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(-)-Dihydro-apovincaminic Acid Ethyl Ester, Preparation and Use as a Chiral Modifier in Enantioselective Heterogeneous Catalytic Hydrogenations

***A. Tungler[a], T. Máthé[b], T. Tarnai, K. Fodor, G. Tóth[c], J. Kajtár[d], I. Kolossváry[e], B. Herényi[f], R. A. Sheldon[g]**

[a]Department of Organic Chemical Technology, Technical University of Budapest, H-1521. Müegyetem rkp. 3.
[b]Organic Chemical Technology Research Group of the Hungarian Academy of Sciences
[c]Technical Analytical Research Group of HAS, Dept. of General and Analytical Chemistry, Technical University of Budapest
[d]Department of Organic Chemistry, Eötvös University, Budapest
[e]Department of Chemical Information Technology, Technical University of Budapest
[f]Gedeon Richter Co., Budapest
[g]Laboratory of Organic Chemistry and Catalysis, Delft University of Technology

Abstract: The preparation, characterisation and use of (-)-dihydro-apovincaminic acid ethyl ester as a chiral modifier in heterogeneous catalytic asymmetric hydrogenations is reported. The epimeric compositions were determined using NMR and HPLC methods and circular dichroism spectroscopy was used to detect the interaction between the chiral modifier and the substrate.

Chiral modifiers for enantioselective heterogeneous catalytic hydrogenations can be classified into three main groups: alkaloids, α-hydroxy acids and α-amino acids. The most well known examples are Ni catalysts modified with tartaric acid for the hydrogenation of β-keto esters[1] and Pt catalysts modified with cinchona alkaloids for the hydrogenation of α-keto esters[2]. Both systems are effective (ee's up to 95%) in the hydrogenation of C=O double bonds in a specific class of substrates.

In an effort to find new chiral modifiers with different or broader substrate specifity we have screened several vinca and morphine-type alkaloids in the hydrogenation of various prochiral substrates[3]. A vinca-type alkaloid, (-)-dihydro-apovincaminic acid ethyl ester [(-)-dihydro-vinpocetine, DHVIN, **II**] proved to be an effective chiral additive in the hydrogenation of both C=C and C=O double bonds. The unsaturated compound **I**, apovincaminic acid ethyl ester, (vinpocetine,VIN) is a synthetic drug which is used in the treatment of oxygen-deficiency of the brain[4]. A patent[5] describes the preparation of the dihydro compounds **II** and **III** by the Pd black mediated hydrogenation of **I**. The two epimeric products **II** and **III** were obtained in yields of 42% and 9% respectively, by crystallisation.

In the present study, the hydrogenation of **I**, the determination of its epimeric composition with NMR and HPLC methods, the separation and the molecular modelling of the epimers is described. The interaction of **II**

as a chiral modifier with the substrates of asymmetric hydrogenations, isophorone and ethyl pyruvate, in methanolic solution was detected using circular dichroism spectroscopy.

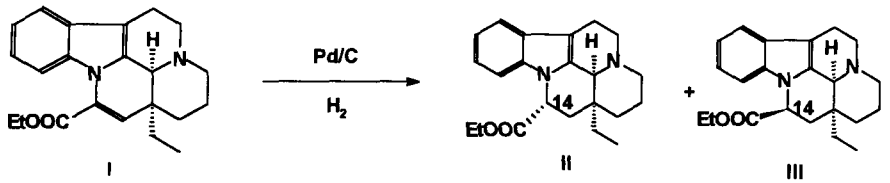


Figure 1.

The hydrogenation of vinpocetin

The results of the hydrogenation experiments with different catalysts are shown in Table1.

Table 1.

Catalyst (g)	Solvent (cm^3)	Additive (g)	Temp.(C^o)	Conv.(%)	Epimer ratio II/III
Pd/C Selcat 10% Pd, D≈0.5 1	200	-	25	100	75/25
2	200	-	25	100	71/29
1	100	-	25	100	78/22
1	100	H_2SO_4 1	25	100	85/15
1	100	AcOH 5	25	100	83/17
1	100	-	50	100	83/17
1	100	-	70	100	77/23
Pd black D≈0.1, 1	200	-	25	0	-
1	200	-	70	80	81/19
Pd/TiO_2 D≈0.2, 1	200	-	25	0	-
Pd/Al_2O_3 D≈0.2, 1	200	-	25	85	82/18
Pt/C Heraeus 1	200	-	25	0	-
Ru/C own 1	200	-	25	0	-
Rh/C own 1	200	-	25	100	91/9

The amount of the substrate was 10g in every reaction.

