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Studies of Alicyclic α -Amino Acids. II.¹⁾ Synthesis and Unequivocal Assignment of Stereochemistry of 1-Amino-*trans*- and *cis*-4-hydroxycyclohexane-1-carboxylic Acids

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Stereospecific synthesis of isomeric 4-benzoyloxycyclohexane-spiro-5'-hydrantoin from 4-benzoyloxycyclohexanone was achieved *via* the Bucherer hydantoin synthesis and the Strecker cyanate route. Subsequent hydrolysis of both hydantoins resulted in the formation of 1-amino-*trans*- and *cis*-4-hydroxycyclohexane-1-carboxylic acids. The stereochemistry of both amino acids was established unequivocally by the transformation of phthalimide of the *cis*-amino acid to the corresponding lactone. Thus, it is concluded that while the Strecker synthesis leads to the exclusive formation of the *cis*-amino acid, the Bucherer synthesis gives the *trans*-amino acid predominantly. The present result provides chemical evidence for the stereochemistry of 1-amino-4-alkylcyclohexane-1-carboxylic acids which have been assigned ambiguously. Physicochemical data of pairs of isomeric 4-substituted amino acids and their derivatives are also summarized.

Synthesis of alicyclic α -amino acids merits attention from the medicinal and biological points of view.³⁾ Munday⁴⁾ has prepared certain alkylsubstituted-1-aminocyclohexane-1-carboxylic acids by the Bucherer hydantoin and the Strecker synthesis. He has found that while the latter synthesis leads to one stereoisomer (S-amino acid: *cis*, *axial* carboxyl group) in each case, the former gives both possible stereoisomers, the other stereoisomer (B-amino acid: *trans*, *equatorial* carboxyl group) greatly preponderating (see Chart 1). The configurations assigned are based on the resistance to hydrolysis of the 1-amino-4-*tert*-butyl and -4-isopropylcyclohexanenitrile hydrochloride, infrared spectra (IR) and the dissociation constants of the amino acids.

We have expanded Munday's result to the synthesis of two epimeric 3-amino-5 α -cholestan-3-carboxylic acids.¹⁾ Cremlyn, *et al.*,⁵⁾ however, have claimed that configurations⁴⁾ previously assigned to alkylsubstituted-1-aminocyclohexane-1-carboxylic acids are reversed on the basis of deamination experiments, measurement of dissociation constants, IR and nuclear

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4) L. Munday, *J. Chem. Soc.*, **1961**, 4372; *idem, ibid.*, **1964**, 1413.

5) R.J.W. Cremlyn and M. Chisholm, *J. Chem. Soc.*, (C), **1967**, 2269.

magnetic resonance (NMR) spectra. Such confusion of the stereochemistry in the cyclohexane α -amino acid arises primarily from lack of conclusive evidence that may be obtained chemically.⁶⁾ In a continuation of our study on alicyclic α -amino acids, we attempted the synthesis of 1-amino-*trans*- and *cis*-4-hydroxycyclohexane-1-carboxylic acids (IVa) and (Va) with the purpose of clarifying the stereochemistry of the 4-substituted cyclohexane α -amino acids obtained by the Bucherer and the Strecker method.⁷⁾

In this paper, we describe synthesis and unequivocal assignment of stereochemistry of IVa and Va, which provide chemical evidence supporting Munday's assignment in the

Chart 1

Chart 2

- 6) Most recently, we received papers which have described an unequivocal assignment of configurations of isomeric 2-aminonorbomane-2-carboxylic acids by X-ray crystallography: Synthesis by the Bucherer procedure was found to give mainly the isomer with the carboxyl group *exo*, whereas the Strecker procedure gave the isomer with the amino group in that orientation. (P.A. Apgar and M.L. Ludwig, *J. Am. Chem. Soc.*, **94**, 964 (1972); H.S. Tager and H.N. Christensen, *ibid.*, **94**, 968 (1972)).
- 7) There has been no example of synthesis of cyclohexane α -amino acids possessing a hydroxy function in the cyclohexane ring, excepting conversion of quinic acid to 1-amino-3,4,5-trihydroxycyclohexane-1-carboxylic acid by Achiwa and Yamada (K. Achiwa and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 537 (1966)).

stereochemistry of 1-amino-4-alkylcyclohexane-1-carboxylic acids. Correlations between physicochemical properties and configurations of 1-amino-4-substitutedcyclohexane-1-carboxylic acids and their derivatives are also pointed out.

