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Synthesis of D-Alanine under the Asymmetric Induction due to Molecular Asymmetry[1]

Hisayuki Matsuo,[2a] Hiroko Kobayashi and Takashi Tatsuno[2]

The Institute of Physical and Chemical Research[2]

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In biological systems, asymmetric synthesis is highly efficient. In organic synthesis, however, asymmetric induction is seldom 100% efficient in simple molecule, even when the asymmetric centers are close neighbors.

Since Prelog[3] presented his first model for asymmetric synthesis of optically active atrolactic acid, there have been many approaches to this target. Among them, Berson's asymmetric synthesis[4] sounds especially interesting, which revealed that the stereochemical control displayed by molecular asymmetry due to optically active biphenyl or binaphthyl derivatives was highly important in the asymmetric synthesis of atrolactic acid. On the other hand, the group of Cram[5] proposed optically active 4-carboxy-[2-2]paracyclophane as a novel model of molecular asymmetry.

For the purpose to investigate on the asymmetric induction due to paracyclophane derivative mentioned above, the catalytic reduction of optically active (—)-N-(4-[2-2]paracyclophanecarbonyl) dehydroalanine (III) was carried out to afford D-alanine in the optical yield of *ca.* 6%, as is described in the present paper.

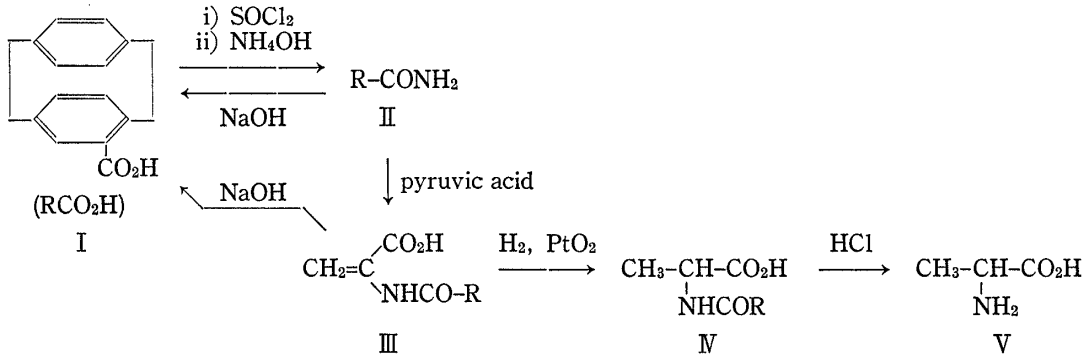

Chart 1

As shown in Chart 1, the optically active 4-carboxy-[2-2]paracyclophane, $[\alpha]_D^{20}$ —141.9, I that obtained by the method of Cram, was converted to the corresponding carboxamide (II) *via* acid chloride. Amide (II) was condensed with pyruvic acid in a similar manner described for the preparation of N-benzoyldehydroalanine by Wieland, to afford the optically

1) A part of this paper was read at the 22nd Annual Meeting of Pharmaceutical Society of Japan, Sendai, 1966.
2) Location: *Yamato-Machi, Kita-Adachi-Gun, Saitama*; *a*) To whom inquiries should be addressed; Present Address: *Institute for Protein Research, Osaka University, Kita-ku, Osaka.*
3) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).
4) J.A. Berson and M.A. Greenbaum, *J. Am. Chem. Soc.*, **79**, 2340 (1957); **80**, 445 (1958); **81**, 6456 (1959); **80**, 653 (1958).
5) D.J. Cram and N.L. Allinger, *J. Am. Chem. Soc.*, **77**, 6289 (1955).

active III, whose structure was supported by nuclear magnetic resonance (NMR), infrared (IR) and elemental analysis data.

Alkaline hydrolysis of II and III regenerated the starting I without any loss in its optical activity. Therefore, the route to compound III did not involve any racemization.