D is the dispersion of the catalysts (ratio of surface metal atoms to all metal atoms), determined by TEM and H_2/CO adsorption.

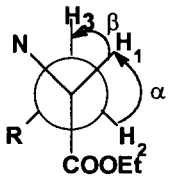
Both Pd and Rh were active catalysts for the hydrogenation of the 14,15 double bond of **I**, Ru and Pt were inactive. The stereoselectivity increased in the presence of acids. The product epimeric mixture was separated into **II** and **III**. After the second crystallisation the epimeric purity of both compounds was above 98%, determined by chiral HPLC. In all asymmetric hydrogenations and spectroscopic measurements these pure epimers were used.

Structure of dihydro-vinpocetin

II and **III** modify both Pd catalysts in the asymmetric hydrogenation of the C=C double bond of isophorone and Pt catalysts in the hydrogenation of the C=O bond of ethyl pyruvate, the modifying effect of **II** is much greater(Table 2.). It is known that the molecules of vinca type alkaloids have a special form: namely the other rings are disposed perpendicularly with respect to the plain of the indole ring[6].

During hydrogenation of **I** the cis epimer **II** is the major product (Table 1. 70-90%). According to the NMR results and the calculations made with the Altona equation[7] using the data of the NMR spectrum in **II** the torsion angles (Figure 2.) are α=78° and β=24°. This means that in **II** the COOEt and the 16-ethyl group are both in an equatorial position.

Major



H_1 $\delta \approx 4.87$

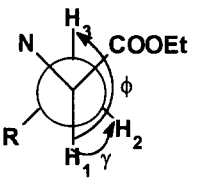
J_{H1H3}=8.1

J_{H1H2}=1.2

α=78°

β=24°

Minor



$\delta \approx 4.63$

J_{H1H3}=12.1

J_{H1H2}=5.0

γ=51°

ϕ=180°

Figure 2.

The molecular modelling calculations show that in the most stable conformer of **II** (Figure 3a.) the COOEt and ethyl groups are situated in the plane of the indole ring. This explains the greater modifying effect of **II** (Table 2.). Both epimers can adsorb with the relatively flat part of the molecule (α face) on the catalyst surface, but the carboxyl-group can exert its anchoring effect only in **II**. The rings of **II** incorporating the tertiary basic N tend to bend upwards from the catalyst surface, rendering the basic nitrogen accessible for an interaction with the carbonyl-groups of the substrates.

It is probable that **I** adsorbs during its hydrogenation with the α face on the surface of the catalyst, similarly to **II**. If this is the case, then the H atom adding to the C-14 atom, being in axial position in the hydrogenated product (the major epimer is **II**), had to attack from the "top-side"[8]. This reaction constitutes an example of Pd mediated hydrogenations involving "top-side" hydrogen addition. Recently Somorjai and coworkers provided an explanation[9] for the "top-side" hydrogen addition.

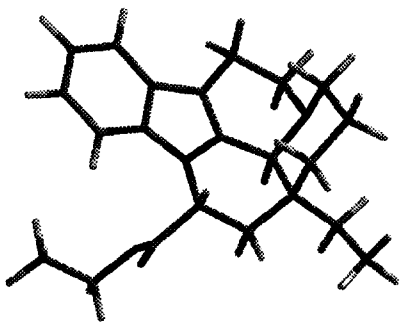


Figure 3a. **II**, (-)-dihydrovinpocetine

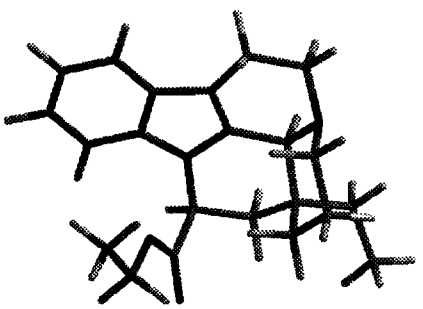
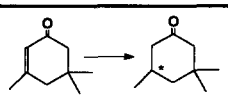
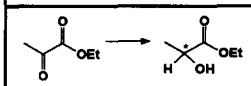