When a mixture of 4-benzoyloxycyclohexanone (I),⁸⁾ potassium cyanide and ammonium carbonate in aqueous ethanol in a sealed tube was heated at 100° for 1 hr, a mixture of hydantoin (IIa) and (IIIa) was obtained in a total yield of 90%. The ratio of IIa to IIIa was determined to be 3:1 by gas chromatographic analysis of a mixture of amino acids IVa and Va (after trifluoroacetylation) obtained by hydrolysis of the crude mixture of hydantoin prior to separation. Separation of two isomers IIa, mp 261° and IIIa, mp 285° was achieved by careful fractional recrystallization of the mixture from methanol. The minor hydantoin IIIa in above Bucherer hydantoin synthesis was prepared exclusively by the following procedure. To a solution of I in ethanol was added at 0° a mixture of potassium cyanide and ammonium chloride in water (Strecker condition). After being allowed to stand for several days, the reaction mixture was saturated with hydrogen chloride to precipitate aminonitrile hydrochloride (VI), mp 165°, in 50% yield. A mixture of VI and potassium cyanate in aqueous acetic acid was heated at 100° for 1 hr. After addition of hydrochloric acid, the reaction mixture was further heated, diluted with water and kept standing to deposit IIIa in 70% yield. The hydantoin IIIa thus obtained was identical in every respect with a sample obtained as a minor product in the Bucherer hydantoin synthesis.

Treatment of IIa and IIIa with dimethyl sulfate in alkaline solution resulted in the formation of the N₃-methyl derivatives (IIb), mp 221°, and (IIIb) mp 212°. Some physical properties of isomeric hydantoin and their N₃-methyl derivatives are listed in Table I.

TABLE I. Some Physical Properties of Two Epimeric Hydantoin and Their N₃-Methyl Derivatives

Compound	mp (°C)	IR cm ⁻¹ (KBr)				NMR τ (DMSO- <i>d</i> ₆)			
		ν NH		ν C=O		N ₁ -H	N ₃ -H	N ₃ -CH ₃	C ₄ -H
IIa	260—261	3200	3050	1760	1710	1.55	—0.63	—	5.0 b
IIb	220—221	3200		1760	1710	1.22 (2.85)	—	7.11 6.94	5.0 b 4.8 b) ^{a)}
IIIa	285	3480	3270	1740	1710	1.53	—0.65	—	4.88 b
IIIb	211—212	3280		1760	1710	1.22 (2.02)	—	7.11 6.92	4.8 b 4.63 b) ^{a)}

a) solvent: CDCl₃ b: broad

Cremlyn's assignment to the stereochemistry of 4-*tert*-butylcyclohexane-spiro-hydantoin is partly based on that the NMR signal due to the less acidic N₁-proton of the major hydantoin in the Bucherer synthesis appears in lower field than the corresponding signal of the hydantoin obtained by the Strecker cyanate route (solvent: DMSO-*d*₆). This was ascribed to that in the former the N₁-proton is deshielded by the C—C bonds of the cyclohexane ring (*i. e.* it is in a pseudo-equatorial position), whereas in the latter it is shielded by these bonds and occupies a pseudo-axial position.

In the NMR spectra of IIa, b and IIIa, b, however, the chemical shifts in DMSO-*d*₆ for their N₁-protons are almost identical in each pair of isomers. On the other hand, the NMR spectra of the N₃-methyl hydantoin IIb and IIIb in CDCl₃ show a marked difference between the resonances of their N₁-protons (2.85 τ for IIb, 2.02 τ for IIIb), which is in complete contrast with Cremlyn's observation. If Cremlyn's argument is applied equally to our case, an N₁-H group in IIb may adopt the axial position while IIIb has an equatorial N₁-H group.

