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Studies of Alicyclic α-Amino Acids. IV.[1] Conformational Analysis of Alicyclic α-Amino Acids and Stereochemistry of the Strecker and the Bucherer Reactions[2]

Yoshifumi Maki, Takashi Masugi, and Koji Ozeki

Gifu College of Pharmacy[3]

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Conformational analysis of a pair of isomeric alicyclic α-amino acids was made by comparison of relative rates for alkaline hydrolysis of their ethyl esters. It was found that in a sharp contrast with the case of 2-norbornanone, employment of the Strecker and the Bucherer reactions in 2-bornanone resulted in the predominant formation of the corresponding amino acid possessing *exo*-amino and *endo*-carboxyl groups. On the basis of this finding, the stereochemical courses of the Strecker and the Bucherer reactions in the synthesis of alicyclic α-amino acid are also discussed.

Munday[4] has postulated that conformationally rigid alkyl-1-aminocyclohexane-1-carboxylic acids produced upon hydrolysis of their Bucherer hydantoins possess carboxyl and amino functions locked in the equatorial and axial positions, respectively. Their conformational isomers, prepared *via* the Strecker cyanate method, were assigned the reverse configuration[5] (*cf.* II-Sa←Ia→II-Ba in Chart 1). Cremlyn, *et al.*[6,7] have arrived at the opposite conclusion on the basis of some physicochemical data and the deamination experiment, leaving in doubt which interpretation is correct.

Thus, the assignments of configurations in the cyclohexane α-amino acids based on pK values, spectra and reactivities have been the subject of some disagreement.

We have previously described the physicochemical data for the conformational assignments of two epimeric 3-amino-5α-cholestane-3-carboxylic acids[8] and the chemical proof which establishes unequivocally the stereochemistry of 1-amino-*trans*- and *cis*-4-hydroxycyclohexane-1-carboxylic acids (II-Bb and II-Sb).[9] These results are compatible with the Munday's aspect. More recently, the conclusive assignments of configurations of isomeric 2-aminonorbornane-2-carboxylic acids (IV-S and IV-B) have been made by X-ray crystallography.[10,11] Enzymatic studies[12] on isomeric 2-amino-*trans*-decalin-2-carboxylic acid esters have provided the results inconsistent with the Cremlyn's assignments for their configurations.

This paper demonstrates a convenient and general method, involving the comparison of rates for the alkaline hydrolysis of esters, for conformational analysis of a pair of isomeric

1) Part III: Y. Maki, T. Masugi, T. Hiramitsu, and T. Ogiso, *Chem. Pharm. Bull.* (Tokyo), **21**, 2460 (1973).
2) A part of this paper was presented at the 93rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1973).
3) Location: *492–36 Mitahora, Gifu.*
4) L. Munday, *J. Chem. Soc.*, **1961**, 4372.
5) The suffixes, S. and B, of the amino acid numbers represent the amino acids prepared by the Strecker and the Bucherer methods, respectively.
6) R.J.W. Cremlyn and M. Chisholm, *J. Chem. Soc.*, **1967**, 2269.
7) R.J.W. Cremlyn, R.M. Ellam, and T.K. Mitra, *J. Chem. Soc.* (*C*), **1971**, 1674.
8) Y. Maki, K. Obata, and M. Sato, *Chem. Pharm. Bull.* (Tokyo), **13**, 1377 (1965).
9) Y. Maki and T. Masugi, *Chem. Pharm. Bull.* (Tokyo), **21**, 685 (1973).
10) H.S. Tagar and H.N. Christensen, *J. Am. Chem. Soc.*, **94**, 968 (1972).
11) P. Apgar and M. Ludwig, *J. Am. Chem. Soc.*, **94**, 964 (1972).
12) M.S. Matta and M.F. Rohde, *Tetrahedron Letters*, **1972**, 4157.

alicyclic α-amino acids. The stereochemical courses of the Strecker and the Bucherer reactions in the synthesis of alicyclic α-amino acids are discussed on the basis of the formation of 2-aminobornane-2-carboxylic acid (VII), which is the amino acid obtained exclusively from (+)-2-bornanone by both the reactions. Evidence in support of the stereochemistry of VII, which adopts *exo*-amino and *endo*-carboxyl groups (1*R*,2*R*,4*R*-configurations) is also presented.