Figure 3b. **III**, (+)-dihydrovinpocetine

Effect of dihydro-vinpocetine

The effect of **II** and **III** on the enantiomeric excess and rate of the reactions was investigated and compared with that of the dihydrocinchonidine (DHCIN) in the hydrogenation of isophorone and ethyl pyruvate (Table 2.). In the hydrogenation of isophorone the highest enantiomeric excess (40%) was achieved with **II** and Pd black catalyst, the modifiers all decreased the reaction rate. More and less dispersed catalysts (Pd on carbon and Pd powder) produced smaller enantiomeric excesses (10 and 19% respectively). The modifier protonated with strong acids (H_2SO_4, F_3CCOOH) was ineffective[10]. In the hydrogenation of ethyl pyruvate the modifiers increased the reaction rate, dihydrocinchonidine with one order of magnitude, the vinca-alkaloid **II** only with 30-50%. Probably this is one of the reasons why the chiral effect of **II** is less than that of the dihydrocinchonidine.

Table 2.

Reaction mol substrate	**Catalyst g**	**Enantiomeric excess % modifiers**		
		II	**III**	**DHCIN**
 0.05	Pd black (0.3)	40	10	20
	Pd powder (0.5)	19	6	10
	Pd/C (0.1)	10	4	3
 0.1	Pt/Al_2O_3 (0.1)	30	14	72
	Pt/C (0.1)	27	13	55

Solvent 100 cm^3 methanol, 0.1g modifier, additive 0.5g acetic acid.

Interaction between substrate and modifier

The CD spectrum of **II** was recorded in methanolic solution. Thereafter the spectrum was recorded again several times with a methanolic solution of **II** containing acetic acid (molar ratio of II/AcOH=1/1) and different, increasing amounts of isophorone or ethyl pyruvate. Finally differential spectrum of the solution of **II** and the solution containing **II**, acetic acid and isophorone or ethyl pyruvate was composed.

The spectrum of **II**- measuring it between 250-400 nm- contains three bands: two negative ones with peaks about 275 and 320 nm and a positive one about 290 nm. They belong to the vinca-type alkaloid containing indole-chromophore. On the addition of excess isophorone or ethyl pyruvate to the solution of **II** the peaks in the spectra are shifted to lower wavelengths and the intensity of the bands is altered (Figure 4a.). These alterations can be explained by preparing the differential spectrum. Increasing the amount of the substrates

from molar ratio 1/1 to 100/1 to the alkaloid in several steps, there appears a new negative Cotton effect about 300 nm and its intensity is increasing parallel with the substrate concentration (Figure 4b). The appearance of this band is consistent with the interaction of **II** with isophorone or ethyl pyruvate. The diminished intensity of the second (positive) band in the spectrum of the alkaloid can be explained by the development of that new band.

The established interaction between the molecules of the substrates and the modifier influences the original electron transitions of the alkaloid. Therefore beside the band of the keto-chromophore there are three additional bands in the differential spectrum. All three belong to the characteristic bands of **II**. Their additive or opposing effect results in the increase or decrease of the bands including the shift of their peaks too, as it is shown in Figure 4a.

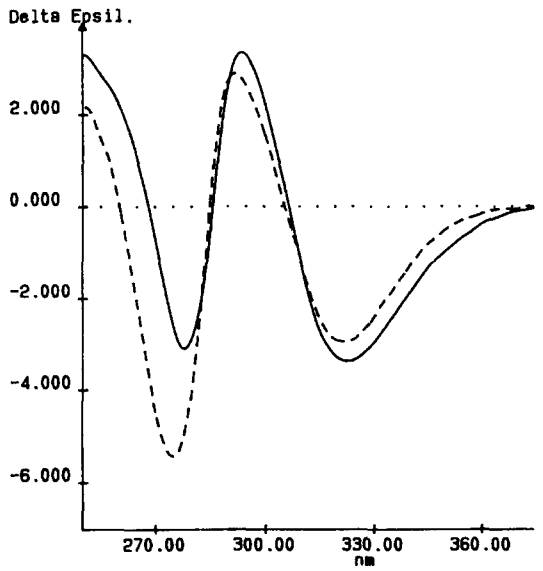


Figure 4a.
CD spectra of **II**.
-- without substrate, ----- with substrate in great excess