Hydrolysis of the hydantoins IIa and IIIa to the corresponding amino acid IVa and Va (B-amino acid and S-amino acid) was accomplished by heating with aqueous barium hydroxide in a sealed tube at 150° for 15 hr. Thus, amino acids IVa, mp 275°, and Va, mp 294°, were obtained in 75% and 65% yields respectively. Both isomeric amino acids IVa and Va were shown to be homogeneous by thin-layer and gas chromatographic analysis and characterized

TABLE II. mp, IR and NMR Spectral Data of Amino Acids (IVa and Va) and Their Derivatives

Compound	mp (°C)	IR cm ⁻¹ (KBr)				NMR τ (DMSO- <i>d</i> ₆)		
		ν NH	ν OH	δ NH	ν C=O	NH	C ₄ -H	-CH ₃
IVa	273—275	3500—2300		1580 1530	1640			
IVb	220	3350 3250		1540	1700 1640	2.19 6.6 b	8.15	
IVc	265—266	3330		1550	1730 1710 1620	2.12 5.4 b	8.04 8.27	
IVd	164—165	3300		1550	1720 1640	3.39 ^a 5.25 ^a	6.25 ^a 7.92 ^a 7.96 ^a	
Va	292—294	3600—2500		1630 1560	1560			
Vb	234	3350 3200		1540	1690 1620	2.20 6.35 b	8.18	
Vc	275—276	3340		1550	1720 1700 1620	2.03 5.20 b	7.98 8.17	
Vd	181—182	3300		1530	1720 1640	3.84 ^a 5.05 b ^a	6.25 ^a 7.87 ^a 7.95 ^a	

^a) solvent: CDCl₃ b: broad

Fig. 1. IR Spectra of Isomeric 1-Amino-4-hydroxycyclohexane-1-carboxylic Acids IVa and Va in the 1700—1500 cm⁻¹ Region (KBr)

Fig. 2. IR Spectra of Isomeric 1-Amino-4-hydroxycyclohexane-1-carboxylic Acids IVa and Va in the 1700—1500 cm⁻¹ Region after Deuterium Exchange (KBr)

by their conversions to derivatives such as N-acetates (IVb and Vb), O,N-diacetates (IVc and Vc) and O,N-diacetates methyl esters (IVd and Vd).

Table II summarizes some physical properties of both isomeric amino acids IVa, Va and their derivatives. There is a noticeable difference between the IR spectra of IVa and Va (KBr) in the 1700—1500 cm^{-1} region as shown in Fig. 1: the former exhibited well-resolved three absorption bands, but the latter has two absorption bands in this region. Deuterium exchange (recrystallization of IVa and Va from D_2O) makes it possible to distinguish a carboxylate C=O stretching band from ammonium NH deformation bands in their IR spectra. (*cf.* Fig. 2)

Each of the IR spectra of IVa and Va in the region shows a closely similar pattern to that of the corresponding isomeric 1-amino-4-alkylcyclohexane-1-carboxylic acids obtained *via* the Bucherer and the Strecker synthesis according to Munday's procedure.⁴⁾

In the NMR spectra of each isomeric pair of IVb—d and Vb—d, all of the C_4 -proton of the former series appears broader signals in higher field than those of the latter series.

Table III lists mp, *Rf* and *pK_a* values of isomeric pairs of 4-substituted cyclohexane-1-carboxylic acids (B-amino acids and S-amino acids) including IVa and Va.

TABLE III. Some Physical Properties of Isomeric 1-Amino-4-substituted-cyclohexane-1-carboxylic Acids

Compound	C_4 -Substituent	mp ($^{\circ}\text{C}$)	<i>Rf</i> ^{a)}	<i>pK₁</i>	<i>pK₂</i>
B-Amino acid (IVa)	OH	273—274	0.38	2.30	9.62
S-Amino acid (Va)	OH	292—294	0.41	2.50	9.50
B-Amino acid	CH_3	305—310	0.57	2.25	9.78
S-Amino acid	CH_3	356—360	0.69	2.53	9.40
B-Amino acid	<i>t</i> - C_4H_9	300—304	0.89		
S-Amino acid	<i>t</i> - C_4H_9	345—350	0.92		

a) paperchromatography (*n*-BuOH: AcOH: H_2O = 4:1:5)

It is worthwhile noting that differences in those physical data between the B- and S-amino acids show similar tendency in all pairs.

