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Stereochemical Studies. XXIII.[1] Stereochemistry of the Thermal Isocyanide-Cyanide Rearrangement[2,3]

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Thermal rearrangements of $R(+)$-2-(2-carboethoxy-1-phenyl)propyl isocyanide ($R(+)$-VIII), $S(+)$-2-(2-methyl-1-phenyl)butyl isocyanide ($S(+)$-XVI) and $R(+)$-2-(2-phenyl)butyl isocyanide ($R(+)$-XXVIII), were carried out under several reaction conditions.

Although the reflux of a diphenyl ether solution of $R(+)$-VIII or heating $R(+)$-VIII without solvent afforded almost completely racemized cyanide ($S(+)$-X) (at most 9% retention of configuration) as the sole reaction product in excellent yields, treatment of $S(+)$-XVI with a procedure similar to that used with $R(+)$-VIII gave $S(+)$-cyanide ($S(+)$-XXIII) with 90% (reflux of a diphenyl ether solution) and 47% (heating without solvent) retention of configuration.

The thermal reaction of $R(+)$-XXVIII gave three different olefins (XXXIV, XXXV, and XXXVI), in addition to the normal reaction product ($R(+)$-XXIX) with a low retention of configuration (at most 19%).

These observations were discussed from various aspects including the effect of asymmetric solvation due to diphenyl ether and the relative stability of the radical intermediates formed.

From theoretical,[5a,b,e] stereochemical,[5c,d,f] and kinetical[5a-c] studies, the thermal rearrangement of isocyanide (I) to cyanide (II) has been considered a typical unimolecular reaction, proceeding through a cyclic transition state, *i.e.* III, with high retention of configuration at the asymmetric carbon involved.

In stereochemical studies over the last ten years on an optically active quarternary carbon[6] we have paid much attention to the possible application of this novel thermal rearrangement to the optically active isocyanide (IV) carrying an isocyanide group at its optically active quarternary carbon. Since the isocyanide (IV) is easily derived from the optically active tertiary amine (V), and the expected product (VI) will be converted to carboxylic acid (VII), this rearrangement will surely be one of the most effective methods for transforming the asym-

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[1] Part XXII: S. Terashima, K. Takashima, T. Sato, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 1135 (1973).

[2] Presented at the 89th and 91st Annual Meetings of the Pharmaceutical Society of Japan, Nagoya, April, 1969, and Fukuoka, April, 1971.

[3] Part of this report has been communicated in two separate papers; *a*) S. Yamada, K. Takashima, T. Sato, and S. Terashima, *Chem. Commun.*, **1969**, 811; *b*) S. Yamada, M. Shibasaki, and S. Terashima, *ibid.*, **1971**, 1008.

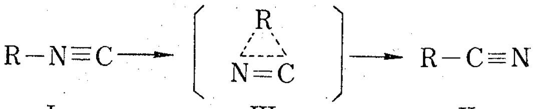
[4] Location: *Hongo, Bunkyo-ku, Tokyo.*

[5] *a*) G. Kohlmaier and B.S. Rabinovitch, *J. Phys. Chem.*, **63**, 1793 (1959); *b*) F.W. Schneider and B.S. Rabinovitch, *J. Am. Chem. Soc.*, **84**, 4215 (1962); *c*) J. Casanova, Jr., N.D. Werner, and R.E. Schuster, *J. Org. Chem.*, **31**, 3473 (1966); *d*) R.W. Horobin, N.R. Khan, and J. McKenna, *Tetrahedron Letters*, **1966**, 5087; *e*) G.W. van Dine and R. Hoffmann, *J. Am. Chem. Soc.*, **90**, 3227 (1968); *f*) S. Terashima, K. Takashima, T. Sato, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 1135 (1973).

[6] Our chemical establishments in this field have been published in two serial articles: "Stereochemical Studies," Part XXII: see references 1; "Studies on α-Alkyl-α-amino Acids," Part XV: see M. Shibasaki, S. Terashima and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 552 (1973).

metry of optically active tertiary amine (V) to that of VII,[7] if it proceeds with the same high retention of configuration reported for secondary isocyanide prepared from the secondary amine.[5c,f,9,10]

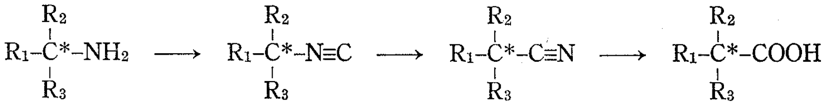
Thus, we were prompted to make a detailed investigation of this rearrangement using several kinds of IV, and found that this thermal reaction proceeded through a novel radical intermediate to afford racemized cyanide (VI) when the isocyanide (IV) carrying a functional group, which possibly stabilized the radical intermediate formed, was submitted for rearrangement. This differed completely from results of the established reaction mechanism[5] applied to the secondary isocyanide. The optically active tertiary cyanide (VI) could also be produced with a high retention of configuration from the isocyanide (IV) having no functional group to stabilize the radical intermediate, when the isocyanide (IV) was treated under special reaction conditions.



I III II

R=alkyl, aryl, *etc.*

Chart 1



$$R_1\text{-}\overset{R_2}{\underset{R_3}{C^*}}\text{-}NH_2 \longrightarrow R_1\text{-}\overset{R_2}{\underset{R_3}{C^*}}\text{-}N{\equiv}C \longrightarrow R_1\text{-}\overset{R_2}{\underset{R_3}{C^*}}\text{-}C{\equiv}N \longrightarrow R_1\text{-}\overset{R_2}{\underset{R_3}{C^*}}\text{-}COOH$$

V IV VI VII

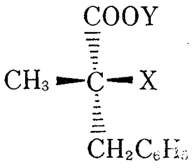
R_1, R_2, R_3=alkyl, aryl, and not H

Chart 2

Preliminary experiments using racemic compounds are described in detail in the experimental section.

Result and Discussion

First, rearrangement of *R*(+)-2-(2-carboethoxy-1-phenyl)propyl isocyanide (*R*(+)-VIII) which carries an isocyanide group at the quarternary asymmetric carbon adjacent to the ester group, was attempted. *R*(+)-VIII could be easily prepared from *R*(+)-α-methylphenylalanine ethyl ester (*R*(+)-IX) whose absolute configuration has been established,[11,12] and the expected rearranged product, *S*(+)-2-(2-carboethoxy-1-phenyl)propyl cyanide(*S*(+)-X),



R(+)-VIII : X=N≡C, Y=Et
R(+)-IX : X=NH_2, Y=Et
S(+)-X : X=C≡N, Y=Et
S(+)-XI : X=C≡N, Y=H
R(+)-XII : X=NHCHO, Y=Et
R(−)-XIII : X=$NHCOCH_3$, Y=Me

Chart 3

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7) This kind of transformation is sometimes required as a reverse reaction of the Hofmann, Curtius, and Schmidt rearrangements (see reference 8).

8) K.K. Lee, S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 2540 (1969).

9) When this thermal rearrangement was carried out using *S*(−)-1-phenylethyl isocyanide, the rearranged *S*(−)-hydrotropanitrile was obtained with 56% retention of configuration due to the probable racemization of the starting material and the reaction product under the reaction conditions (see references 5*f*).

10) In reference 5*c*, the thermal rearrangement of *S*(+)-2-butyl isocyanide proceeded with 87% retention of configuration, and 13% racemization of the rearranged product was considered due to isocyanide-promoted elimination of the α-hydrogen from the produced cyanide.

11) S. Yamada and S. Terashima, *Chem. Pharm. Bull.* (Tokyo), **16**, 1953 (1968).

12) S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 1138 (1966).

could also be derived from $S(+)$-2-cyano-2-methyl-3-phenylpropionic acid ($S(+)$-XI) whose absolute configuration has been unequivocally determined by chemical correlation.[13]

Formylation[14] of $R(+)$-IX, α_D^{20} $+1.226°$ (l=0.1, neat) (100% optically pure),[11,12] with acetic and formic mixed anhydride, followed by dehydration[5c] with phosphorus oxychloride–pyridine, afforded $R(+)$-VIII, α_D^{24} $+1.069°$ (l=0.1, neat), $[\alpha]_D^{25}$ $+14.8°$ (benzene) by way of the $R(+)$-N-formyl derivative ($R(+)$-XII), $[\alpha]_D^{21}$ $+34.4°$ (ethanol).

Preparation of optically pure $S(+)$-X, α_D^{24} $+1.739°$ (l=0.1, neat) was accomplished by the treatment of optically pure $S(+)$-XI, $[\alpha]_D^{22}$ $+24.8°$ (chloroform)[13] with diazoethane[15,16] in ether.

The thermal rearrangement of $R(+)$-VIII was carried out by changing the reaction conditions as shown in Table I.

TABLE I. Thermal Rearrangements of $R(+)$-2(2-Carboethoxy-1-phenyl)propyl Isocyanide ($R(+)$-VIII)[a]

Run	Reac. Solv.	Reac. Temp. (°C)		Reac. time (hr)	Formed $S(+)$-2(2-carboethoxy-1-phenyl)propyl cyanide ($S(+)$-X)				
		Temp. of Reac. Mix.	Bath Temp.		Crude[b] yield (%)	Isolated[c] yield (%)	bp (°C) (mmHg)	α_D (l=0.1, neat)[d] (t)	Reten. of[e] Confign. (%)
1	$(C_6H_5)_2O$	256[f]	280–285	3	92	77	126—127 (4)	+0.155 (18)	9
2	nujol	220—230	260—265	1.5	90	75	120—125 (3)	+0.033 (21)	2
3	—[g]	220—230	260—270	0.75[h]	90[i]	50	124—127 (4)	+0.033	2
4	—[g]	—[j]	205	22	70[i]	40	110—114 (2)	+0.006 (22)	0.3

a) All reactions were performed under a nitrogen atmosphere.
b) After purification with column chromatography.
c) After complete purification by fractional distillation.
d) Measured on a sample purified by fractional distillation.
e) $S(+)$-X showing α_D^{24} $+1.739°$ (l=0.1, neat) was assumed to be 100% optically pure.
f) Boiling point of diphenyl ether.
g) Carried out without solvent.
h) The reaction was followed by infrared (IR) spectra measurements.
i) This sample contained a trace amount of the starting isocyanide which was visible by IR spectrum.
j) not measured

Refluxing a diphenyl ether solution of $R(+)$-VIII (bath temperature 280—285°) under a nitrogen atmosphere for 3 hr, afforded $S(+)$-X, α_D^{18} $+0.155°$ (l=0.1, neat) in 92% yield as the sole reaction product. The degree of retention of configuration was determined as 9% by comparing the observed optical rotation of the reaction product with that of authentic $S(+)$-X. When the thermal reaction was conducted at 220—230° for 1.5 hr using nujol as the solvent, the $S(+)$-X obtained in 90% yield showed almost complete racemization. And, when the thermal rearrangement of $R(+)$-VIII was carried out at 220—230° for 0.75 hr, or at 205° (bath temperature) for 22 hr without solvent, almost completely racemized $S(+)$-X was obtained in 90 and 70% yields, respectively.