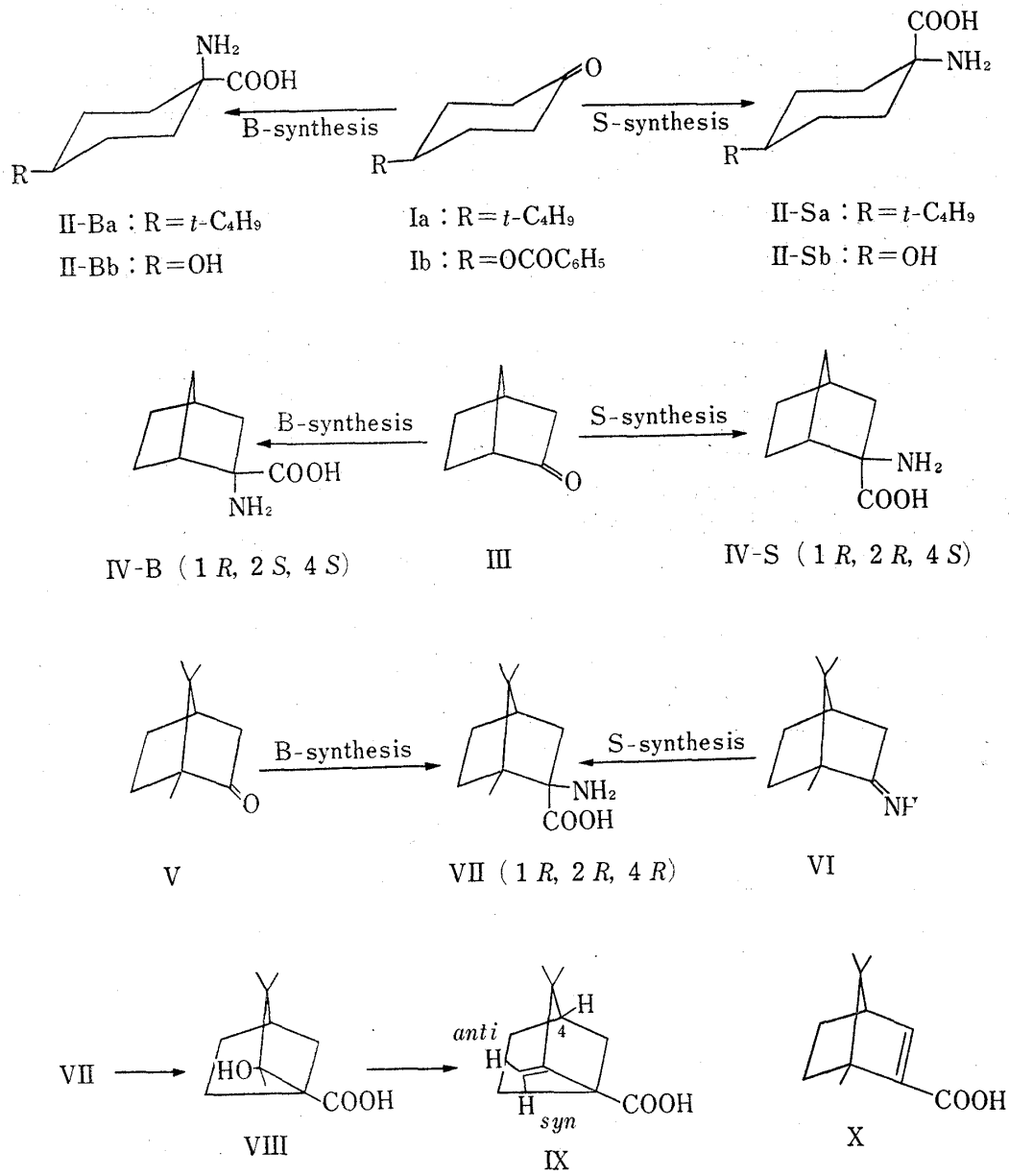

Chart 1

Substantial evidence suggests that the *exo*-position of the norbornane system is sterically more accessible than the *endo*-position.[13] Christensen, *et al.*[10] have pointed out that the N-formyl group on the *endo*-amino function of IV-B suffers acid-catalyzed hydrolysis at a rate approximately 30% greater than that for the *exo*-N-formyl group of the isomer IV-S, although it is not consistent with the expectation of greater steric hindrance at the *endo*-side of the norbornane system. This conflicting result can be ascribed to that the rate for hydrolysis of the formylamino grouping does not reflect its steric environment, because the reactive

13) H.C. Brown, *Chem. Brit.*, **1966**, 199.

site of the hydrolysis is distant from the norbornane ring. In this point of view, the comparison of the alkaline hydrolysis rates of a pair of isomeric amino acid esters, possessing the reactive site of the hydrolysis close to the alicyclic ring, seems to be more favorable for their conformational analysis.

A common method for comformational analysis of the carboethoxy group located in alicyclic rings is the measurement of the alkaline saponification rate. Eliel, *et al.*[14] have determined the rates of saponification of ethyl *trans*- and *cis*-4-*t*-butylcyclohexane-1-carboxylates by means of a titration technique.

In the cases of the amino acid esters, however, the quantitative analysis of the amino acid formed as a result of saponification by the titration is tedious because of the zwitterionic nature of the amino acid. We deviced a convenient method for conformational analysis of an isomeric pair of α-amino acid ethyl esters, which involves gas chromatographic estimation of the resulting ethanol at various times during the saponification.

The comparison of rates for the saponification of ethyl esters of IV-B and IV-S whose conformations have been unambiguously established was first carried out (see experimental part for details).

Fig. 1 shows plots of ethanol concentrations *vs.* times. The distinct difference between the slopes of two curves clearly demonstrates that the ester of IV-B (eq. ethoxycarbonyl group) is more easily saponified than the ester of IV-S (ax. ethoxycarbonyl group) in agreement with their conformations previously assigned. Thus, it was realized that the comparison of rates for the alkaline hydrolysis of a pair of isomeric amino acid esters by the present procedure is applicable to conformational analysis of an alicyclic α-amino acids.