The *cis*-configuration of Va was confirmed by its transformation to lactone (IX). When IVa and Va were heated with phthalic anhydride in DMF at 170° for 6 hr, phthalimide (VII), mp 188°, and (VIII), mp 212° were obtained in 45% and 55% yields respectively. VIII was smoothly cyclized to lactone IX, mp 167° in 90% yield when heated above its mp without solvent. The structure of IX was fully supported by the presence of a lactone C=O band at 1770 cm^{-1} (KBr) in its IR spectrum and a signal at 5.25 τ (C_4 -H) in its NMR spectrum. Under the same conditions, VII was recovered unchanged.

Thus, we can conclude that employment of the Bucherer conditions for I leads to the preferential formation of *trans*-amino acid IVa, whereas the Strecker synthesis gives exclusively *cis*-amino acid Va. There appears to be no significant difference between alkyl substituents and the benzyloxy group at position 4 of cyclohexanone for determination of the stereochemical course of the Bucherer and the Strecker reactions. The present result, therefore, can be expanded to the cases of 4-alkylsubstituted cyclohexanones, supporting Munday's assignment for the configurations of 1-amino-4-alkylcyclohexane-1-carboxylic acids.

The tendency of differences of physical data observed commonly in pairs of B- and S-amino acids accommodate well to this conclusion and can be used conveniently for the assignment of stereochemistry of 1-amino-4-substituted cyclohexane-1-carboxylic acids.

Attempts to obtain informations concerning ring conversion of these amino acids and stereospecificity of the Bucherer and the Strecker reaction are now in progress.

Experimental

Paper chromatography (PPC) was performed by the ascending technique using Toyo Roshi No. 50 filter paper and *n*-BuOH:AcOH:H₂O (4:1:5) was used as solvent. NMR spectra were measured on a Hitachi R-20B spectrometer with tetramethylsilane as an internal standard and were reported in τ values. Gas chromatography (GC) was carried out on a Shimadzu GC-3BF instrument employing a 1.5 m $\times$ 3 mm stainless steel column packed with 5% GE-XF-1105 at 150°. Dissociation constants (pK_1 and pK_2) were measured by Metrohm Potentiograph E-436.

1-Amino-4-benzoyloxycyclohexanenitrile Hydrochloride (VI)—A mixture of 4-benzoyloxycyclohexanone I (10 g), KCN (3.5 g) and NH₄Cl (3.7 g) in 50% EtOH stood at room temperature for 5 days. The resulting solution was diluted with H₂O and saturated with HCl gas on ice cooling. After being allowed to stand overnight in an ice box, the precipitate thus obtained was collected by filtration and recrystallized from MeOH to give VI (6 g) as colorless crystals, mp 165°. *Anal.* Calcd. for C₁₄H₁₁O₂N₂Cl: C, 59.93; H, 5.71; N, 9.98. Found: C, 59.65; H, 5.65; N, 9.72. IR cm⁻¹ (KBr): 2100 (CN).

cis-4-Benzoyloxycyclohexane-1-spiro-5'-hydantoin (IIIa)—A mixture of VI (1 g) and KCNO (0.57 g) in 90% AcOH was heated at 90–100° for 1 hr. After addition of conc. HCl (3 ml), the reaction mixture was further heated for 15 min, diluted with H₂O and cooled. The resulting precipitate was collected by filtration and recrystallized from MeOH to give IIIa (0.8 g) as colorless crystals, mp 285°. *Anal.* Calcd. for C₁₅H₁₆O₄N₂: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.52; H, 5.74; N, 9.69. IR cm⁻¹ (KBr): 3480, 3270 (NH), 1740, 1710 (C=O). NMR (DMSO-*d*₆) τ : -0.65 (1H, singlet, NH), 1.53 (1H, singlet, NH), 1.9–2.7 (5H, multiplet, aromatic protons), 4.88 (1H, broad, C₄-H).