To determine where thermal rearrangement afforded the racemized compound, the following two experiments were done. When a diphenyl ether solution of $S(+)$-X, α_D^{25} $+1.613°$ (l=0.1, neat) was heated under reflux for 2.5 hr, to examine the thermal stability of $S(+)$-X under this reaction condition, no racemization was observed in the recovered starting material.

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13) S. Terashima, K.K. Lee, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 2533 (1969).
14) S. Akabori, T. Ikenaka, and K. Matsuki, *Nippon Kagaku Zasshi*, **73**, 112 (1952).
15) *Org. Syn.*, Coll. Vol. II, p. 278.
16) A.L. Wilds and A.L. Meader, Jr., *J. Org. Chem.*, **13**, 763 (1948).

Moreover, when rearrangement of *R*(+)-VIII was interrupted before completion of the reaction by heating *R*(+)-VIII at 210° (bath temperature) for 0.25 hr without solvent, rearranged *S*(+)-X was obtained with complete racemization, and unrearranged *R*(+)-VIII, which was isolated as methyl *R*-(−)-2-acetamido-2-methyl-3-phenylpropionate (*R*(−)-XIII), mp 81—82°, $[\alpha]_D^{16}$ −67.9° (chloroform), was 100% optically pure. Thus, it was evident that racemization had occurred during the thermal rearrangement of *R*(+)-VIII. In addition, since this thermal reaction proceeded rapidly in a non-polar solvent (*i.e.* nujol) and afforded almost racemized cyanide in a high yield, we assumed a radical mechanism for the rearrangement of *R*(+)-VIII, which differs from the mechanism for the rearrangements of *S*(+)-2-butyl isocyanide,[5c)] and *S*(−)-1-phenylethyl isocyanide.[5f)]

To confirm the existence of this novel mechanism, the thermal rearrangement of (±)-VIII in diphenyl ether was carried out in the presence of *p*-benzoquinone as a radical scavenger.[17)] Repeated purification of the reaction products by silica gel column chromatography gave a lactone (XIV) in 5% yield, with concomitant formation of the usual reaction product. The structure of the XIV, thus obtained, was confirmed from elemental analysis and its spectral data. Formation of XIV seems to clearly demonstrate the presence of the radical (XV) in the reaction medium.

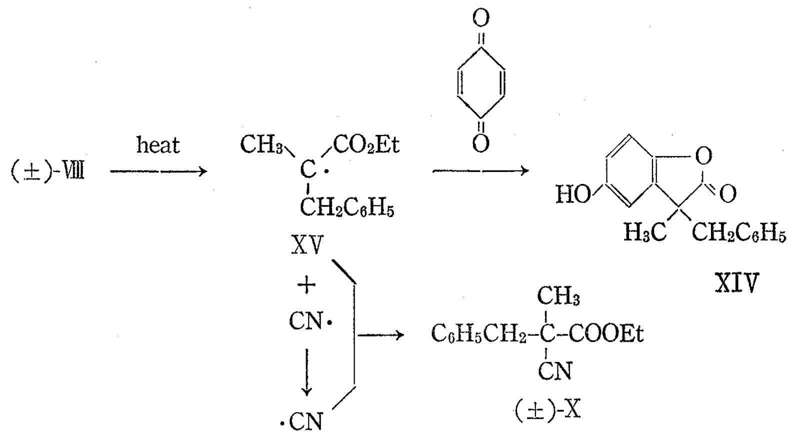

Chart 4

Next, to determine why *R*(+)-VIII afforded almost completely racemized *S*(+)-X through the reaction involving a homolytic fission of the C-N bond; *i.e.* to find out whether the radical-stabilizing effect of ester group or that of the quarternary carbon was responsible for the production of the radical intermediate (XV) from *R*(+)-VIII, the thermal rearrangement of *S*(+)-2-(2-methyl-1-phenyl)butyl isocyanide (*S*(+)-XVI), in which the ester group of *R*(+)-VIII was replaced by a simple alkyl group, was attempted.

Preparation of *S*(+)-XVI, α_D^{20} +1.240° (l=0.1, neat) (85.2% optically pure) was accomplished from (+)-2-(2-methyl-1-phenyl)butylamine ((+)-XVII), $\alpha_D^{21.5}$ +0.420° (l=0.1, neat) (85.2% optically pure), using a procedure similar to that for *R*(+)-VIII, by way of the (+)-N-formyl derivative ((+)-XVIII). The absolute configuration and optical purity of (+)-XVI were determined to be *S*-configuration and 85.2%, respectively by the conversion of (+)-XVII, α_D^{20} +0.362° (l=0.1, neat) to its N-benzoyl derivative ((+)-XIX), $[\alpha]_D^{20}$ +46.2° (chloroform), followed by comparison of its optical rotation with that of authentic *S*(+)-XIX, $[\alpha]_D^{20}$ +62.9° (chloroform), prepared from optically pure *R*(+)-3-benzamido-3-methyl-4-phenylbutan-2-one (*R*(+)-XX), $[\alpha]_D^{25}$ +151° (methanol),[12,18)] by way of its thioketal (*R*-XXI).

As described in detail in the experimental section, the racemic isocyanide ((+)-XVI) was synthesized from the racemic formamide ((±)-XVIII) prepared by the Ritter reaction[19)]

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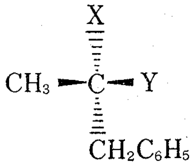
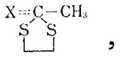
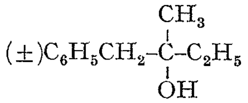
17) W.A. Pryer, "Free Radicals," McGraw-Hill, New York, 1966, p. 323.

18) S. Yamada and S. Terashima, *Chem. Pharm. Bull.* (Tokyo), 16, 1816 (1968).

19) H.D. Moed, J. Van Dijk, and H. Niewind, *Rec. Trav. Chim.*, 74, 919 (1955).



S(+)-XVI : X=Et, Y=N≡C
S(+)-XVII : X=Et, Y=NH_2
S(+)-XVIII : X=Et, Y=NHCHO
S(+)-XIX : X=Et, Y=$NHCOC_6H_5$
R(+)-XX : X=$COCH_3$, Y=$NHCOC_6H_5$
R-XXI :  , Y=$NHCOC_6H_5$
S(+)-XXIII : X=Et, Y=C≡N
S(+)-XXIV : X=$COCH_2Br$, Y=C≡N
S(+)-XXV : X=$COCH_3$, Y=C≡N



$$(\pm)C_6H_5CH_2\text{-}\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}\text{-}C_2H_5$$

(±)-XXII

Chart 5

of (±)-2-methyl-1-phenylbutan-2-ol ((±)-XXII), and the racemic amine ((±)-XVII) derived from (±)-XVIII was resolved using *d*-tartaric acid, to afford the *S*(+)-XVII described above.

Preparation of authentic *S*(+)-2-(2-methyl-1-phenyl)butyl cyanide (*S*(+)-XXIII) was also attempted before the thermal rearrangement of *S*(+)-XVI was made.

The acid chloride prepared from *S*(+)-XI, $[\alpha]_D^{25}$ +20.7° (chloroform) (83.4% optically pure)[13] was treated with diazomethane in ether, followed by treatment with aqueous hydrobromic acid, to afford the *S*(+)-bromoketone (*S*(+)-XXIV), $[\alpha]_D^{24}$ +48.5° (methanol), which was reduced with zinc-acetic acid to give *S*(+)-3-cyano-3-methyl-4-phenylbutan-2-one (*S*(+)-XXV), α_D^{22} +2.940° (l=0.1, neat). Reduction of *S*(+)-XXV with sodium borohydride, followed by tosylation, and reduction with sodium borohydride in dimethyl sulfoxide[20] furnished the synthesis of *S*(+)-XXIII. This *S*(+)-XXIII showed $[M]_{350}^{30}$ +38.8° (methanol),[21] and its optical purity was 83.4%.[22]

Table II. Thermal Rearrangements of (±)- and *S*(+)-2(2-Methyl-1-phenyl)butyl Isocyanide ((±)- and *S*(+)-XVI)[a]

Run	Starting isocyanide	Reac. Solv.	Reac. Temp. (°C)		Reac. time (hr)	Formed (±)- and *S*(+)-2(2-methyl-1-phenyl) butyl cyanide ((±)- and *S*(+)-XXIII)				
			Temp. of Reac. Mix.	Bath Temp.		Crude[b] yield (%)	Isolated[c] yield (%)	bp (°C) (mmHg)	$[M]_{350}$[d] (c, t, MeOH)	Reten. of[e] Confign. (%)
1	(±)-XVI	$(C_6H_5)_2O$	256[f]	280	3	90	81	100—102 (9.5)	—	—
2	*S*(+)XVI[g]	$(C_6H_5)_2O$	256[f]	280	3	86	69	100—102 (11)	+32.9° (1.770, 21)	90
3	(±)-XVI	—[h]	—[i]	260	6	80	63	115 (15)	—	—
4	*S*(+)-XVI[j]	—[h]	—[i]	260	6	75	43	121—122 (19)	+18.5° (1.490, 28)	47

a) All reactions were carried out under a nitrogen atmosphere.
b) After purification by silica gel column chromatography.
c) After completely purified by fractional distillation.
d) Determined with a distilled sample using optically rotatory dispersion measurement.
e) *S*(+)-XXIII showing $[M]_{350}^{30}$+38.8° (c=0.850, MeOH) was assumed to be 83.4% optically pure.
f) boiling point of diphenyl ether (bp 256° (760 mmHg))
g) *S*(+)-XVI showing α_D^{20}+1.149° (l=0.1, neat) (78.9% optically pure) was used.
h) Carried out without solvent.
i) not determined
j) *S*(+)-XVI showing α_D^{20}+1.240° (l=0.1, neat) (85.2% optically pure) was used.

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20) H.M. Bell, C.W. Vanderslice, and A. Speher, *J. Org. Chem.*, 34, 3923 (1969).
21) Determined by measuring the optically rotatory dispersion curve.
22) Since no racemization of the original asymmetric center of the *S*(+)-XI carrying cyano group was expected during conversion of *S*(+)-XI to *S*(+)-XXIII, and the asymmetric center produced by the reduction of *S*(+)-XXV was removed by the reduction after tosylation, the *S*(+)-XXIII obtained, was considered to have the same optical purity as *S*(+)-XI.