Previously, conformational analysis of two epimeric steroidal α-amino acids has been made by monitoring their ease of alkaline hydrolysis of the corresponding esters[8] by means of thin-layer chromatography. The present method, however, is more reliable and convenient.

The conformations of II-Sa and II-Ba appear to be deduced from the conclusion on these of II-Sb and II-Bb.[9] The comparison of the hydrolysis rates of II-Sa and II-Ba ethyl esters by the present method strongly supports their conformations previously proposed (see Fig. 2).

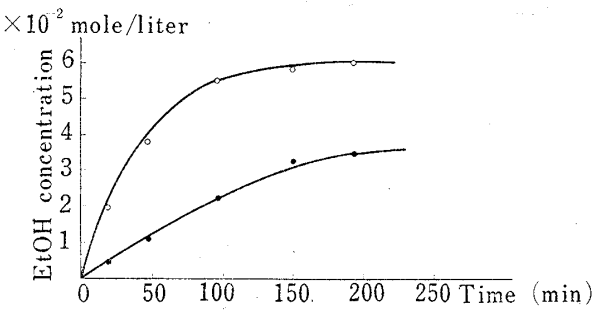

Fig. 1. Hydrolysis of Ethyl Esters of Two Epimeric 2-Aminonorbornane-2-carboxylic Acids, (IV-S) (closed circles) and (IV-B) (open circles)

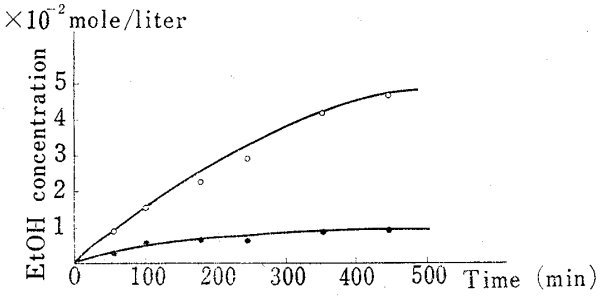

Fig. 2. Hydrolysis of Ethyl Esters of Two Isomeric 1-Amino-4-*t*-butylcyclohexane-1-carboxylic Acids, (II-Sa) (closed circles) and (II-Ba) (open circles)

More recently, Matta and Rohde[12] have shown that the measurement of the reactivity of α-chymotrypsin toward two isomeric *p*-nitrophenyl 2-acetylamino-*trans*-decalin-2-carboxylates makes it possible to determine their conformations. It is worthwhile noting that the enzymatic hydrolysis is efficient for conformational analysis of alicyclic α-amino acid esters in the same way as the alkaline hydrolysis.

Hoyer[15] has reported the synthesis of 2-aminobornane-2-carboxylic acid *via* the corresponding spirohydantoin of (+)-2-bornanone (V) and the aminonitrile obtained by cyana-

14) E.L. Eliel, H. Hankenstock, and R.V. Acharya, *J. Am. Chem. Soc.*, **83**, 2351 (1961).
15) H.L. Hoyer, *Chem. Ber.*, **83**, 491 (1950).

tion of 2-bornanimine (VI), and its separation into two epimeric isomers. The synthesis of the amino acids according to the Hoyer's procedures was reinvestigated.

Contrary to Hoyer's observations, identity and homogeneity of the amino acids prepared by the two alternative routes were proved by infrared (IR), nuclear magnetic resonance (NMR) and mass spectra, and gas–liquid chromatography. This finding implies that the Bucherer and the Strecker[16] reactions proceed with high stereoselectivity *via* the same stereochemical course under the striking influence of steric hindrance in the *exo*-face of the bornane ring. The structure of the amino acid was shown to be 2-aminobornane-2-carboxylic acid adopting an *exo*-amino group (1*R*,2*R*,4*R*-configurations), based on the following reasons.

It has been found that the NH-deformation bands of the *endo*-amino group in IV-B is better resolved than those of the *exo*-amino group in IV-S in their IR spectra.[10] The IR spectrum of VII reveals the unresolved NH-deformation bands similar to those of IV-S, suggesting the *exo*-orientation of the amino group in VII.

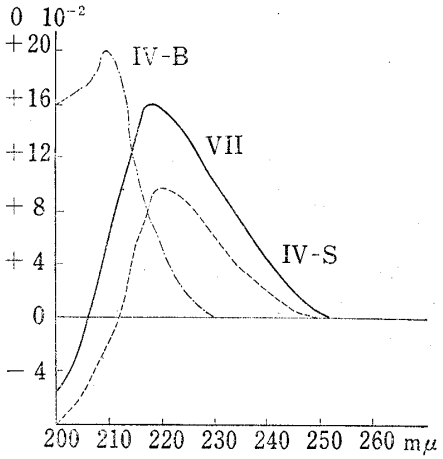

Fig. 3. Spectra of the Circular Dichroism in Water Solution of (1*R*, 2*S*, 4*S*)- and (1*R*, 2*R*, 4*S*)-2-Aminonorbornane-2-carboxylic Acids (IV-B and IV-S) and (1*R*, 2*R*, 4*R*)-2-Aminobornane-2-carboxylic Acid (VII)