The catalytic reduction of dehydroalanine (III) over Adams' Pt in ethanolic solution smoothly proceeded at room temperature and under the atmospheric pressure to give a reduction product (IV) as a waxy solid, whose NMR spectrum showed complete disappearance of vinyl proton signal present at τ 3.85 in III, while appearance of doublet methyl at τ 8.4 and quartet α-H at τ 6.9, indicating complete reduction of C=C bond in III.

In order to avoid the optical resolution at this step, the waxy reduction product, (−)-N-(4-[2-2]paracyclophanecarbonyl) alanine (IV) was directly submitted to acid hydrolysis without further purification. Hydrolysis of IV was carried out in EtOH solution containing 6N HCl under reflux for 24 hours.

After storage in a refrigerater, the precipitated I was filtered off and the HCl layer was extracted with $CHCl_3$ for complete removal of remained I. HCl layer thus obtained was passed through a column of Amberlite IR-120 (H^+) and then eluted with 14% ammonia. The eluate thus obtained was lyophilized to furnish the final product, alanine (V) in a yield of 64%, calculated from III. Alanine isolated above was identified in the comparison with authentic specimen paper and gas chromatographically. [α]-Values of alanine thus obtained and its N-chloroacetyl derivative at several different wavelengths are listed in Table I. As seen from these data, our synthetic alanine was proved to be in excess of D-form and its optical purity was approximately 6%. At present time, optical purity and absolute configuration of the compound (II) remained unknown. Therefore, we can not discuss about this type of asymmetric synthesis in detail but the present work revealed that molecular asymmetry due to paracyclophane derivative displayed asymmetric induction in the catalytic reduction of carbon–carbon double bond in its neighborhood.

Table I. Specific Optical Rotation of Synthetic(D-) and Authentic (L-) Alanine and Its Chloroacetyl Derivative

Wave-length (μ)	Alanine			Chloroacetyl-alanine		
	[α]^{20}		Optical purity (%)	[α]^{20}		Optical purity (%)
	Synthetic (D)	Authentic (L)		Synthetic (D)	Authentic (L)	
589	−0.8	+13.0	6.2	+2.21	−41.97	5.3
578	−0.9	+14.1	6.4	+2.33	−44.45	5.3
546	−1.1	+16.0	6.9	+2.60	−51.92	5.1
436	−2.2	+30.5	7.2	+4.43	−90.55	4.9
365	−3.8	+55.5	6.9			

Experimental

(−)-4-Carboxamido-[2-2]paracyclophane (II)——(−)-4-Carboxy-[2–2]paracyclophane (I), was prepared by the method of Cram, *et al.*[5] mp 209—212, $[\alpha]_D^{20}$ −141.9 (c=1, $CHCl_3$) (lit. $[\alpha]_D^{24}$ −157). To a solution of I (5.1 g) in benzene (55 ml) was added $SOCl_2$ (7.3 g) and the whole was refluxed at 95° for 3 hr.

Evaporation of organic solvent *in vacuo* afforded the corresponding acid chloride as a waxy solid. The chloride thus obtained was dissolved in dry acetone (166 ml) and treated with conc. NH_4OH (90 ml) at 5° for 5 min. After addition of water (31 ml) to the resulting solution, acetone was evaporated *in vacuo* at room temperature and the remaining aqueous solution was extracted with AcOEt, which was washed with aq. Na_2CO_3 and water, succesively and dried over Na_2SO_4. Evaporation of AcOEt afforded a crude amide (II) in a yield of 4.26 g (83.9%). Recrystallization from $CHCl_3$ gave colorless needles of mp 179—181°, $[\alpha]_D^{21}$ −135.3 (c=1, $CHCl_3$).

In another experiment using less optically pure I as a starting material, two kinds of II were obtained at the step of recrystallization from $CHCl_3$, the one was racemic II (colorless cubes of mp 215—216.5°) and the other was optically active II as described above. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3399 (NH), 1670 (CONH). *Anal.* Calcd. for $C_{17}H_{17}ON$: C, 81.24; H, 6.82; N, 5.57. Found: C, 80.83; H, 6.52; N, 5.46. Alkaline hydrolysis of (−)-II regenerated (−)-I of $[\alpha]_D^{20}$ −142 ($c=1$, $CHCl_3$).