Thermal rearrangement was carried out under two different kinds of conditions as shown in Table II. Preliminary experimental results obtained with (±)-isocyanide ((±)-XVI) are also shown in this Table.

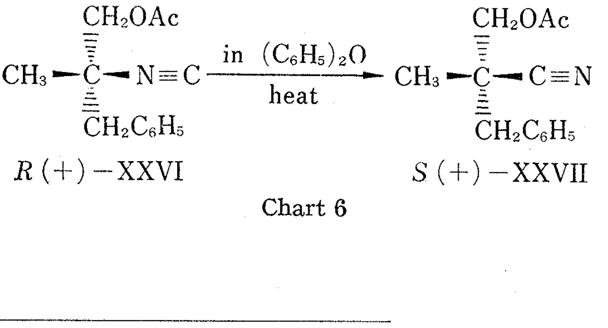
A diphenyl ether solution of *S*(+)-XVI (78.9% optically pure) was refluxed (bath temperature 280°) under a nitrogen atmosphere for 3 hr, to give *S*(+)-XXIII, $[M]^{21}_{350}$ +32.9° (methanol)[21] in 86% yield as the sole reaction product (Table II, run 2). The degree of retention of configuration was calculated as 90% by comparing its molecular rotation with that of authentic *S*(+)-XXIII, $[M]^{30}_{350}$ +38.8° (methanol)[21] (83.4% optically pure). However, when *S*(+)-XVI (85.2% optically pure) was heated at 260° (bath temperature) for 6 hr under a nitrogen atmosphere without solvent, *S*(+)-XXIII showing $[M]^{28}_{350}$ +18.5° (methanol)[21] was produced in 75% yield with 47% retention of configuration (Table II, run 4). Since no racemization of the starting *S*(+)-XVI was observed under the same reaction condition as that used in the thermal rearrangement, and since the thermal stability of *S*(+)-XXIII should undoubtedly be larger than that of *S*(+)-X, the observed racemization of *S*(+)-XXIII, *i.e.*, 10% and 53%, might be due to the intervention of a radical intermediate. Unfortunately it is not clear whether the enhanced retention of configuration achieved in the thermal reaction of *S*(+)-XVI, is due completely to an asymmetric radical intermediate or to the existence of a cyclic transition state, *i.e.* III. Considering the large difference in the retention of configuration between the rearrangement with diphenyl ether and that without solvent, it is conceivable that diphenyl ether played an important role in raising the degree of retention of configuration observed in *S*(+)-XXIII, *i.e.* diphenyl ether solvated asymmetrically at least part of the radical intermediate. The same improvements in the degree of retention of configuration were also observed in rearrangements of *S*(+)-VIII (Table I run 1 and 3), and *R*(+)-2-(2-phenyl)butyl isocyanide (*R*(+)-XXVIII) (Table III run 2 and 4).

At any rate, it was obvious that the reason why *R*(+)-VIII afforded almost completely racemized *S*(+)-X through the radical intermediate, was because the ester group at the asymmetric carbon probably stabilized the formed radical more effectively than did the simple alkyl group.

Thus, we conclude that the optically active tertiary isocyanide (IV) will afford the optically active tertiary cyanide (VI) with a high retention of configuration when IV, carrying no functional group which can stabilize the radical intermediate, is heated in a diphenyl ether solution. But it is still not clear whether the reaction proceeds exclusively through the radical intermediate or, in part, through a cyclic transition state (III).

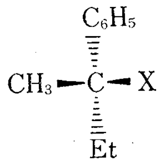
This conclusion was verified by the successful conversion of *R*(+)-2-(1-acetoxy-2-methyl-3-phenyl)propyl isocyanide (*R*(+)-XXVI) to *S*(+)-2(1-acetoxy-2-methyl-3-phenyl)propyl cyanide (*S*(+)-XXVII) with 75.6% retention of configuration.[23]

Finally, the thermal rearrangement of *R*(+)-XXVIII which was expected to produce a more stable radical at its benzylic position than did *R*(+)-VIII, was carried out. As anticipa-



R(+)-XXVI *S*(+)-XXVII

Chart 6



R(+)-XXVIII: X=N≡C
R(+)-XXIX : X=C≡N
R(−)-XXX : X=COOH
R(+)-XXXI : $X=NH_2$
R(+)-XXXII : X=NHCHO
R-XXXIII : $X=CONH_2$

Chart 7

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[23] M. Shibasaki, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 552 (1973).

ted, *R*(+)-XXVIII afforded a mixture of three kinds of olefins which had never before been observed in the thermal reactions of *R*(+)-VIII and *S*(+)-XVI, as well as the usual reaction product, *R*(+)-2-(2-phenyl)butyl cyanide (*R*(+)-XXIX) with a low retention of configuration.

Preparation of *R*(+)-XXVIII, α_D^{20} +0.090° (l=0.1, neat), (80.8% optically pure) was achieved from *R*(−)-2-methyl-2-phenylbutyric acid (*R*(−)-XXX), $[\alpha]_D^{15}$ −24.9° (benzene) (80.8% optically pure)[24,25] by way of *R*(+)-2-(2-phenyl)butylamine (*R*(+)-XXXI), $\alpha_D^{9.5}$ +1.235° (l=0.1, neat), and its N-formyl derivative (*R*(+)-XXXII), $[\alpha]_D^{20}$ +4.2° (benzene).

Authentic *R*(+)-XXIX, $[M]_{300}^{17}$ +47.7° (benzene)[21] (75.3% optically pure) was synthesized from *R*(−)-XXX, $[\alpha]_D^{15}$ −23.2° (benzene) (75.3% optically pure) *via* the *R*-amide (*R*-XXXIII).

Thermal rearrangements of *R*(+)-XXVIII were carried out with the two different kinds of conditions used on *S*(±)-XVI. Results are shown in Table III with preliminary experimental data obtained on (±)-XXVIII.

TABLE III. Thermal Rearrangements of (±)- and *R*(+)-2(2-Phenyl)butyl Isocyanide ((±)-and *R*(+)-XXVIII)[a]

Run	Starting isocyanide	Reac. Solv.	Reac. Temp. (°C)		Reac. time (hr)[b]	Formed (±)- and *R*(+)-2 (2-phenyl)butyl cyanide ((±)- and *R*(+)-XXIX)			Yields[c] (%) of formed olefins		
			Temp. of Reac. Mix.	Bath Temp.		Yield[c] (%) (isolated yield)[d]	$[M]_{300}$[e] (c, t, benzene)	Reten. of Confign. (%)[f]	XXXIV	XXXV	XXXVI
1	(±)-XXVIII	$(C_6H_5)_2O$	256[g]	280	3	19	—	—	—[h]	—[h]	—[h]
2	*R*(+)-XXVIII[i]	$(C_6H_5)_2O$	256[g]	280	3	21(20)	+9.5° (0.462, 20)	19	35	4	28
3	(±)-XXVIII	—[j]	—	260	5	52(51)	—	—	—[h]	—[h]	—[h]
4	*R*(+)-XXVIII[i]	—[j]	—	260	5	61(55)	0° (1.012, 19)	0	10	1	11

a) All reactions were carried out under a nitrogen atmosphere.
b) The reaction was monitored by IR spectra measurements of the reaction mixture.
c) Determined by quantitative gas chromatographic analysis on the reaction mixture.
d) After purified by silica gel column chromatography.
e) Determined by the measurement of optically rotatory dispersion curve using distilled *R*(+)-XXIX.
f) *R*(+)-XXIX showing $[M]_{300}^{17}$+47.7° (c=1.214, benzene) was assumed to be 100% optically pure.
g) Boiling point of diphenyl ether (bp 256° (760 mmHg)).
h) Determination of yield was not attempted.
i) *R*(+)-XXVIII showing α_D^{20}+0.090° (l=0.1, neat) (80.8% optically pure) was used.
j) Carried out without solvent.

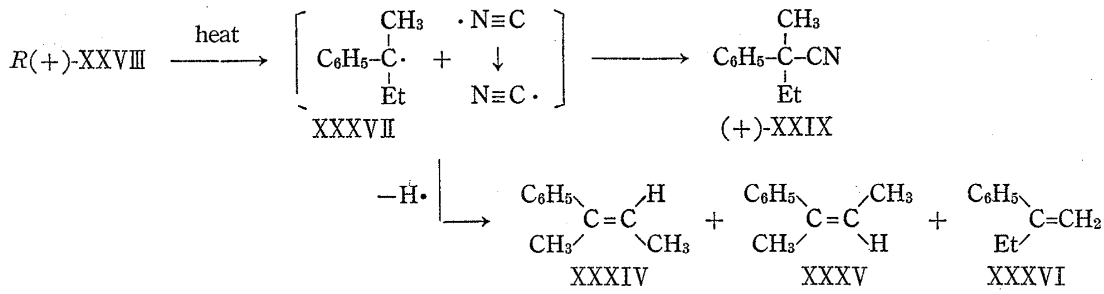

Chart 8

Refluxing a diphenyl ether solution of *R*(+)-XXVIII (bath temperature 280°) for 3 hr under a nitrogen atmosphere afforded *R*(+)-XXIX, $[M]_{300}^{20}$ +9.5° (benzene)[21] in a 21% yield,[26] and three kinds of olefins; *cis*-2-phenyl-2-butene (XXXIV), *trans*-2-phenyl-2-butene (XXXV), and 2-phenyl-1-butene (XXXVI) in 35, 4, and 28% yields.[26] The degree of retention of configuration for *R*(+)-XXIX was determined as 19% by comparison with independently

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[24] H. Mizuno, S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 1749 (1967).
[25] H. Mizuno, S. Terashima, and S. Yamada, unpublished results.
[26] Determined by quantitative gas chromatographic analysis (see experimental).

prepared authentic *R*(+)-XXIX. Of the three olefins, XXXIV, and XXXV were isolated from the reaction mixture obtained by the thermal reaction of (±)-XXVIII (Table III, run 1), using silica gel column chromatography. These were identified with authentic samples prepared by dehydration[27] of racemic 2-phenylbutan-2-ol with 4N sulfuric acid followed by the separation with a spinning band distillation. Since separation of XXXVI in the pure state was unsuccessful, identification of XXXVI with the authentic sample prepared by the above dehydration reaction was performed by comparing their retention time on gas chromatographic analysis. Heating *R*(+)-XXVIII without solvent for 5 hr at 260° (bath temperature), however gave completely racemized cyanide (XXIX), $[M]^{17}_{300}$ 0° (benzene)[21] in a 61% yield,[26] along with the three different olefins (XXXIV, XXXV, and XXXVI) in 10, 1, and 11% yields.[26]

A comparison of the two experimental results obtained in the reaction of *R*(+)-XXVIII clearly showed that a change in the reaction condition, from a refluxing in diphenyl ether to heating without solvent, increased the yield of the rearranged cyanide (XXIX) by sacrificing the degree of its retention of configuration and the net yield of the different olefins (XXXIV, XXXV, and XXXVI). However, the relative ratio of formed olefins was not seriously affected by the change in reaction condition.