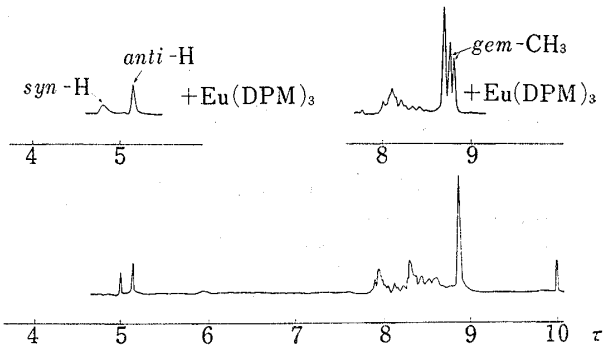

Fig. 4. NMR Spectra of 3,3-Dimethyl-2-methylenenorbornane-1-carboxylic Acid (IX) (100 MHz, in $CDCl_3$)

The spectrum of the circular dichroism in water of VII resembles that[10] of (−)-IV-S (1*R*,2*R*,4*S*-configurations) rather than (−)-IV-B (1*R*,2*S*,4*S*-configurations)[17] as shown in Fig. 3. On the assumption of no significant contribution of C_1-methyl and C_7-*gem*-dimethyl groups in the bornane ring to the circular dichroism, this fact may allow to predict the 1*R*,2*R*,4*R*-configurations (*exo*-amino group) of VII.

The stereochemistry of VII was established on the basis of the result of its deamination experiment.

The deamination of 1-aminocyclohexane-1-carboxylic acids to the corresponding 1-hydroxy acids has been first carried out by Skita and Levi.[18] Cremlyn, *et al.*[7] have shown that the Strecker amino acids, *e.g.*, II-Sa, give mainyl hydroxy acid, while the corresponding Bucherer isomers, *e.g.*, II-Ba, lead to the formation of a considerable amount of unsaturated

16) The synthesis of VII *via* cyanation of 2-bornanimine seems to be identical in mechanistic points of view with the Strecker synthesis (*cf.* J. W. Morrison and H. S. Mosher, "Asymmetric Organic Reaction," Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1971, p. 328). In agreement of this aspect, the aminonitrile obtained by cyanation of 4-*t*-butylcyclohexanimine was identical with a specimen prepared from Ia under the Strecker conditions in every respect (see experimental part).

17) The amino acids ((−)-IV-S and (−)-IV-B)[10] have been prepared using optical active (−)-2-norbornanone as a starting materials.

18) A. Skita and R. Levi, *Chem. Ber.*, **41**, 2925 (1908).

carboxylic acids. These observations well accomdate to their conformations, *e.g.*, II-Sa and II-Ba, although Cremlyn, *et al.* have claimed the reverse ones based on the assumption that the deamination may take place *via* a twist-boat conformation of the amino acids.

Thus, the structure and distribution of products in the deamination of alicyclic α-amino acids depend upon the conformation of the amino function, and therefore analysis of the deamination products is advantageous for the determination of stereochemistry of the amino acids.

The deamination of VII was carried by acting sodium nitrite in acetic acid at room temperature. The product was analyzed with a gas-liquid chromatograph interfaced with a mass spectrometer.

The mass spectrum of the main product (yield 95%) showed a parent peak at *m/e* 180, indicating that the product is formed as a result of loss of an ammonia. Its IR spectrum exhibits the presence of a carboxyl group in the molecule ($\nu_{C=O}$ 1700 cm^{-1}).

The NMR spectrum reveals a signal corresponding to protons of two methyl groups at 8.88 τ and two signals assignable to two vinyl protons at 5.00 τ and 5.24 τ. The methyl signal splitted slightly and a vinyl proton signal at 5.00 τ is more deshielded than a signal at 5.24 τ by adding a lanthanide shift reagent ($Eu(DPM)_3$) (see Fig. 4). The deshielded vinyl proton signal is broader than that in the high field. This is explicable in terms of a homoallylic coupling between a *syn*-vinyl proton and C_4-proton observed in the camphene system.[19] Accordingly, the product contains two nonequivalent methyl groups and an end *o*- methylene group in which a *syn*-proton would be close to a carboxyl function. These data are fit to assign 3,3-dimethyl-2-methylenenorbornane-1-carboxylic acid (IX) to the main product.

Upon the treatment of VII with sodium nitrite in sulfuric acid at 0° according to the Hoyer's method,[14] hydroxy acid (VIII)[20] was obtained in 90% yield. Acid-catalized dehydration of VIII gave easily IX which is identical with our product in every respect. These facts