3'-Methyl-hydantoin (IIIb) was obtained upon treatment of IIIa in alkaline medium with (CH₃)₂SO₄, mp 211–212°. *Anal.* Calcd. for C₁₆H₁₈O₄N₂: C, 63.56; H, 6.00; N, 9.65. Found: C, 63.52; H, 6.06; N, 9.51. IR cm⁻¹ (KBr): 3280 (NH), 1760, 1710 (C=O). NMR (DMSO-*d*₆) τ : 1.22 (1H, singlet, NH), 1.8–2.6 (5H, multiplet, aromatic protons), 4.8 (1H, broad, C₄-H), 7.11 (3H, singlet, CH₃), 7.5–8.5 (8H, multiplet, ring methylenes). NMR (CDCl₃) τ : 1.8–2.9 (5H, multiplet, aromatic protons), 2.02 (1H, singlet, NH), 4.63 (1H, broad, C₄-H), 6.92 (3H, singlet, CH₃), 7.5–8.6 (8H, multiplet, ring methylenes).

trans- and cis-4-Benzoyloxycyclohexane-1-spiro-5'-hydantoins (IIa and IIIa)—A mixture of I (5 g), KCN (2 g) and (NH₄)₂CO₃ (10 g) in 60% aqueous EtOH was heated at 90–100° in a sealed tube for 1 hr. After addition of some H₂O and then cooling, the reaction mixture deposited crystals, which were collected, washed well with H₂O and dried. A mixture of IIa and IIIa (6 g) thus obtained was separated by fractional recrystallization from MeOH to give pure hydantoin IIa (less soluble in MeOH), 2.6 g, mp 260–261° as a major product. *Anal.* Calcd. for C₁₅H₁₆O₄N₂: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.36; H, 5.72; N, 9.61. IR cm⁻¹ (KBr): 3200, 3050 (NH), 1760, 1710 (C=O). NMR (DMSO-*d*₆) τ : -0.63 (1H, singlet, NH), 1.55 (1H, singlet, NH), 1.9–2.5 (5H, multiplet, aromatic protons), 5.0 (1H, broad, C₄-H).

In the same manner as the case of IIIb, 3'-methyl-hydantoin (IIb) was obtained from IIa as colorless crystals, mp 220–221°. *Anal.* Calcd. for C₁₆H₁₈O₄N₂: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.73; H, 6.03; N, 9.63. IR cm⁻¹ (KBr): 3200 (NH), 1760, 1710 (C=O). NMR (DMSO-*d*₆) τ : 1.22 (1H, singlet, NH), 1.8–2.6 (5H, multiplet, aromatic protons), 5.0 (1H, broad, C₄-H), 7.11 (3H, singlet, CH₃), 7.5–8.5 (8H, multiplet, ring methylenes). NMR (CDCl₃) τ : 1.8–2.9 (5H, multiplet, aromatic protons), 2.85 (1H, singlet, NH), 4.8 (1H, broad, C₄-H), 6.94 (3H, singlet, CH₃), 7.5–8.5 (8H, multiplet, ring methylenes).

Hydantoin IIIa was obtained from the mother liquor (more soluble in MeOH), 0.7 g, mp 285°. The hydantoin IIIa thus obtained was identical in every respect with a sample prepared from aminonitrile hydrochloride VI as described above.

The ratio of IIa to IIIa in the crude hydantoins was determined to be 3:1 by gas chromatographic analysis (after trifluoroacetylation) of a mixture of amino acids IVa and Va obtained by hydrolysis of the crude hydantoin prior to separation.

1-Amino-trans- and cis-4-hydroxycyclohexane-1-carboxylic Acid (IVa and Va)—Hydantoin IIa (5 g) was heated in a sealed tube with Ba(OH)₂ (10 g) in H₂O (60 ml) at 150–160° for 15 hr. The hot solution was filtered and then boiled in order to remove ammonia formed in the reaction. The reaction mixture was acidified with conc. H₂SO₄ to deposit BaSO₄ and benzoic acid. After removal of these compounds by filtration, the filtrate was centrifuged to separate still remaining BaSO₄. The clear solution thus obtained was neutralized with basic PbCO₃ to precipitate PbSO₄. After removal of PbSO₄, H₂S gas was bubbled through the solution to remove excess lead ion as PbS. The aqueous solution thus obtained was extracted with ether and the ether layer was concentrated to dryness under reduced pressure. Recrystallization of the residue from H₂O-acetone afforded *trans*-amino acid IVa (2.5 g) as colorless crystals, mp 273–275°. *Anal.* Calcd. for C₇H₁₃O₃N: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.65; H, 8.24; N, 8.87. PPC: *R*_f=0.38 (*n*-BuOH:AcOH:H₂O=4:1:5). GC: *t*_R=5.6 min. IR cm⁻¹ (KBr): 3500–2300 (NH₃⁺, OH), 1640 (C=O), 1580, 1530 (NH₃⁺).

