *Entry 3*). ^{1}H-NMR: 2.702 (H–C(1)); 4.44 (H–C(2)); 3.028 (OH); 3.731 (CH_3O); J(1,2) $\approx$ 4.2, J(1,5) = 8.5 and 10, J(2, OH) = 3, J(2,3) $\approx$ 3.5 and 3.5.

trans-**2**: ^{1}H-NMR: 2.673 (H–C(1)); 4.38 (H–C(2)); 2.31 (OH); 3.713 (CH_3O); J(1,2) = 6.4, J(1,5) $\approx$ 8.7 and 8.7, J(2,3) $\approx$ 6.5 and 6.5.

cis-**4**: $[\alpha]_D^{20} = -4.30$ (0.5 dm, neat). ^{1}H-NMR: 2.476 (H–C(1)); 4.140 (H–C(2)); 3.220 (OH); 4.170 (CH_3CH_2); 1.275 (CH_3CH_2); $\Delta\nu_{1/2}$ (H–C(2)) = 13, J(1,6a) = 11.2, J(1,2) and J(1,6e) = 3 and 2.55, resp.

trans-**4**: $[\alpha]_D^{20} = -5.10$ (1 mm, neat; *Entry 5*). 2.25 (H–C(1)); 3.77 (H–C(2)); 2.07 (OH); 4.17 (CH_3CH_2); 1.270 (CH_3CH_2); J(1,2) = 10.01, J(1,6a) = 10.17, J(1,6e) = 4.78, J(2,3a) = 12.98, J(2,3e) = 3.83.

We acknowledge the support for this research by the *Hungarian Academy of Sciences* (grant 320/1986). We thank Dr. *Gy. Dombi* for the NMR spectra.

REFERENCES

[1] M. Bartók, Gy. Wittmann, G. B. Bartók, Gy. Göndös, *J. Organomet. Chem.*, accepted.

[2] a) C. J. Sih, C. S. Chen, *Angew. Chem. Int. Ed.* **1984**, *23*, 570; b) T. Oishi, H. Akita, *J. Synth. Org. Chem. Jpn.* **1983**, *41*, 1031; c) T. Fujisawa, T. Sato, T. Ito, *ibid.* **1986**, *44*, 519; d) D. Seebach, M. F. Züger, *Helv. Chim. Acta* **1982**, *65*, 495; e) D. Seebach, M. F. Züger, *Tetrahedron Lett.* **1984**, *25*, 2747.

[3] R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1987**, *109*, 5856.

[4] I. Ojima, K. Hirai, in 'Asymmetric Synthesis', Ed. J. D. Morrison, Academic Press, New York, 1985, Vol. 5, Chapt. 4.

[5] a) T. Harada, Y. Imachi, A. Tai, Y. Izumi, 'Metal-Support and Metal-Additive Effects in Catalysis', Elsevier, Amsterdam, 1982, p. 377; b) L. J. Bostelaar, Ph. D. thesis, State Univ. Leiden, The Netherlands, 1984; c) S. Tatsumi, *Bull. Chem. Soc. Jpn.* **1968**, *41*, 408; e) T. Tanabe and Y. Izumi, *ibid.* **1973**, *46*, 1550; f) L. H. Gross, P. Rys, *J. Org. Chem.* **1974**, *39*, 2429; g) T. Harada, Y. Izumi, *Chem. Lett.* **1978**, 1195; h) A. Tai, T. Harada, Y. Hiraki, S. Murakami, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1414; i) A. A. Vedenyapin, B. G. Chankvetadze, E. I. Klabunovskii, *React. Kinet. Catal. Lett.* **1984**, *24*, 77; j) A. Tai, H. Watanabe, T. Harada, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1468; k) A. Tai, K. Ito, T. Harada, *ibid.* **1981**, *54*, 223; l) M. Yokozeki, K. Shimokoshi, E. Miyazaki, *J. Phys. Chem.* **1985**, *89*, 2397.

[6] B. S. Deol, D. D. Ridley, G. W. Simpson, *Aust. J. Chem.* **1976**, *29*, 2459.

[7] D. Buisson, R. Azerad, *Tetrahedron Lett.* **1986**, *27*, 2631.

[8] G. Bernáth, Gy. Göndös, P. Márai, L. Gera, *Acta Chim. Acad. Sci. Hung.* **1972**, *74*, 471.

[9] a) Gy. Dombi, I. Pelczer, J. A. Szabó, Gy. Göndös, G. Bernáth, *Acta Chim. Acad. Sci. Hung.* **1980**; *104*, 287; b) B. Herradon, D. Seebach, *Helv. Chim. Acta* **1989**, *72*, 690; c) D. Seebach, S. Roggo, T. Maetzke, H. Braunschweiger, J. Cercus, M. Krieger, *ibid.* **1987**, *70*, 1605.

[10] a) Y. Izumi, *Adv. Catal.* **1984**, *32*, 215; b) T. Harada, M. Yamamoto, S. Onaka, M. Imaida, H. Ozaki, A. Tai, Y. Izumi, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2323; c) A. Hoek, H. M. Woerde, W. M. H. Sachtler, in 'New Horizons in Catalysis', Eds. T. Seiyama and K. Tanabe, Elsevier, Kodansha, Amsterdam, 1981, p. 376.

[11] Gy. Wittmann, G. B. Bartók, M. Bartók, G. V. Smith, *J. Mol. Catal.*, accepted.

[12] M. Bartók, Gy. Wittmann, Gy. Göndös, G. V. Smith, *J. Org. Chem.* **1987**, *52*, 1139.