Since the thermal stability of *R*(+)-XXVIII and *R*(+)-XXIX under the condition of thermal rearrangement was established in a manner similar to cases described before, it was evident that the observed racemization had occurred during the thermal reaction. Moreover, when tri-*n*-butyltin hydride was employed as a radical scavenger[28] for this reaction, gas chromatographic analysis showed that no formation of the olefinic reaction products occurred, and that *sec*-butylbenzene was exclusively prepared in 61% yield.[28] This observation indicates that the radical intermediate (XXXVII) produced by homolytic C-N bond fission, afforded almost completely or completely racemized cyanide (XXIX) by a coupling reaction and the three different olefins (XXXIV, XXXV, and XXXVI) by elimination of the hydrogen radical. Formation of olefins from *R*(+)-XXVIII might be due to the formation of a more highly stabilized radical intermediate (XXXVII) than those derived from *R*(+)-VIII and *S*(+)-XVI.

Although enhancement of the degree of retention of configuration was also observed when the reaction condition was changed, as with *R*(+)-VIII and *S*(+)-XVI, and is explanable as the result of asymmetric solvation by diphenyl ether, the dramatic change in the yields of the cyanide (XXIX) and olefins observed at the same time cannot be explained.

From results of the thermal rearrangement of *S*(−)-1-phenylethyl isocyanide, which gave *S*(+)-hydrotropanitrile with 56% retention of configuration by way of the cyclic transition state (III),[5f] the stabilizing effect of the quarternary carbon where the isocyanide group was present, should play an additional role in affording rearranged cyanides from *R*(+)-VIII, *S*(+)-XVII, and *R*(+)-XXVIII with various degrees of retention of configuration, by way of radical intermediates.

Experimental[29]

(±)-N-Formyl-α-methylphenylalanine Ethyl Ester ((+)-XII)——Acetic anhydride (4.0 g, 0.039 mole) was gradually added to a solution of (±)-IX[11] (2.0 g, 0.0097 mole) in 99% formic acid (15 ml). After being

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27) D.J. Cram, *J. Am. Chem. Soc.*, 71, 3883 (1949).

28) H.G. Kuivila, *Advan. Organometal. Chem.*, 1, 47 (1964).

29) All melting points and boiling points are uncorrected. Infrared (IR) spectra measurements were performed with spectrometers, Models DS-402 and IR-S, Japan Spectroscopic Co., Ltd. Nuclear magnetic resonance (NMR) spectra were determined with a spectrometer, Model 3H-60, Japan Electron Optics Lab. All signals are expressed by the ppm downfield from tetramethylsilane used as the internal standard. Ultraviolet (UV) spectra were measured using a Hitachi Recording Spectrometer, Model EPS-3T, Hitachi Co., Ltd. Optical activities were measured with Yanagimoto Photo Direct Reading Polarimeters, Models OR-20 and OR-50. Optical rotatory dispersion (ORD) curve measurements were carried out with a spectrometer Model ORD/UV-5, Japan Spectroscopic Co., Ltd. Gas chromatographic analyses were performed using Yanagimoto Gas Chromatographs, Models GCG-3D and 550T. Mass spectra were determined with a Hitachi RMU-6D instrument using a direct inlet system.

stirred at 50—60° for 2 hr, the whole was diluted with water (15 ml), then stirred at room temperature for an additional 2 hr. Evaporation *in vacuo*, followed by the addition of water (10 ml) and evaporation, gave a pale yellow oil (2.4 g). This was dissolved in ether (30 ml), then it was successively washed with 5% Na_2CO_3, satd. NaCl, 5% HCl, and satd. NaCl. After drying it over anhyd. sodium sulfate, filtration and evaporation *in vacuo* gave an oil (2.0 g), which was fractionally distilled to afford (±)-XII as a colorless oil (1.9 g, 81%), bp 172—174° (6.5 mmHg). *Anal.* Calcd. for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.23; H, 7.30; N, 5.96. IR ν_{max}^{neat} cm^{-1}: 3300 (NH), 1740 (ester), 1670, 1497 (amide). NMR (in CCl_4): 1.22 (3H, triplet, J=7.2 cps, $CH_2C\underline{H}_3$), 1.52 (3H, singlet, $C\underline{H}_3$), 3.25 (2H, quartet, J=13.5 cps, $C_6H_5C\underline{H}_2$), 4.10 (2H, quartet, J=7.2 cps, J=$C\underline{H}_2CH_3$), 7.10 (6H, singlet, $C_6\underline{H}_5$+N$\underline{H}$), 7.85 (1H, doublet, J=1.2 cps, C$\underline{H}$O).

***R*(+)-N-Formyl-α-methylphenylalanine Ethyl Ester (*R*(+)-XII)**——The same treatment of *R*(+)-IX[11] (α^{20}+1.226° (l=0.1, neat), 100% optically pure) (21.0 g, 0.110 mole) as that used for (±)-IX afforded *R*(+)-XII as a colorless oil (20.3 g, 86%), bp 161.5—163° (4 mmHg), $[\alpha]_D^{15}$ +35.8° (c=1.395, ethanol). Part of this oil was redistilled *in vacuo*, giving an analytical sample, bp 157° (5 mmHg), $[\alpha]_D^{21}$ +34.4° (c=1.452, ethanol). *Anal.* Calcd. for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.52; H, 7.11; N, 6.03. The IR spectrum of this oil measured in a neat state was identical with that of (±)-XII.

(±)-2-(2-Carboethoxy-1-phenyl)propyl Isocyanide ((±)-VIII)——Phosphorus oxychloride (1.53 g, 0.010 mole) was gradually added to a mixture of (±)-XII (3.82 g, 0.016 mole), chloroform (4.85 g, 0.041 mole), and pyridine (9.3 g, 0.12 mole) with stirring in an ice bath. The whole was stirred at room temperature for 24 hr, then it was diluted with ice-water (50 ml). After stirring this for 1.5 hr at room temperature, the lower chloroform layer was separated. The upper aqueous layer was further extracted with chloroform (20 ml×2), then the combined organic layers were washed with water and dried over anhyd. sodium sulfate. Filtration and evaporation *in vacuo* afforded a dark blue oil (2.8 g), which was purified with column chromatography using alumina (300 g, solvent: *n*-hexane–ethyl acetate 8: 1). Fractions containing the desired (±)-VIII were combined, and evaporated *in vacuo*, to give a pale yellow oil (2.3 g). This was submitted to fractional distillation and gave pure (±)-VIII as a colorless oil (1.78 g, 50%), bp 95—98.5° (0.08 mmHg). Part of this oil was re-distilled *in vacuo*, then underwent elemental analysis, bp 105° (0.10 mmHg). *Anal.* Calcd. for $C_{13}H_{15}O_2N$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.88; H, 7.04; N, 6.23. IR ν_{max}^{neat} cm^{-1}: 2145 (N≡C), 1750 (ester). NMR (in CCl_4): 1.17 (3H, triplet, J=7.2 cps, $CH_2C\underline{H}_3$), 1.56 (3H, singlet, $C\underline{H}_3$), 3.03 (2H, quartet, J=13.8 cps, $C_6H_5C\underline{H}_2$), 4.10 (2H, quartet, J=7.2 cps, $C\underline{H}_2CH_3$), 7.19 (5H, singlet, $C_6\underline{H}_5$).

***R*(+)-2-(2-Carboethoxy-1-phenyl)propyl Isocyanide (*R*(+)-VIII)**——Treatment of *R*(+)-XII ($[\alpha]_D^{20}$ +36.2° (c=1.182, ethanol)) (3.58 g, 0.015 mole) using a procedure similar to that used for (±)-XII afforded pure *R*(+)-VIII as a colorless oil (1.95 g, 59%), after purification with alumina column chromatography followed by fractional distillation, bp 106.5—107.5° (0.07 mmHg), α_D^{24} +1.069° (l=0.1, neat), $[\alpha]_D^{25}$ +14.8° (c=1.584, benzene). *Anal.* Calcd. for $C_{13}H_{15}O_2N$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.07; H, 7.06; N, 6.29. The IR spectrum of this oil was superimposable on that of (±)-VIII in the same state.

***S*(+)-2-Cyano-2-methyl-3-phenylpropionic Acid (*S*(+)-XI) and Its Ethyl Ester (*S*(+)-2-(2-Carboethoxy-1-phenyl)propyl Cyanide) (*S*(+)-X)**——Resolution of (±)-XI using the established procedure[13] was carried out with brucine, to afford optically pure *S*(+)-XI, mp 88—89°, $[\alpha]_D^{22}$ +24.8° (c=2.55, chloroform) (lit.[13] mp 87.5—89°, $[\alpha]_D^{18}$ +27.4 (c=2.56, chloroform); lit.[30] mp 87.5—88.5°, $[\alpha]_D^{25}$ +25.1° (c=2.43, chloroform) lit.[31] mp 88—89°, $[\alpha]_D^{18}$ +25.7° (c=2.4, chloroform). Treatment of the ether solution of *S*(+)-XI with diazoethane,[15,16] followed by the usual work-up, gave *S*(+)-X as a colorless oil in 63% yield; bp 147.4—149° (8 mmHg); α_D^{24} +1.739° (l=0.1, neat); $[\alpha]_D^{24}$ +18.7° (c=4.20, benzene). *Anal.* Calcd. for $C_{13}H_{15}O_2N$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.85; H, 7.01; N, 6.73. IR ν_{max}^{neat} cm^{-1}: 2236 (C≡N), 1745 (ester). Gas chromatographic analysis of this oil (30% SE-30 on Diasolid L, 2.25 m, 206°) showed a single peak whose retention time was 14.0 min.