In a similar manner as above, *cis*-amino acid Va was obtained from hydantoin IIIa as colorless crystals, mp 292–294°, in 65% yield. *Anal.* Calcd. for C₇H₁₃O₃N: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.91; H, 8.33; N, 9.02. PPC: *R*_f=0.41 (*n*-BuOH:AcOH:H₂O=4:1:5). GC: *t*_R=4.8 min. IR cm⁻¹ (KBr): 3600–2500 (NH₃⁺, OH), 1630 (NH₃⁺), 1560 (broad, COO⁻, NH₃⁺).

1-Acetyl-amino-*trans*- and *cis*-4-hydroxycyclohexane-1-carboxylic Acids (IVb and Vb)—A mixture of IVa (1 g), pyridine (10 ml), H₂O (14 ml) and Ac₂O (2.3 ml) was stirred for 7 hr at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was recrystallized from MeOH to give IVb (0.8 g) as colorless crystals, mp 220°. *Anal.* Calcd. for C₉H₁₅O₃N: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.87; H, 7.65; N, 7.04. IR cm⁻¹ (KBr): 3350, 3250 (NH, OH), 1700, 1640 (C=O), 1540 (NHCOCH₃). NMR (DMSO-*d*₆) τ : 2.19 (1H, singlet, NH), 6.60 (1H, broad, C₄-H), 8.15 (3H, singlet, NHCOCH₃).

Similarly, Vb was obtained as colorless crystals, mp 234°. *Anal.* Calcd. for C₉H₁₅O₃N: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.67; H, 7.35; N, 7.16. IR cm⁻¹ (KBr): 3350, 3200 (NH, OH), 1690, 1620 (C=O), 1540 (NHCOCH₃). NMR (DMSO-*d*₆) τ : 2.20 (1H, singlet, NH), 6.53 (1H, broad, C₄-H), 8.18 (3H, singlet, NHCOCH₃).

1-Acetyl-amino-*trans*- and *cis*-4-acetoxycyclohexane-1-carboxylic Acids (IVc and Vc)—A solution of IVa (0.3 g) in Ac₂O and dry pyridine stood at room temperature overnight. The reaction mixture was poured into ice water and the precipitate was collected by filtration. When the filtrate was concentrated under reduced pressure, the second solid was obtained. Recrystallization of the product from acetone-ether gave IVc (0.26 g) as colorless needles, mp 265–266°. *Anal.* Calcd. for C₁₁H₁₇O₅N: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.52; H, 7.01; N, 5.87. IR cm⁻¹ (KBr): 3330 (NH), 1730–1710 (C=O), 1620, 1550 (NHCOCH₃). NMR (DMSO-*d*₆) τ : 2.12 (1H, singlet, NH), 5.40 (1H, broad, C₄-H), 8.04 (3H, singlet, OCOCH₃), 8.27 (3H, singlet, NHCOCH₃).

In a similar manner as above, Va was acetylated smoothly to give Vc as colorless crystals, mp 275–276°. *Anal.* Calcd. for C₁₁H₁₇O₅N: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.23; H, 7.16; N, 5.57. IR cm⁻¹ (KBr): 3340 (NH), 1720–1700 (C=O), 1620, 1550 (NHCOCH₃). NMR (DMSO-*d*₆) τ : 2.03 (1H, singlet, NH), 5.20 (1H, broad, C₄-H), 7.98 (3H, singlet, OCOCH₃), 8.17 (3H, singlet, NHCOCH₃).