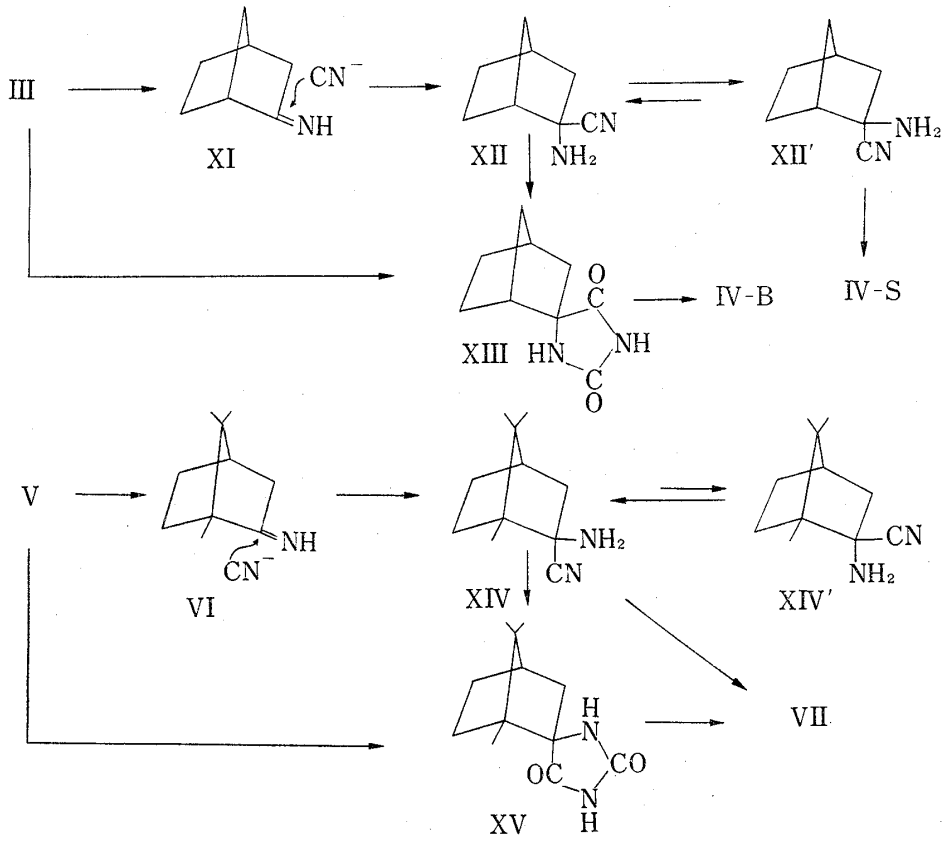

Chart 2

19) S.H. Grover and J.B. Stothers, *J. Am. Chem. Soc.*, **91**, 4331 (1969).
20) E. Pfankuch, *Ann.*, **483**, 288 (1930).

clearly indicate that the deamination of the amino acid at room temperature takes place successively Wagner-Meerwein rearrangment and dehydration to give IX (*cf.* Chart 1).

On the basis of mechanistic consideration of above results, the structure of the amino acid can be ascribed to VII with an *exo*-amino group. If the amino acid has an *endo*-amino group, the deamination product must be α,β-unsaturated carboxylic acid (X) formed by direct elimination.

The *exo*-side of the norbornane system is more accessible to a wide variety of reagent than is the *endo*-side. The different steric situation prevails in the bornane system where the *exo*-face of the molecule is strongly screened by the *gem*-dimethyl group at C_7.[13,21]

Our present finding that the Bucherer reaction gives exclusively VII with the *exo*-amino group in the same as the case of the Strecker reaction is highly instructive to account for the stereochemical courses of both reactions in the synthesis of alicyclic α-amino acids.

The key intermediate of the Bucherer[22] as well as the Strecker reaction[16] has been considered to be aminonitrile. The stereochemistry of the aminonitriles presumably formed by cyanation of the imine intermediates, *e.g.*, VI and XI, destines the conformations of the resulting amino acids (see Chart 2).

The equilibrium ratio for the isomeric aminonitriles must largely be a function of the amino group since it has been found little preference for the *endo*- or *exo*-position in the equilibration of norbornane-2-carbonitrile.[23] It has been demonstrated a kinetic preference for the aminonitrile isomer (XII) with amino group *endo*, although the isomer (XII′) with that group *exo* appears to be the more thermodynamically stable one.[10]

The formation of the spiro-hydantion (XIII) in the Bucherer reaction may play a role to lock the initial conformation of aminonitrile XII, which is first formed under the kinetical control. On the other hand, the key intermediate in the Strecker reaction is aminonitrile XII′ resulting from the thermodynamic control.[24]

In the bornane system, however, aminonitrile (XIV) rather than (XIV′) must be the key intermediate of both reactions because XIV prefers kinetically as well as thermodynamically to XIV′. Accordingly, in a sharp contrast to the case of 2-norbornanone, the Bucherer reaction of 2-bornanone results in the formation of the amino acid VII with an *exo*-amino group *via* XIV generated by the *endo*-side attack of cyano anion to the C=N bond in VI (*cf.* Chart 2).

Our present work provided a notable observation for understanding the stereochemical courses in the Strecker and the Bucherer reactions of alicyclic ketones.

Experimental[25]

Ethyl 1-Amino-*trans*- and *cis*-4-*t*-butylcyclohexane-1-carboxylate Hydrochlorides (Ethyl Esters of II-Ba and II-Sa)——1-Amino-*trans*- and *cis*-4-*t*-butylcyclohexane-1-carboxylic acids, II-Ba and II-Sa, were pre-

21) E.L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, p. 303.

22) The formation of hydantoin under the Bucherer conditions has been proved to involve the attack of initially formed aminonitrile at the carbamic acid carbon (M. Murakami and J. Ibata, *Nippon Kagaku Zasshi*, **85**, 494 (1964)).

23) P. Wilder and D.B. Knight, *J. Org. Chem.*, **30**, 3078 (1965).