Thermal Rearrangement of *R*(+)-2-(2-Carboethoxy-1-phenyl)propyl Isocyanide (*R*(+)-VIII)——Run 1: A diphenyl ether solution (20 ml) of *R*(+)-VIII (α_D^{24} +1.069° (l=0.1, neat), 100% optically pure) (2.00 g, 9.2 mmole) was gently refluxed (bath temperature 280—285°) under a nitrogen atmosphere for 3 hr. The reddish brown solution was poured onto a silica gel column after being cooled, and the diphenyl ether was thoroughly washed from the column with petr. ether. Subsequent elution with a mixture of *n*-hexane and ethyl acetate (8: 1) gave crude *S*(+)-X as a pale yellow oil (1.84 g, 92%) after evaporation of the elution solvent. Purification by fractional distillation gave pure *S*(+)-X as a colorless oil (1.55 g, 77%), bp 126—127° (4 mmHg), α_D^{18} +0.155° (l=0.1, neat). The IR spectrum of this oil measured in a neat state was identical with that of the authentic *S*(+)-X. The degree of retention of configuration was calculated as 9%, on the assumption that the *S*(+)-X showing α_D^{24} +1.739° (l=0.1, neat) was 100% optically pure. Gas chromatographic analysis of this oil (30% SE-30 on Diasolid L, 2.25 m, 206°) showed a single peak whose retention time was identical with that of the authentic *S*(+)-X.

Run 2: A mixture of *R*(+)-VIII (α_D^{24} +1.069° (l=0.1, neat), 100% optically pure) (2.00 g, 9.2 m mole) in anhyd. nujol (20 ml) was heated at 220—230° (bath temperature, 260—265°) under a nitrogen atmos-

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30) J. Kenyon and W.A. Ross, *J. Chem. Soc.*, **1951**, 3407.
31) D.J. Cram and P. Haberfield, *J. Am. Chem. Soc.*, **83**, 2363 (1961).

phere for 1.5 hr. After being cooled, the whole was worked up in a manner similar to that for run 1, to afford crude *S*(+)-X as a pale yellow oil (1.80 g, 90%). This was purified by fractional distillation to give pure *S*(+)-X as a colorless oil (1.50 g, 75%), bp 120—125° (3 mmHg), α_D^{21} +0.033° (l=0.1, neat). The IR spectrum of this oil was identical with that of authentic *S*(+)-X in the same state. From the assumption made for run 1, the degree of retention of configuration was calculated as 2%. Gas chromatographic analysis of this oil (run 1) showed a single peak whose retention time was identical with that of authentic *S*(+)-X.

Run 3: *R*(+)-VIII (α_D^{24} +1.069° (l=0.1, neat), 100% optically pure) (3.0 g, 0.014 mole) at 220—230° (bath temperature, 260—270°) was heated under a nitrogen atmosphere without solvent for 0.75 hr. The reaction was monitored by periodic measurements of the IR spectrum of the reaction mixture in a neat state. After absorption due to the isocyanide group disappeared, the whole was purified by silica gel column chromatography (65 g, solvent: *n*-hexane–ethyl acetate 8: 1), to give crude *S*(+)-X as a pale yellow oil (2.7 g, 90%). Distillation *in vacuo* gave a colorless oil bp 134—136° (4 mmHg) (2.4 g, 80%). Since the IR spectrum of this oil, measured in a neat state, showed the presence of a trace amount of starting material, the whole was dissolved in a mixture of 10% HCl and ethanol (1: 1) (15 ml), after which the aqueous mixture was refluxed for 0.5 hr. Extractive isolation of the neutral product with ether, followed by evaporation *in vacuo*, gave crude *S*(+)-X as a pale yellow oil (2.2 g, 73%). This was again purified by fractional distillation to give completely pure *S*(+)-X as a colorless oil (1.5 g, 50%), bp 124—127° (4 mmHg), α_D^{23} +0.033° (l=0.1, neat). The IR spectrum of this oil, measured in a neat state, was identical with that of authentic *S*(+)-X in the same state. Gas chromatographic analysis (run 1) showed that this oil was homogeneous. From the assumption made for run 1, the degree of retention of configuration was calculated as 2%.

Run 4: *R*(+)-Isocyanide (*R*(+)-VIII) (α_D^{24} +1.069° (l=0.1, neat), 100% optically pure) (3.0 g, 0.014 mole) was heated at 205° (bath temperature) under a nitrogen atmosphere for 22 hr. After the reaction was over, the whole was purified by silica gel column chromatography (200 g, solvent: *n*-hexane–ethyl acetate 6: 1), to give crude *S*(+)-X as a pale yellow oil (2.1 g, 70%). Since this oil also contained a trace amount of the starting isocyanide, it was treated as in run 3, to afford crude *S*(+)-X as a pale yellow oil (1.6 g, 53%) after evaporation of the ether extract. Purification with fractional distillation gave pure *S*(+)-X as a colorless oil (1.2 g, 40%), bp 110—114° (2 mmHg), α_D^{22} +0.006° (l=0.1, neat). The IR spectrum of this oil, measured in a neat state, was identical with that of authentic *S*(+)-X. Gas chromatographic analysis (see run 1) showed that this oil was pure. From the assumption made for run 1, the degree of retention of configuration was calculated as 0.3%.

Thermal Stability of Ethyl *S*(+)-2-Cyano-2-methyl-3-phenylpropionate (*S*(+)-X)——A diphenyl ether solution (31 ml) of *S*(+)-X (α_D^{25} +1.613° (l=0.1, neat)) (3.1 g, 0.014 mole) was refluxed for 2.5 hr (bath temperature *ca.* 280°), then it was worked up in a manner similar to that for the thermal rearrangement of *R*(+)-VIII (run 1). Isolated crude *S*(+)-X was purified by fractional distillation, giving pure *S*(+)-X as a colorless oil (2.3 g, 74%), bp 140—142 (6 mmHg), α_D^{23} +1.635° (l=0.1, neat), $[\alpha]_D^{23}$ +19.5° (c=4.23, benzene). The IR spectrum of this oil, measured in a neat state, was superimposable on that of authentic *S*(+)-X.

Interruption of the Thermal Rearrangement of *R*(+)-2-(2-Carboethoxy-1-phenyl)propyl Isocyanide (*R*(+)-VIII): Thermal Stability of *R*(+)-2-(2-Carboethoxy-1-phenyl)propyl Isocyanide (*R*(+)-VIII) and Isolation of the Starting *R*(+)-VIII as Methyl R(−)-2-Acetamido-2-methyl-3-phenylpropionate (*R*(−)-XIII)—— *R*(+)-Isocyanide (*R*(+)-VIII) (α_D^{24} +1.069° (l=0.1, neat), 100% optically pure) (3.0 g, 0.014 mole) was heated at 210° (bath temperature) under a nitrogen atmosphere for 0.25 hr.[32] The IR spectrum of the reaction mixture, measured in a neat state, showed this to be a mixture of the starting *R*(+)-VIII and the rearranged *S*(+)-X. IR ν_{max}^{neat} cm^{-1}: 2250, 2180. The whole was diluted with a mixture of 10% HCl and ethanol (1: 1) (30 ml), and was refluxed for 0.5 hr. The yellow oil obtained by evaporation of the acidic solution was dissolved in water (60 ml), and extracted with ether. Combined ethereal extracts were successively washed with dil. Na_2CO_3, and satd. NaCl, then were dried over anhyd. sodium sulfate. Filtration and evaporation *in vacuo* afforded crude *S*(+)-X as a yellow oil. This was purified by fractional distillation *in vacuo* to give pure *S*(+)-X as a colorless oil (0.67 g, 22%), bp 115—117° (3 mmHg), α_D^{22} +0.012° (l=0.1, neat). The degree of retention of configuration was determined as 0.7%, from the assumption that the *S*(+)-X showing α_D^{24} +1.739° (l=0.1, neat) was 100% optically pure. The IR spectrum of this oil was identical with that of authentic *S*(+)-X in the same state.

The aqueous acidic layer was evaporated *in vacuo*, affording a pale yellow oil (1.75 g). This was dissolved in a 1: 1 mixture of 47% HBr and water (17 ml), and the whole was refluxed for 3 hr. After being kept at room temperature overnight, the solution was evaporated *in vacuo* to give hygroscopic crystals. These were dissolved in water and passed through an ion exchange resin column (Amberlite-IR-120, H^+ form, 30 eq.). The column was washed with water, then free amino acid was eluted with dilute aqueous ammonia. Evaporation of the alkaline solution gave crude α-methylphenylalanine as a pale brown powder (1.3 g). This was acetylated with acetic anhydride-pyridine according to the reported procedure[12] to give crude N-acetyl-α-methylphenylalanine (1.54 g, 50% based on *R*(+)-VIII) as colorless crystals, mp 186—189°. IR ν_{max}^{KBr} cm^{-1}:

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[32] This reaction condition was selected because of the expected easy separation of the rearranged product and the starting isocyanide.

3320, 1720, 1630, 1560, 700. This IR spectrum was identical with that of authentic *R*(+)-acid.[12] Treatment of the crude acid with diazomethane in methanol, followed by the usual work-up and purification with silica gel column chromatography[8] gave *R*(−)-XIII as a colorless viscous oil (1.56 g, 47% based on *R*(+)-VIII), $[\alpha]_D^{16}$ −67.9° (c=1.70, chloroform), which immediately solidified on standing at room temperature, mp 81—82°. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1740 (ester), 1650, 1540 (amide). This IR spectrum was identical with that of authentic *R*(−)-XIII.[8] Since 100% optically pure *R*(−)-XIII has been reported to show mp 81—82°, $[\alpha]_D^{23.5}$ −60.1° (c=1.970, chloroform),[8] the *R*(−)-XIII obtained is considered to be 100% optically pure.

Thermal Rearrangement of (±)-2-(2-Carboethoxy-1-phenyl)propyl Isocyanide ((±)-VIII) in the Presence of *p*-Benzoquinone as a Radical Scavenger——A mixture of (±)-VIII (3.0 g, 0.014 mole) and *p*-benzoquinone (3.1 g, 0.028 mole) in diphenyl ether (20 ml) was refluxed (bath temperature 280—285°) under a nitrogen atmosphere for 2 hr, to give a black solution. After being cooled, the whole underwent column chromatography using silica gel (500 g, solvent: *n*-hexane–ethyl acetate 8 : 1). Diphenyl ether and a mixture of the isocyanide and the cyanide were washed from the column, then fractions containing the lactone (XIV) were eluted. After evaporation of the elution solvent, the crude XIV thus obtained was again purified by silica gel column chromatography (solvent: *n*-hexane–ethyl acetate 4 : 1), to afford almost pure XIV (0.18 g, 5% based on (±)-VIII) as crystals. Recrystallization from benzene, followed by filtration and washing with benzene, gave colorless prisms, mp 166.5—167° (sinter at 163°). Further recrystallization from benzene afforded an analytical sample as colorless prisms, mp 166.5—167°. *Anal.* Calcd. for $C_{16}H_{14}O_3$: C,75.71; H, 5.50. Found: C, 75.57; H, 5.55. IR ν_{max}^{KBr} cm^{-1}: 3410 (OH), 1770 (5-membered lactone), 1615 (aromatic ring). NMR (in CD_3OD): 1.55 (3H, singlet, $C\underline{H}_3$), 3.10 (2H, singlet, $C\underline{H}_3$), 4.83 (1H, singlet, $O\underline{H}$), 6.40—7.25 8H, multiplet, aromatic protons). UV $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε): 295 (3.38) (UV spectrum of *p*-hydroquinone:[33] UV λ_{max}^{EtOH} mμ (log ε): 294 mμ (3.5)). Mass Spectrum *m/e*: 254 (M$^+$), 163 (M-91 ($C_6H_5CH_2$)), 91 ($C_6H_5CH_2$).