(−)-N-(4-[2-2]Paracyclophanecarbonyl)dehydroalanine (III)——The optically active II obtained above ($[\alpha]_D^{20}$ −135.3) was submitted to dehydrative condensation with pyruvic acid in a similar manner as Wieland[6] reported for N-benzoyldehydroalanine. A solution of II (2.13 g) and pyruvic acid (2.28 g) in trichloroethylene (26 ml) was refluxed for 10 hr and the resulting water was azeotropically removed in the presence of silica gel. After standing at room temperature overnight, the resulting reaction mixture was extracted with satd. $NaHCO_3$. Acidification of aqueous layer with conc. HCl (Congo red) afforded white solid, which was collected and washed to give a crude III of mp 154—155° in a yield of 0.58 g (21.3%). Recrystallization from $CHCl_3$–hexane afforded colorless prisms of mp 164—166°, $[\alpha]_D^{20}$ −81.12 ($c=1.01$, $CHCl_3$) (single spot on TLC (silica gel: $CHCl_3$–EtOH 20:3)). NMR (in $CDCl_3$) τ: 3.4 (7H, unresolved broad mult., aromatic), 3.85 (2H, CH_2=), 6.9 (8H, $-CH_2-$). IR ν_{max}^{KBr} cm^{-1}: 3400, 3000, 2920, 1710, 1670, 1508. *Anal.* Calcd. for $C_{20}H_{19}O_3N$: C, 74.74; H, 5.96; N, 4.36. Found: C, 75.20; H, 6.40; N, 4.29.

Catalytic Hydrogenation of Compound III——The dehydroalanine derivative (III; 0.2 g) obtained above was dissolved in EtOH (36 ml) and hydrogenated over Adams' catalyst at room temperature and under atmospheric pressure. After completion of one molar H_2 uptake, catalyst was filtered off and EtOH was removed by evaporation *in vacuo* to afford a waxy reduction product (IV) in a quantitative yield.

The crude product thus obtained was submitted to the following hydrolysis step without further purification, in order to avoid an possible separation of diastereomers in purification procedure. Spectroscopic data of the crude product (IV) are as follows: NMR (in $CDCl_3$) τ: 3.45 (7H, multiplet, aromatic), 5.18 (1H, quartet, $-CH-CO_2H$), 6.9 (8H, unresolved broad, $-CH_2-$), 8.4 (3H, doublet, CH_3-). IR ν_{max}^{Nujol} cm^{-1}: 1730 (CO_2H), 1660 (–CONH–).

D-Alanine (V) (Hydrolysis of Compound IV)——To a solution of the reduction product (IV: 0.181 g) in EtOH (27 ml) was added 15 ml of 6N HCl and the whole was refluxed for 24 hr. After storage in a refrigerater, the precipitated solid (recovered I) was removed by filtration and EtOH was evaporated *in vacuo*. Remained HCl layer was extracted with $CHCl_3$ to remove completely recovered I. The clear HCl layer was passed through a column of Amberlite IR-120 (H^+) (15 g), then washed with water until eluate became neutral and finally eluted with 14% NH_4OH.

Ammoniacal eluate was collected and lyophilized to afford D-alanine in a yield of 0.032 g (64% from III). D-Alanine showed single spot (ninhydrin positive) on the paper chromatograms which were obtained in two different solvent systems (BuOH–AcOH–water 12:3:5, and phenol-saturated water). *Rf* values of D-alanine were exactly the same to those of authentic L-alanine in above solvent systems. For further confirmation, D-alanine (V) was converted to chloroacetyl derivative, which was identified gas chromatographyically. Optical rotatory power of D-alanine and its chloroacetyl derivative was measured at different wave-lengths as listed in Table I. From the basis of these results, optical purity of D-alanine thus obtained was approximately 6%.

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6) T. Wieland, G. Ohnacker and W. Ziegler, *Chem. Ber.*, **90**, 194 (1957).