24) In agreement with these aspects, we have previously observed that the corresponding hydantoin of 5α-cholestan-2-one is obtained by the Bucherer reaction, while its transformation to aminonitrile by the strecker reaction is unsuccessful. This finding is explicable in terms of thermodynamical instability of the Strecker aminonitrile and stabilization by locking of the Bucherer aminonitrile formed under kinetical control owing to the steric hindrance of *axial* 19-methyl group.

25) All melting points are uncorrected. Gas chromatographic analyses were performed on a Shimadzu GC-4A, a Shimadzu GC-3BF and a Hitachi 023 using 1.5 m×3 mm stainless steel columns packed with 20% PEG, 5% GE-XF-1105 and 30% SE-30. IR spectra were run on a Hitachi-215 spectrophotometer. NMR spectra were recorded at 60 MHz with a Hitachi R-20B and at 100 MHz with a JEOL JNR-4H using TMS as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. CD spectra were measured with a JASCO ORD/UV-5. Optical rotation were determined with a JASCO DIP-SL automatic polarimeter.

pared by the Munday's procedure.[4] A solution of II-Ba (1 g) in absolute EtOH (30 ml) containing 3 ml of conc. H_2SO_4 was refluxed for 15 hr. After removal of EtOH, the residue was neutralized with aqueous Na_2CO_3 and taken up with ether. The ether layer was washed with H_2O. dried over anhyd. Na_2SO_4, and then saturated with dry HCl gas on ice cooling. The precipitate thus obtained was recrystallized from MeOH to ive gethyl 1-amino-*trans*-4-*t*-butylcyclohexane-1-carboxylate hydrochloride (0.5 g) as colorless crystals, mp 145—146°. *Anal.* Calcd. for $C_{13}H_{26}O_2NCl$: C, 59.52; H, 9.48; N, 5.31. Found: C, 59.42; H, 9.68; N, 5.52. IR ν_{max}^{KBr} cm^{-1}: 3000 (broad, NH_3^+), 1720 (CO), 1620, 1600, 1540 (NH_3^+). NMR (DMSO-d_6) τ: 1.00 (3H, broad, $N\underline{H}_3^+$), 5.70 (2H, q, J=7 cps, $COOC\underline{H}_2CH_3$), 8.80 (3H, t, J=7 cps, $COOCH_2C\underline{H}_3$), 9.10 (9H, s, $3\times C\underline{H}_3$).

Ethyl 1-amino-*cis*-4-*t*-butylcyclohexane-1-carbocxylate hydrochloride was obtained from II-Sa by the same method as described above. mp 230°. *Anal.* Calcd. for $C_{13}H_{26}O_2NCl$: C, 59.52; H, 9.48; N, 5.31. Found: C, 59.25; H, 9.75; N, 4.98. IR ν_{max}^{KBr} cm^{-1}: 3000 (broad, NH_3^+), 1740 (CO), 1590, 1520 (NH_3^+). NMR (DMSO-d_6) τ: 1.20 (3H, broad, $N\underline{H}_3^+$), 5.73 (2H, q, J=7 cps, $COOC\underline{H}_2CH_3$), 8.65 (3H, t, J=7 cps, $COOCH_2C\underline{H}_3$), 9.15 (9H, s, $3\times C\underline{H}_3$).

Two Isomeric Ethyl 2-Aminonorbornane-2-carboxylate Hydrochlorides (Ethyl Esters of IV-B and IV-S)——2-Aminonorbornane-2-carboxylic acids, IV-B and IV-S, were prepared according to the Christensen's procedure.[10] Both esters were obtained from IV-B and IV-S in a manner similar to the above cases, respectively. Ethyl ester hydrochloride of IV-B: mp 190—191°. *Anal.* Calcd. for $C_{10}H_{18}O_2NCl$: C, 48.43; H, 7.27; N, 5.65. Found: C, 48.31; H, 7.21; N, 5.81. IR ν_{max}^{KBr} cm^{-1}: 3100 (broad, NH_3^+), 1730 (CO), 1590, 1560, 1520 (NH_3^+). NMR (DMSO-d_6) τ: 1.20 (3H, broad, NH_3^+), 5.80 (2H, q, J=7 cps, $COOC\underline{H}_2CH_3$), 8.75 (3H, t, J=7 cps, $COOCH_2C\underline{H}_3$). Ethyl ester hydrochloride of IV-S: mp 262—265°. *Anal.* Calcd. for $C_{10}H_{18}O_2NCl$: C, 48.43; H, 7.27; N, 5.65. Found: C, 48.28; H, 7.09; N, 5.66. IR ν_{max}^{KBr} cm^{-1}: 3000 (broad, NH_3^+), 1740 (CO), 1595, 1520 (NH_3^+). NMR (DMSO-d_6) τ: 1.20 (3H, broad, $N\underline{H}_3^+$), 5.77 (2H, q, J=7 cps, $COOC\underline{H}_2CH_3$), 8.72 (3H, t, J=7 cps, $COOCH_2C\underline{H}_3$).