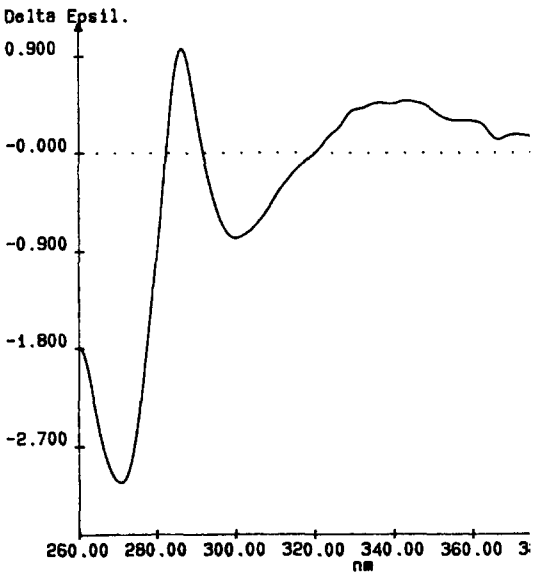


Figure 4b.
Differential spectrum of **II** with substrate in 100/1 molar ratio to the alkaloid, minus of **II** without substrate

Hydrogenations with combinations of a vinca- and a cinchona-type modifier

Hydrogenation experiments were carried out (Pd/isophorone, Pt/ethyl pyruvate) where **II** and dihydrocinchonidine (DHCIN) were applied together (Figure 5,6), the cinchona modifier in increasing concentrations. The cinchona alkaloid eliminated already at smaller concentrations the effect of **II**, even if the enantiomer excesses induced by it were less than in the presence of the vinca alkaloid alone.

Conclusions

Vinpocetine(**I**) is hydrogenated by Pd and Rh catalysts mainly to (-)-dihydro-vinpocetine (**II**). The hydrogen addition to the C-14 atom occured by "top-side" attack if the **I** adsorbed with the α face on the catalyst

surface. As the epimer composition doesn't change significantly upon changing catalyst amount, temperature and substrate concentration, the stereochemical course of the reaction is determined by the shape and adsorption characteristics of the substrate molecule **I**.

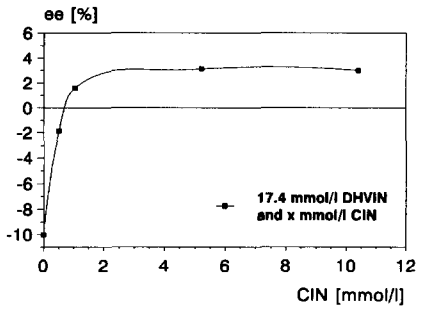


Figure. 5.

Hydrogenation of isophorone in the presence of **II** and DHCIN.

Positive ee% corresponds excess of (+)-dihydroisophorone. Reaction conditions: 0.1g 10% Pd/C catalyst, solvent 100 cm^3 methanol, 0.5g acetic acid, 7g isophorone, temperature 25°C, atmospheric pressure.

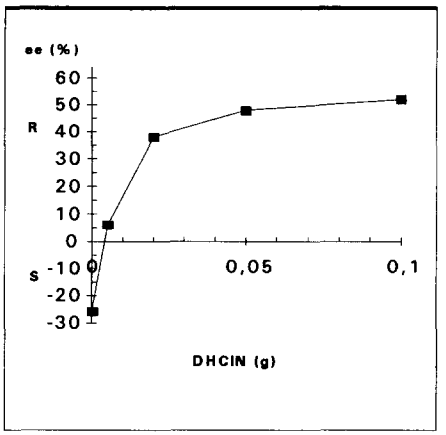


Figure 6.

Hydrogenation of ethyl pyruvate in the presence of **II** and DHCIN.

Reaction conditions: 0,1g Pt/Al_2O_3 , thermal-treated (Engelhard), 0,1 mol ethyl pyruvate, 0,1g DHVIN+0,5 g acetic acid+DHCIN, solvent 100 cm^3 methanol, temperature 25°C, pressure 50 bar, rpm : 1500 min^{-1}.