***R*-3-Benzamido-3-methyl-4-phenylbutan-2-one Ethylene Thioketal (*R*-XXI)**——A mixture of *R*(+)-XX (mp 133—134°, $[\alpha]_D^{25}$ +151° (c=0.766, methanol), 100% optically pure)[18] (lit.[18] mp 132.5—133.5°, $[\alpha]_D^{12}$ +167° (c=0.444, methanol)) (1.56 g, 5.5 mmole) and 1,2-ethanedithiol (1.6 ml, 0.019 mole) in boron trifluoride etherate (1.6 ml) was stirred at 65—70° for 13 hr. The whole was diluted with 10% NaOH (16 ml), then with 5% NaOH (16 ml), after which it was extracted with benzene. Combined benzene extracts were successively washed with satd. NaCl, 5% HCl, and satd. NaCl, then were dried over anhyd. sodium sulfate. Filtration and evaporation *in vacuo* gave a yellow viscous oil (2.12 g), which was purified by column chromatography using silica gel (100 g, solvent: benzene). Fractions containing the desired *R*-XXI were combined, and evaporated *in vacuo* to afford almost pure *R*-XXI as a colorless oil (1.45 g, 74%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1660 (amide). The oil was immediately used in the next desulfurization without further purification.

***S*(+)-2-Benzamido-1-phenyl-2-methylbutane (*S*(+)-XIX)**——A mixture of *R*-XXI (1.45 g, 4.1 mmole) and Raney Ni for desulfurization[34,35] prepared from Ni-Al alloy (32 g) in anhyd. ethanol (150 ml) was refluxed with stirring for 5 hr. Filtration of the Ni catalyst, followed by a wash with ethanol and evaporation *in vacuo*, gave a semisolid (0.78 g), which was purified by silica gel column chromatography (100 g, solvent: methylene chloride), to give *S*(+)-XIX as a colorless solid (0.20 g, 18%), mp 98—101°. Several recrystallizations from isopropyl ether–*n*-hexane gave an analytical sample as colorless pillars, mp 100.5—102.5°, $[\alpha]_D^{20}$ +62.9° (c=0.916, chloroform). *Anal.* Calcd. for $C_{18}H_{21}ON$: C, 80.86; H, 7.92; N, 5.24. Found: C,80.90; H, 7.99; N, 5.22. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3442 (NH), 1667 (amide). NMR (in CCl_4): 0.88 (3H, triplet, J=7.0 cps, $-CH_2C\underline{H}_3$), 1.25 (3H, singlet, $C\underline{H}_3$), 1.35—2.3 (2H, multiplet, $-C\underline{H}_2CH_3$), 3.08 (2H, quartet, J=14 cps, $C_6H_5C\underline{H}_2$), 5.53 (1H, singlet, $-N\underline{H}$), 6.75—7.75 (10H, multiplet, $2C_6\underline{H}_5$).

(±)- and *S*(+)-2(2-Methyl-1-phenyl)butylamine ((±)- and *S*(+)-XVII)——(±)-Amine ((±)-XVII) was prepared by hydrolysis of the (±)-XVIII derived from (±)-XXII using the reported procedure.[19] The (±)-XVII obtained, showed bp 82—85° (3.5 mmHg) (lit.[19] bp 117—120° (14 mmHg)). IR ν_{max}^{neat} cm^{-1}: 3380, 1605.

Resolution of the (±)-XVII and determination of its absolute configuration and optical purity were achieved with the following experimental procedures.

d-Tartaric acid (45.0 g, 0.30 mole) was gradually added to a refluxing solution of (±)-XVII (45.0 g, 0.28 mole) in anhyd. ethanol (1125 ml). The hot ethanolic solution was kept at room temperature until precipitation of the colorless crystals ceased. Collection of the crystalls by filtration, followed by three repeated recrystallizations from anhyd. ethanol and decomposition of the salt with aqueous alkaline, as usual, gave crude *S*(+)-XVII as a pale yellow oil (5.0 g, 22%) after evaporation of the ethereal extract Fractional distillation *in vacuo* afforded pure *S*(+)-XVII as a colorless oil (4.6 g, 20%), bp 103° (7.5 mmHg), $\alpha_D^{21.5}$ +0.420° (l=0.1, neat). The IR spectrum of this oil, measured in a neat state, was identical with that of (±)-XVII.

Using the established procedure,[18] the *S*(+)-XVII (α_D^{20} +0.362° (l=0.1, neat)) obtained from another resolution lot, was treated with benzoyl chloride-pyridine. The usual work up, followed by chromatographic

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33) R.A. Morton and A.L. Stubbs, *J. Chem. Soc.*, **1940**, 1347.

34) R. Mozingo, D.E. Wolf, S.A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

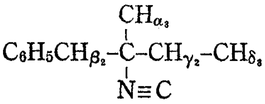
35) S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 572 (1966).

purification using silica gel gave pure S(+)-XIX as a colorless solid after evaporation of the elution solvent, mp 90—93° $[\alpha]_D^{20}$ +46.2° (c=0.368, chloroform). The IR spectrum of this solid, measured in a chloroform solution, was identical with that of authentic S(+)-XIX. Since the optical purity of this solid was calculated as 73.4%, from the assumption that the S(+)-XIX showing $[\alpha]_D^{20}$ +62.9° (c=0.916, chloroform) was 100% optically pure, the S(+)-XVII showing $\alpha_D^{21.5}$ +0.420° (l=0.1, neat) was determined to be 85.2% optically pure. The absolute configuration of S(+)-XVII was clearly established from the above experiment.

(±)-2-Formamido-2-methyl-1-phenylbutane ((±)-XVIII)——This was prepared from (±)-XXII using the Ritter reaction according to the reported procedure.[19] The oily (±)-XVIII obtained in 72% yield, showed bp 163—165° (4 mmHg) (lit.[19] bp 160—180° (5 mmHg)). IR ν_{max}^{neat} cm^{-1}: 3480 (NH), 1680 (amide).

***S*(+)-2-Formamide-2-methyl-1-phenylbutane (*S*(+)-XVIII)**——Treatment of S(+)-XVII (4.1 g, 0.025 mole) ($\alpha_D^{21.5}$ +0.420° (l=0.1, neat), 85.2% optically pure) with acetic and formic mixed anhydride similar to the procedure for (±)-IX or that reported,[5f] gave crude S(+)-XVIII as a pale yellow oil (4.5 g, 94%) after extractive isolation with benzene followed by evaporation. Fractional distillation *in vacuo* afforded pure S(+)-XVIII as a colorless oil (4.25 g, 89%), bp 163° (3.5 mmHg), $[\alpha]_D^{25}$ +34.9° (c=0.734, chloroform). The IR spectrum of this oil, measured in a neat state, was identical with that of (±)-XVIII. This oil was immediately used for the next dehydration.

(±)-2-(2-Methyl-1-phenyl)butyl Isocyanide ((±)-XVI)——Using the same treatment for (±)-XVIII (13.7 g, 0.071 mole) as for (±)-XII have crude (±)-XVI as a pale yellow oil (10.5 g, 85%) after chromatographic purification using alumina. Fractional distillation *in vacuo* afforded pure (±)-XVI as a colorless oil (9.9 g, 80%), bp 107—108° (2 mmHg). *Anal.* Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 83.09; H, 8.74; N, 8.34. IR ν_{max}^{neat} cm^{-1}: 2140 (N≡C). NMR (in CCl_4): 1.04 (3H, triplet, $J_{\gamma\delta}$=7.0 cps, $CH_2C\underline{H}_3$), 1.23 (3H, triplet, $J_{\alpha N}$=2 cps, $C\underline{H}_3$), 1.28—1.78 (2H, triplet × quartet, $J_{\gamma N}$=2 cps, $J_{\gamma\delta}$=7.0 cps, $C\underline{H}_2CH_3$), 2.78 (2H, triplet × quartet, $J_{\beta N}$=2 cps, $J_{\beta\beta}$=12 cps), 7.17 (5H, singlet, $C_6\underline{H}_5$).[36]



$$\begin{array}{c} \quad CH_{\alpha_3} \\ \quad | \\ C_6H_5CH_{\beta_2}\text{–}C\text{–}CH_{\gamma_2}\text{–}CH_{\delta_3} \\ \quad | \\ \quad N\equiv C \end{array}$$

***S*(+)-2-(2-Methyl-1-phenyl)butyl Isocyanide (*S*(+)-XVI)**——Treatment of S(+)-XVIII ($[\alpha]_D^{25}$ +34.9° (c=0.734, chloroform)) (4.15 g, 0.022 mole) similar to that for (±)-XVI gave S(+)-XVI (2.99 g, 78%) as a colorless oil, bp 127—128° (5 mmHg), α_D^{20} +1.240° (l=0.1, neat). *Anal.* Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 83.19; H, 8.81; N, 7.95. IR and NMR spectra of this oil were identical with those of (±)-XVI.

(±)-3-Cyano-3-methyl-4-phenylbutan-2-one ((±)-XXV)——An ethereal solution (50 ml) of (±)-acid chloride (5.01 g, 0.023 mole), bp 127—129° (1.5 mmHg) prepared from (±)-XI[13] (4.4 g, 0.023 mole) (mp 93—94°) (lit.[13] mp 94—95°) using the established procedure,[13] was gradually added at −5° to a solution of diazomethane in ether (160 ml) prepared from 5 eq. amounts of nitrosomethyl urea. After being stirred at the above temperature for 1 hr, the whole was diluted with 47% HBr (22 ml), then it was stirred for an additional 3 hr. The upper ethereal layer was separated, and the lower aqueous phase was further extracted with ether. Ethereal layers were combined and washed with satd. NaCl, then were dried over anhyd. sodium sulfate. Filtration and evaporation *in vacuo* gave crude (±)-XXIV as a yellow oil (6.59 g, quantitative yield). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (C≡N), 1750 (ketone).