Bornane-2-spiro-5′-hydantoin (XV)——A mixture of (+)-2-bornanone (V) (9.8 g), NaCN (12.7 g) and $(NH_4)_2CO_3$ (30 g) in MeOH (50 ml) was heated under pressures around 10 atomospheres of CO_2 gas in autoclave at 120—130° for 10 hr. After cooling, the brown reaction mixture was suspended in water, acidified with conc. HCl, and then extracted with ether to remove unchanged V. The remaining solid was dissolved in 20% aqueous NaOH while hot and again acidified with conc. HCl. The resulting precipitate was collected by filtration and recrystallized from MeOH to give hydrantoin (XV) (4 g) as colorless needles, mp 262—263°. (lit.[15] mp 255—256°.) Further hydantoin was not obtained from the reaction mixture. *Anal.* Calcd. for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N, 12.69. Found: C, 64.99; H, 8.05; N, 12.78. IR ν_{max}^{KBr} cm^{-1}: 3300—3100 (broad, NH), 1760, 1710 (CO). NMR (DMSO-d_6) τ: −0.56 (1H, diffuse, N$\underline{H}$), 2.60 (1H, diffuse, N$\underline{H}$), 6.4—9.4 (7H, m, ring protons), 9.05, 9.12, 9.20 (3H, each s, $3\times C\underline{H}_3$).

XV was also prepared *via* 2-aminobornane-2-carbonitrile (XIV) hydrochloride as follows: To a solution of 2-bornanimine (VI) hydrochloride[26] (3.5 g) in H_2O, KCN (4.1 g) in H_2O was added dropwise with stirring at 0—5°. The reaction mixture was repeatedly extracted with ether. The combined ether extract was washed with H_2O, dried over anhyd. Na_2SO_4, and then saturated with dry HCl gas on ice cooling. The resulting precipitate was collected by filtration and recrystallized from MeOH to give XIV hydrochloride (2 g) as colorless crystals, mp 271—273°. *Anal.* Calcd. for $C_{11}H_{19}N_2Cl$: C, 61.46; H, 8.38; N, 13.04. Found: C, 61.34; H, 8.25; N, 13.26. IR ν_{max}^{KBr} cm^{-1}: 2100 (CN).

A mixture of XIV hydrochloride (1 g) and KCNO (1 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 H_2O and cooled. The resulting precipitate was collected by filtration and recrystallized from MeOH to give XV (1 g) as colorless crystals. Identity of XV with a sample prepared by the Bucherer reaction of V was demonstrated by comparison of their mp, IR, and NMR spectra.

2-Aminobornane-2-carboxylic Acid (VII)——Hydantoin XV (2 g) was heated with $Ba(OH)_2$ (5 g) in H_2O (80 ml) in a sealed tube at 125—130° for 36 hr. The resulting precipitate was collected by filtration and extracted repeatedly with hot MeOH. The combined MeOH solution was concentrated to dryness under reduced pressure. The filtrate was treated with excess of $(NH_4)_2CO_3$ until no further precipitation occurerd. After removal of the precipitate, the filtrate was concentrated to dryness under reduced pressure. Recrystallization of the combined residue from MeOH gave amino acid (VII) (0.2 g) as colorless needles, mp 276—277° (lit.[15] mp 278°). *Anal.* Calcd. for $C_{11}H_{19}O_2N$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.73; H, 9.70; N, 9.69. IR ν_{max}^{KBr} cm^{-1}: 3500—2500 (NH_3^+), 1600 (broad), 1580. 1500 (NH_3^+, COO^-). NMR (DMSO-d_6) τ: 7.75—8.2 (7H, m, ring protons), 8.95, 9.05, 9.15 (3H, each s, $3\times C\underline{H}_3$). Gas chromatographic analysis (5% GX-XF-1105, 1.5 m×3 mm, 200°) showed a single peak. t_R=5.2 min. Circular dichroism (CD) (c=1.001, H_2O) (θ)[27] (mμ): 0 (251), +800 (240), +1060 (230), +1600 (218) (positive maximum), +1400 (215), +550 (210), 0 (206), −400 (203). $[\alpha]_D^{20}$ −41° (c=1, MeOH) (lit.[15] $[\alpha]_D^{20}$ −56.6° (c=5, AcOH)).

2-Acetamidobornane-2-carboxylic Acid (Acetate of VII)——A solution of VII (0.7 g) in dry pyridine and Ac_2O was allowed to stand overnight at room temperature. The reaction mixture was poured into ice

26) J. Houben and E. Pfankuch, *Chem. Ber.*, **60**, 586 (1927).

water and the product precipitated was collected by filtration. Concentration of the filtrate under reduced pressure gave the second crop of the product. The crude product thus obtained was recrystallized from MeOH to give acetate (0.6 g) as colorless needles, mp 237—238°. *Anal.* Calcd. for $C_{13}H_{21}O_3N$: C, 65.24; H, 8.85; N, 5.85. Found: C, 65.42; H, 8.94; N, 5.81. IR cm^{-1} ν_{max}^{KBr}: 3450 (NH), 1770 (CO), 1630 (NHCOCH$_3$). NMR (DMSO-d_6) τ: 1.68 (1H, diffuse, NH), 8.00 (3H, s, NHCOCH$_3$), 8.90, 8.93, 9.08 (3H, each, s $3\times CH_3$).