II as a chiral modifier in the asymmetric hydrogenations interacts through the basic N with the carbonyl group of the substrates. The asymmetric effect is greater if the N is protonated by a week acid as acetic acid . Strong acids terminate the interaction, because they form close ion-pairs and the anions exclude the substrate molecules.

The substrate-modifier interaction exists, according to CD, in solution, probably in the form of aggregates. They may contain in sandwich-like form substrate and modifier molecules, which probably remain in adsorbed state on the surface of the catalyst too. The aggregates may be similar to those described in enantiomer separation processes[11].

The adsorption of the modifier is directed on the surface of the catalyst, it occurs through the heteroaromatic indole part, analogous to the adsorption of cinchonidine through the quinoline ring. The adsorption strength of "quinoline" is stronger on the supported Pd and Pt than that of the "indole". This explains why cinchonidine, if it is present, controls asymmetric induction, even in the presence of larger amounts of **II**.

The difference in the effect of the two epimers, **II** and **III** can be explained by their shape: in the cis-epimer **II** the COOEt-group, occupying an equatorial position, can readily interact with the catalyst surface. This gives an explanation, why enantiomeric excesses induced by **II** are greater than that of **III**(Table 2.).

The specifity of a modifier is influenced by: (i) the strength of its adsorption, (ii) the strength and nature of the substrate-modifier interaction in solution, and whether it is preserved in the adsorbed state, and (iii) the "ligand accelerating" or "ligand retarding" effect of the modifier on the rate of the asymmetric hydrogenation reactions.

Experimental

Hydrogenation

The hydrogenation reactions of vinpocetine were carried out in an autoclave equipped with a magnetic turbine stirrer, under 6 bar H_2 pressure in methanolic solution. The product compositions (ratio of **I/II+III** and **II/ III**) were determined with HPLC.

The reaction mixtures, when the conversion was complete, were evaporated and the residue recrystallised from ethanol. The first fraction crystallised was **III** in around 80% purity. The second fraction was **II** in greater than 90% purity. The purity of the epimers could be increased by repeated crystallisation up to 98%.

The characterisation data of **II**:optical rotation $[\alpha]_D^{20}$ = -108, (c=1, $CHCl_3$), melting point:100-102°C. elemental analysis: C 74.9%, H 8.0%, N 7.9% (theoretical 74.9, 7.9, 7.9 % respectively), of **III**: optical rotation $[\alpha]_D^{20}$ = -+117,3, (c=1, $CHCl_3$), melting point:158-160°C, elemental analysis: C 75.0%, H 8.0%, N 7.8%. These pure epimers were used in asymmetric hydrogenations and in the spectroscopic measurements. The asymmetric hydrogenation of isophorone was carried out in methanolic solution at 30°C and 1-50 bar hydrogen pressure, in the presence of acetic acid additive. The hydrogenation reaction of ethyl pyruvate was carried out in methanolic solution, at room temperature and 50 bar hydrogen pressure in the presence of acetic acid.

HPLC chromatography: The analysis was carried out on a chiral AGP column, on room temperature, the eluent was 80% Sörensen buffer and 20% isopropanol. The adsorbance of the eluent was measured at 210 nm.

NMR spectroscopy: The NMR spectra were measured on a Brucker AC-250 spectrometer in $CDCl_3$.

Circular dichroism spectroscopy: CD spectra were recorded on a Jobin Yvon Dichrograph Mark VI. The cell length was 0.1 cm.

Molecular modelling calculations: The molecular mechanics calculations were performed on a Silicon Graphics Indigo^2 workstation . The conformational analyses were carried out using the MacroModel 4.0 computational chemistry program package[12]. The MM2* force field available in MacroModel was applied. It differs from the original MM2 force field[13] only that, it employs the point-charge Coulomb electrostatic equation. The conformational space available to **II** was searched using a particularly efficient systematic unbounded multiple minimum search technique (SUMM)[14] available only in MacroModel. During conformational searches, the ring system of **II** was temporarily cleaved according to the so-called ringmaker approach of Still and Galynker[15]. Structures generated by the SUMM procedure were re-closed and minimized to yield unique conformers within an energy window (25 kJ/mol) above the global minimum. Geometry optimizations were carried out with a TNCG truncated Newton conjugate gradient technique[16] (max. no. of iterations 150, convergence criteria in gradient 0.01 kJ/molAngs) was used.

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