Zinc powder (6.59 g, *ca.* 0.1 g atom) was gradually added at room temperature to a stirred solution of (±)-XXIV (6.59 g, 0.023 mole) in acetic acid (88 ml). After stirring this solution at room temperature for 1 hr, filtration of the solid, followed by evaporation of the acetic acid filtrate *in vacuo*, gave an oily residue. This was dissolved in ether (100 ml), and washed with water. After being dried over anhyd. sodium sulfate, filtration and evaporation *in vacuo* of this solution afforded crude (±)-XXV as a pale yellow oil (3.5 g, 81%). Distillation of this oil *in vacuo* gave pure (±)-XXV as an almost colorless oil (3.3 g, 77%), bp 127—137° (3 mmHg). IR ν_{max}^{neat} cm^{-1}: 2200 (C≡N), 1730 (ketone). NMR (in CCl_4): 1.42 (3H, singlet, $C\underline{H}_3$), 2.18 (3H, singlet, $COC\underline{H}_3$), 2.95 (2H, quartet, J=12 cps, $C_6H_5C\underline{H}_2$), 7.22 (5H, singlet, $C_6\underline{H}_5$). This oil was immediately used for the next step.

***S*(+)-3-Cyano-3-methyl-4-phenylbutan-2-one (*S*(+)-XXV)**——The same treatment of S(+)-XI ($[\alpha]_D^{25}$ +20.7° (c=2.230, chloroform), 83.4% optically pure)[13] (4.0 g, 0.021 mole) as used for (±)-XI gave crude S(+)-XXIV as a colorless solid (4.5 g, 80%), mp 88—90°, $[\alpha]_D^{24}$ +48.5° (c=1.036, methanol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN), 1750 (ketone). This IR spectrum was identical with that of (±)-XXIV.

Treatment of the S(+)-XXIV (4.4 g, 0.016 mole) obtained, similar to that for (±)-XXIV, gave pure S(+)-XXV as a colorless oil (2.6 g, 87%), bp 143.5—145.5° (11 mmHg), α_D^{22} +2.940° (l=0.1, neat) after purification by distillation. *Anal.* Calcd. for $C_{12}H_{13}ON$: C, 76.97; H, 7.00; N, 7.48. Found: C, 77.02; H, 7.08; N, 7.52. IR and NMR spectra of this oil were identical with those for (±)-XXV. This oil was immediately used for the next step.

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36) Similar nitrogen-proton couplings were observed for many kinds of aliphatic isocyanides in reference 5*c*.

(±)-2-(2-Methyl-1-phenyl)butyl Cyanide ((±)-XXIII)——Sodium borohydride (0.46 g, 0.012 mole) was gradually added to a stirred solution of (±)-XXV (1.45 g, 7.7 mmole) in anhyd. ethanol (230 ml). After stirring the whole at room temperature for 3 hr, the ethanol was evaporated *in vacuo* to give a residue, which was diluted with 10% HCl, then extracted with ether. Ethereal extracts were combined and washed with satd. NaCl, then were dried over anhyd. sodium sulfate. Filtration and evaporation *in vacuo* gave a crude diastereoisometric mixture of (±)-2-cyano-3-hydroxy-3-methyl-4-phenylbutane as a yellow oil (1.52 g, quantitative yield). Purification by filtration through a short silica gel column (25 g, solvent: benzene–ethyl acetate 3: 1) gave pure (±)-alcohol as a yellow oil (1.50 g, 100%). TLC analysis (silica gel, solvent: benzene–ethyl acetate 3: 1) of this oil showed a single spot whose *Rf* value was 0.6. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 3400, 1100 (OH). NMR (in CCl_4): 1.08, 1.17 (3H, 2 singlets, $C\underline{H}_3$), 1.25 (3H, doublet, $J=6$ cps, $CHC\underline{H}_3$), 2.35—3.20 (2H, multiplet, $C_6H_5C\underline{H}_2$), 3.20—3.95 (2H, multiplet, $C\underline{H}O\underline{H}$), 7.10 (5H, singlet, $C_6\underline{H}_5$).

A mixture of the (±)-alcohol obtained above (0.38 g, 2 mmole) and tosyl chloride (0.49 g, 2.6 mmole) in anhydrous pyridine (3.8 ml) was stirred at 50° for 72 hr. The whole was poured onto an ice-water, then was extracted with ether. Ethereal extracts were combined and successively washed with water, 10% HCl, water, 10% NaOH and water, after which they were dried over anhyd. sodium sulfate. Filtration and evaporation *in vacuo* gave crude (±)-tosylate as an almost colorless oil (0.59 g, 86%), which solidified on standing. Recrystallization from a mixture of benzene–*n*-hexane gave a pure sample as colorless crystals (0.49 g, 72%), mp 107—109°. TLC analysis (silica gel, solvent: benzene) of the crystals showed a single spot whose *Rf* value was 0.8. NMR (in $CDCl_3$): 1.13, 1.20 (3H, 2 singlets, $C\underline{H}_3$), 1.43 (3H, doublet, $J=6$ cps, $CH\text{–}C\underline{H}_3$), 2.40 (3H, singlet, $C_6H_4C\underline{H}_3$), 2.72 (2H, multiplet, $C_6H_5C\underline{H}_2$), 4.74 (1H, quartet, $J=6$ cps, $C\underline{H}CH_3$), 6.96—7.76 (9H, multiplet, aromatic protons).

Sodium borohydride (2.9 g, 0.076 mole) was gradually added to a dimethyl sulfoxide solution (43 ml) of (±)-tosylate (0.72 g, 2.1 mmole).[20] After stirring it at 100° for 25 hr, the whole was diluted with 10% HCl, then was extracted with benzene. The combined organic layers were washed with water, then dried over anhyd. sodium sulfate. Filtration and evaporation *in vacuo* gave a pale yellow oil (0.28 g), Purification by silica gel column chromatography (20 g, solvent: benzene–*n*-hexane 10: 1), followed by fractional distillation *in vacuo*, gave pure (±)-XXIII as a colorless oil (0.19 g, 53%), bp 130—131° (16—17 mmHg). *Anal.* Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 82.44; H, 8.49; N, 8.25. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2240 (C≡N). NMR (in CCl_4): 1.08 (3H, triplet, $J=7$ cps, $CH_2C\underline{H}_3$), 1.12 (3H, singlet, $C\text{–}C\underline{H}_3$), 1.26—1.76 (2H, multiplet, $\text{–}C\underline{H}_2\text{–}CH_3$), 2.72 (2H, quartet, $J=13$ cps, $C_6H_5C\underline{H}_2$), 7.10 (5H, singlet, $C_6\underline{H}_5$).

***S*(+)-2-(2-Methyl-1-phenyl)butyl Cyanide (*S*(+)-XXIII)**——Reduction of *S*(+)-XXV (α_D^{22} +2.940° ($l=0.1$, neat)) (83.4%, optically pure) (2.0 g, 0.011 mole) with sodium borohydride in anhyd. ethanol, the same as that used for (±)-XXV, followed by the usual work-up, gave a crude diastereoisomeric mixture of *R*(+)-2-cyano-3-hydroxy-2-methyl-1-phenylbutane as a pale yellow oil (2.1 g, quantitative yield), α_D^{22} +3.475° ($l=0.1$, neat). IR and NMR spectra of this oil were identical with those of the racemic alcohol.

Tosylation of the *R*(+)-alcohol (1.43 g, 7.6 mmole) obtained was achieved with a treatment similar to that described for the racemic alcohol, to afford a diastereomeric mixture of *R*(+)-tosylate as colorless crystals (2.11 g, 81%), mp 103—106°, $[\alpha]_D^{28}$ +9.6° ($c=0.686$, methanol), after extractive isolation followed by chromatographic purification. The NMR spectrum of the *R*(+)-tosylate was identical with that of the racemic tosylate.

Treatment of the *R*(+)-tosylate (2.0 g, 5.8 mmole) similar to that for the racemic tosylate gave crude *S*(+)-XXIII as a colorless oil (0.40 g, 40%), after extractive isolation and chromatography. Fractional distillation *in vacuo* gave an analytical sample as a colorless oil (0.16 g, 16%), bp 120—121° (14 mmHg), $[M]^{30}$ ($c=0.850$, methanol) (mμ): +20.4° (400), +38.8° (350), +59.0° (300). *Anal.* Calcd. for $C_{11}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 82.94; H, 8.68; N, 8.11. IR and NMR spectra of this oil were identical with those of (±)-XXIII. The optical purity of this *S*(+)-XXIII was considered to be 83.4%, since racemization and separation of the diastereoisomer could not be expected in the experimental procedure used.

Thermal Rearrangement of (±)- and *S*(+)-2-(2-Methyl-1-phenyl)butyl Isocyanide ((±)- and *S*(+)-XVI)—Run 1: A mixture of (±)-XVI (1.50 g, 8.7 mmole) in diphenyl ether (15 ml) was refluxed (bath temperature 280°) under a nitrogen atmosphere for 3 hr. After being cooled, the whole was directly purified with silica gel chromatography (150 g). Diphenyl ether was first eluted from the column with petr. ether, then an elution with a mixture of petr. ether and ethyl acetate (10 :1) afforded crude (±)-XXIII as a pale yellow oil (1.35 g, 90%). Purification by fractional distillation gave pure (±)-XXIII as a colorless oil (1.21 g. 81%), bp 100—102° (9.5 mmHg). The IR spectrum of this oil, measured in a neat state, was identical with that of authentic (±)-XXIII. Gas chromatographic analysis (15% SE-30 on Diasolid L, 2.25 m, 130°) of this oil showed a single peak whose retention time (17.8 min) was identical with that of authentic (±)-XXIII.

Run 2: Treatment of a diphenyl ether solution (3.6 ml) of *S*(+)-XVI (α_D^{20} +1.149° ($l=0.1$, neat), 78.9% optically pure[37]) (0.36 g, 2.1 mmole) similar to the procedure for run 1 afforded crude *S*(+)-XXIII as a pale yellow oil (0.31 g, 86%) after chromatographic purification. Further purification by fractional distillation *in vacuo* gave pure *S*(+)-XXIII as a colorless oil (0.25 g, 69%), bp 100—102° (11 mmHg), $[M]^{21}$ ($c=1.770$,

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[37] *S*(+)-XVI showing α_D^{20} +1.240° ($l=0.1$, neat) was assumed to be 85.2% optically pure.

methanol) (mμ): +17.3° (400), +32.9° (350), +50.2° (300). The IR spectrum of this oil was identical with that of authentic *S*(+)-XXIII. Gas chromatographic analysis (run 1) of this oil showed a single peak whose retention time was identical with that of authentic *S*(+)-XXIII. Since the optical purity of *S*(+)-XXIII showing $[M]^{30}_{350}$ +38.8° (c=0.850, methanol) was 83.4%, the *S*(+)-XXIII produced by the thermal reaction was 70.7% optically pure, *i.e.* the degree of retention of configuration was calculated as 90%.