Synthesis of 1-Amino-4-*t*-butylcyclohexane-1-carboxylic Acid (II-Sa) *via* 4-*t*-Butylcyclohexanimine——A mixture of 4-*t*-butylcyclohexanone (Ia) (3.25 g) and NH_2OH hydrochloride (2.25 g) in 15% aqueous ammonia (7.5 ml) was stirred at room temperature for 5 hr. The product precipitated was collected by filtration and recrystallized from ether to give 4-*t*-butylcyclohexanone oxime (3.2 g) as colorless needles, mp 138—140° (lit.[27] mp 133°). *Anal.* Calcd. for $C_{10}H_{19}ON$: C, 70.96; H, 11.32; N, 8.28. Found: C, 70.97; H, 11.04; N, 8.54.

To a mixture of oxime (3 g) and $NaNO_2$ (3 g) in ether (30 ml), 20% H_2SO_4 (7.2 ml) was added dropwise with vigorous stirring at 0—5°. After being allowed to stand for 1 hr, the ether layer was washed with H_2O, 35% aqueous ammonia, and then dried over anhyd. Na_2SO_4. The ether solution was diluted with a proper amount of ether and then concentrated under reduced pressure in order to remove ammonia as much as possible. The remaining ether solution was saturated with dry HCl gas to deposit a solid mass. The solid mass was collected by filtration and recrystallized from MeOH to give 4-*t*-butylcyclohexanimine hydrochloride (0.6 g) as colorless crystals, mp 124—125°. *Anal.* Calcd. for $C_{10}H_{20}NCl$: C, 63.24; H, 10.54; N, 7.38. Found: C, 63.20; H, 10.21; N, 7.35. IR ν_{max}^{KBr} cm^{-1}: 2200—1800, 1680 ($C=NH_2^+$).

To a solution of imine hydrochloride (0.6 g) and KCN (0.1 g) in H_2O, the ether saturated with HCN gas was added and then stirred at 5—10° for 1 hr under an effective ventilation. The reaction mixture was repeatedly extracted with ether. The ether extract was washed with H_2O, dried over anhyd. Na_2SO_4, and then saturated with dry HCl gas on ice cooling. The resulting precipitate was collected by filtration and recrystallized from aqueous MeOH to give 1-amino-4-*t*-butylcyclohexanenitrile hydrochloride (0.5 g) as colorless crystals, mp 190—191°. *Anal.* Calcd. for $C_{11}H_{21}NCl$: C, 60.89; H, 9.67; N, 12.91. Found: C, 61.01; H, 9.83; N, 13.15. The aminonitrile hydrochloride thus obtained was identical with a sample prepared directly from Ia by employing the Strecker conditions in every respect. Transformation of the aminonitrile into II-Sa was carried out as described previously.[9]

3,3-Dimethyl-2-methylenenorbornane-1-carboxylic Acid (IX)——To a solution of VII (0.5 g) in AcOH (8 ml), 0.2 g of $NaNO_2$ was added by portions with stirring at room temperature. The reaction mixture was allowed to stand overnight. The resulting sodium acetate was filtered off and the filtrate was concentrated to dryness under reduced pressure. After repeated extraction of the residue with EtOH, the EtOH solution was concentrated under reduced pressure to leave an oily residue. Gas chromatographic analysis (30% SE-30, 1 m×3 mm, 180°) of the residue showed almost exclusive formation of a product whose peak was at t_R=2.8 min. Recrystallization of the residue from ether gave IX as colorless crystals, mp 108—109° (lit.[15] mp 110—111°). *Anal.* Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.12; H, 8.90. IR ν_{max}^{KBr} cm^{-1}: 2800—2500 (OH), 1700 (CO), 1655 (>C=CH$_2$). NMR ($CDCl_3$) τ: 5.00, 5.24 (1H, each s, >C=CH$_2$), 7.80—8.50 (6H, m, ring protons), 8.88 (6H, s, $2\times CH_3$). NMR ($CDCl_3$+Eu(DPM)$_3$) τ: 4.66, 5.19 (1H, each broad, >C=CH$_2$), 8.87, 8.95 (3H, each s, $2\times CH_3$). Mass Spectrum *m/e*: 180 (M^+).

Measurement of the Relative Rate for Alkaline Hydrolysis of a Pair of Isomeric Alicyclic α-Amino Acid Ethyl Esters——To a mixture of 0.2N NaOH (1.5 ml) and propyl alcohol (10 μl, as an internal standard), each of isomeric esters (20 mg) was added independently. Each solution was placed in a thermostat at 25°. Immediately after, a 1 μl aliquot was withdrown by microcylinder and the clock started. This sample and all aliquots at regular time intervals were injected into a gas chromatograph (20% PEG, 1.5 m×3 mm, 90°). All vessels should be stoppered to prevent evaporaion of the solvent. Gas chromatographic analysis of the standard solution which involved EtOH (10 μl) and propyl alcohol (10 μl) in 0.2N NaOH (1.5 ml) under the same condition was carried cut in order to obtain a substantial relation between a concentration of EtOH (mole/liter) and a integral ratio of EtOH to propyl alcohol. On the basis of this relation, the concentrations of EtOH (mole/liter) were calculated from the integral ratio of EtOH to propyl alcohol in chromatogram of all aliquots. Fig. 1 and 2 were drawn by ploting EtOH concentration (10^{-2}mole/liter) *vs.* time (min).

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