Methyl-1-acetyl-amino-*trans*- and *cis*-4-acetoxycyclohexane-1-carboxylates (IVd and Vd)—A solution of IVa (1 g) in abs. MeOH (20 ml) saturated with dry HCl gas was refluxed for 15 hr. The solvent was evaporated under reduced pressure and the residue was acetylated with pyridine-Ac₂O. After being allowed to stand overnight, the reaction mixture was poured into cold H₂O and the precipitate was recrystallized from EtOAc to give IVd (0.8 g) as colorless needles, mp 164–165°. *Anal.* Calcd. for C₁₁H₁₉O₅N: C, 56.02; H, 7.74; N, 5.44. Found: C, 56.15; H, 7.64; N, 5.70. IR cm⁻¹ (KBr): 3300 (NH), 1720 (COOCH₃), 1637, 1550 (NHCOCH₃). NMR (CDCl₃) τ : 3.39 (1H, singlet, NH), 5.25 (1H, broad, C₄-H), 6.25 (3H, singlet, COOCH₃), 7.92 (3H, singlet, OCOCH₃), 7.96 (3H, singlet, NHCOCH₃).

Similarly, Vd was obtained as colorless crystals, mp 182°. *Anal.* Calcd. for C₁₁H₁₉O₅N: C, 56.02; H, 7.74; N, 5.44. Found: C, 55.98; H, 7.47; N, 5.64. IR cm⁻¹ (KBr): 3300 (NH), 1720 (COOCH₃), 1640 (NHCOCH₃). NMR (CDCl₃) τ : 3.83 (1H, singlet, NH), 5.05 (1H, broad, C₄-H), 6.25 (3H, singlet, COOCH₃), 7.87 (3H, singlet, OCOCH₃), 7.95 (3H, singlet, NHCOCH₃).

1-Phthalimido-*trans*- and *cis*-4-hydroxycyclohexane-1-carboxylic Acids (VII and VIII)—A mixture of *trans*-amino acid (IVa) (0.3 g), phthalic anhydride (0.24 g) and Et₃N (0.3 ml) in DMF was refluxed for 6 hr. The reaction mixture was concentrated under reduced pressure and the residue was diluted with cold H₂O (3 ml). The precipitated solid mass was collected by filtration and recrystallized from EtOAc to give VII (0.2 g) as colorless needles, mp 187–188°. *Anal.* Calcd. for C₁₅H₁₆O₅N: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.43; H, 5.37; N, 4.64. IR cm⁻¹ (KBr): 3950 (OH), 1780–1700 (C=O). NMR (DMSO-*d*₆) τ : 2.10 (4H, multiplet, aromatic protons), 6.20 (1H, broad, C₄-H).

Similar treatment of *cis*-amino acid Va gave VIII as colorless needles, mp 211–212° (EtOAc). *Anal.* Calcd. for C₁₅H₁₆O₅N: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.20; H, 5.38; N, 5.11. IR cm⁻¹ (KBr): 3440 (OH), 1780–1700 (C=O). NMR (DMSO-*d*₆) τ : 2.13 (4H, multiplet, aromatic protons), 6.20 (1H, broad, C₄-H).

1-Phthalimido-4-hydroxycyclohexane-1-carboxylic Acid δ -Lactone (IX)—VIII (0.1 g) was heated at 160–165° for 30 min without solvent, stirring with a glass bar occasionally. The resulting oily product was crystallized by addition of CHCl₃ to give IX (0.8 g) as colorless needles, mp 166–167°. *Anal.* Calcd. for C₁₅H₁₃O₄N: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.05; H, 4.74; N, 5.06. IR cm⁻¹ (KBr): 1700, 1740, 1710 (C=O). NMR (CDCl₃) τ : 2.00–2.50 (4H, multiplet, aromatic protons), 5.25 (1H, broad, C₄-H).

IX was obtained directly from *cis*-amino acid Va as follows. Va (0.54 g) and phthalic anhydride (0.4 g) were mixed well and then heated at 145–160° for 30 min with occasional stirring. After cooling, the reaction mixture was dissolved in hot MeOH and filtered to remove insoluble substances. The resulting clear solution was concentrated to dryness and the residue was submitted to chromatography on silica gel in CHCl₃ to isolate pure IX (0.42 g). IX thus obtained was identical in every respect with that obtained from VII.

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