Run 3: Heating (±)-XVI (1.50 g, 8.7 mmole) at 260° (bath temperature) under a nitrogen atmosphere for 6 hr clearly showed the complete disappearance of the starting (±)-XVI on IR spectrum measurement. IR $\nu^{\text{neat}}_{\text{max}}$ cm^{-1}: 2240 (C≡N). Quantitative analysis of the reaction mixture with gas chromatography (15% SE-30 on Diasolid L, 2.25 m, 130°, internal standard: naphthalene, retention time 6.8 min) showed that (±)-XXIII was prepared as the sole reaction product (retention time 17.8 min) in 84% yield. Purification of the reaction mixture using silica gel column chromatography (50 g, solvent: petr. ether–ethyl acetate 10: 1) gave the crude (±)-cyanide as a colorless oil (1.20 g, 80%). Distillation *in vacuo* gave pure (±)-XXIII as a colorless oil (0.95 g, 63%), bp 115° (15 mmHg). The IR spectrum of this oil was identical with that of authentic (±)-XXIII.

Run 4: Treatment of *S*(+)-XVI (α^{20}_{D} +1.240° (l=0.1, neat), 85.2% optically pure) (0.60 g, 3.5 mmole) as in run 3 gave *S*(+)-XXIII in 81% yield, based on quantitative gas chromatographic analysis of the reaction mixture under the same condition. Purification of the reaction mixture using silica gel column chromatography gave crude *S*(+)-XXIII as a colorless oil (0.45 g, 75%). This was further purified by fractional distillation to afford pure *S*(+)-XXIII as a colorless oil (0.26 g, 43%), bp 121—122° (19 mmHg), $[M]^{28}$ (c=1.490, methanol) (mμ): +13.4° (400), +18.5° (350), +29.9° (300). The IR spectrum of this oil measured in a neat state was superimposable on that of authentic *S*(+)-XXIII. Gas chromatographic analysis (run 1) of this oil showed a single peak whose retention time was identical with that of authentic *S*(+)-XXIII. Since the optical purity of this oil was calculated as 39.8%, the degree of retention of configuration in this reaction was 47%.

Thermal Stability of *S*(+)-2-(2-Methyl-1-phenyl)butyl Isocyanide (*S*(+)-XVI)——*S*(+)-Isocyanide(*S*(+)-XVI) (α^{26}_{D} +1.240°(l=0.1, neat)) (85.2% optically pure) (1.20 g, 7.0 mmole) was heated at 260° (bath temperature) under a nitrogen atmosphere for 0.13 hr. The whole was diluted with a mixture of 10% HCl and ethanol (1: 1)(12 ml), then the aqueous solution was refluxed for 0.5 hr. After the ethanol was removed *in vacuo*, the whole was extracted with ether (×3) to remove the neutral product. The acidic aqueous phase was cooled in an ice bath, then was made alkaline (pH>10) with 10% NaOH. The oil which separated was extracted with ether. Ethereal layers were combined and washed with satd. NaCl, then were dried over anhyd. potassium carbonate. Filtration and evaporation *in vacuo* gave crude *S*(+)-XVII as a pale yellow oil (0.25 g, 22%). Purification by fractional distillation *in vacuo* gave pure *S*(+)-XVII as a colorless oil (0.18 g, 16%), bp 138° (18 mmHg), α^{20}_{D} +0.420° (l=0.1, neat). The IR spectrum of this oil in a neat state was identical with that of authentic *S*(+)-XVII, $\alpha^{21.5}_{\text{D}}$ +0.420° (l=0.1, neat). This clearly shows that no racemization of *S*(+)-XVI occurred during thermal reaction.

(±)- and *R*(+)-2-(2-Phenyl)butylamine ((±)- and *R*(+)-XXXI)——These compounds were synthesized from (±)- and *R*(+)-XXX according to the reported procedures.[24,25]

(±)-Amine ((±)-XXXI) isolated as its hydrochloride, mp 227—231.5° (lit.[24] mp 237.5—238°), was identified with authentic (±)-XXXI-hydrochloride[24] by a comparison of their IR spectra. IR $\nu^{\text{KBr}}_{\text{max}}$ cm^{-1}: *ca.* 2900 (broad), 1615, 1515 ($\overset{+}{\text{N}}\text{H}_3$), 780, 760, 695 (mono-substituted benzene). Its hydrochloride obtained was converted to its free base by the usual treatment, bp 98—102° (24.5 mmHg) IR $\nu^{\text{neat}}_{\text{max}}$ cm^{-1}: 3250, 1590 (NH_2), 755, 690 (mono-substituted benzene) and was directly used in the next step.

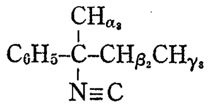
R(+)-Amine (*R*(+)-XXXI) was isolated as its free base, and showed bp 122.5—129.5° (63 mmHg), and $\alpha^{9.5}_{\text{D}}$ +1.235° (l=0.1, neat) (lit.[24] bp 95—96° (10.5 mmHg), $\alpha^{9.5}_{\text{D}}$ +1.516° (l=0.1, neat)). The optical purity of the *R*(+)-XXXI prepared was assumed to be 80.8% since *R*(−)-XXX showing $[\alpha]^{15}_{\text{D}}$ −24.9° (c=1.050, benzene) was used to prepare *R*(+)-XXXI and the optical purity of this *R*(+)-XXX was calculated as 80.8%, from the assumption that the *R*(−)-XXX showing the highest reported optical rotation, $[\alpha]^{14}_{\text{D}}$ −30.8° (c=1.140, benzene),[25] was 100% optically pure.

(±)-2-Formamido-2-phenylbutane ((±)-XXXII)——Treatment of (±)-XXXI (14.2 g, 0.095 mole) with acetic and formic mixed anhydride by a procedure similar to that for (±)-IX, gave crude (±)-XXXII as a pale yellow oil (16.4 g, 98%) after evaporation of the benzene extract. Fractional distillation *in vacuo* afforded pure (±)-XXXII as a colorless oil (15.2 g, 91%), bp 171—172° (0.5 mmHg). This oil solidified on standing at room temperature and showed mp 49.5—52.5°. Recrystallization with ether gave an analytical sample as colorless prisms, mp 51.5—54.5°. *Anal.* Calcd. for $C_{11}H_{15}ON$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.67; H, 8.50; N, 8.13. IR $\nu^{\text{CHCl}_3}_{\text{max}}$ cm^{-1}: 1673 (amide). NMR (in $CDCl_3$): 0.71, 0.80 (3H, 2 triplets, J=7.5 and 7.5 cps, $\text{CH}_2\text{C}\underline{\text{H}}_3$), 1.62, 1.65 (3H, 2 singlets, $\text{C}\underline{\text{H}}_3$), 1.89, 1.92 (2H, 2 quartets, J=7.5 and 7.5 cps, $\text{C}\underline{\text{H}}_2\text{CH}_3$), 7.25 (5H, singlet, $\text{C}_6\underline{\text{H}}_5$), 7.90 (2H, multiplet, $-\text{N}\underline{\text{H}}\text{C}\underline{\text{H}}\text{O}$).

***R*(+)-2-Formamido-2-phenylbutane (*R*(+)-XXXII)**——Treatment of *R*(+)-XXXI ($\alpha^{9.5}_{\text{D}}$ +1.235° (l=0.1, neat), 80.8% optically pure) (21.0 g, 0.14 mole) with the same procedure as that used with (±)-XXXI gave crude *R*(+)-XXXII as a pale yellow oil (24.0 g, 96%), after evaporation of the benzene extracts. Purification by fractional distillation afforded pure *R*(+)-XXXII as a colorless oil (22.0 g, 88%), bp 179.5—

180° (9 mmHg), $[\alpha]_D^{20}$ +4.2° (c=1.100, benzene). *Anal.* Calcd. for $C_{11}H_{15}ON$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.27; H, 8.68; N, 7.86. IR and NMR spectra of this oil were identical with those of the racemic compound.

(±)-2-(2-Phenyl)butyl Isocyanide ((±)-XXVIII)——Using the same treatment for (±)-XXXII (5.2 g, 0.029 mole) as that used for (±)-XII gave crude (±)-XXVIII as a pale yellow oil (2.5 g, 54%) after chromatographic purification with alumina. Fractional distillation *in vacuo* afforded pure (±)-XXVIII as an almost colorless oil (2.0 g, 45%), bp 91—93° (11 mmHg). *Anal.* Calcd. for $C_{11}H_{13}N$: C, 82.97; H, 8.02; N, 8.80. Found: C, 82.81; H, 8.12; N, 9.12. IR ν_{max}^{neat} cm^{-1}: 2140 (N≡C). NMR (in $CDCl_3$): 0.88 (3H, triplet, $J_{\beta\gamma}$= 7.5 cps, CH_2CH_3), 1.72 (3H, triplet, $J_{\alpha N}$=2 cps, $C\underline{H}_3$), 1.80 (2H, trebled quartet, $J_{\beta\gamma}$=7.5 cps, $J_{\beta N}$=2 cps, $C\underline{H}_2CH_3$), 7.31 (5H, singlet, $C_6\underline{H}_5$).[36]



$$C_6H_5-\underset{\displaystyle N\equiv C}{\overset{\displaystyle CH_{\alpha_3}}{\underset{|}{\overset{|}{C}}}}-CH_{\beta_2}CH_{\gamma_3}$$

***R*(+)-2-(2-Phenyl)butyl Isocyanide (*R*(+)-XXVIII)**——Using the same treatment for *R*(+)-XXXII ($[\alpha]_D^{20}$ +4.2° (c=1.100, benzene) 80.8% optically pure) (21.96 g, 0.12 mole) as that used for (±)-XXXII afforded pure *R*(+)-XXVIII as a colorless oil (17.7 g, 90%), bp 71.5—79.5° (4 mmHg), after chromatographic purification with alumina, followed by fractional distillation. This oil showed α_D^{20} +0.090° (l=0.1, neat). *Anal.* Calcd. for $C_{11}H_{13}N$: C, 82.97; H, 8.02; N, 8.80. Found: C, 82.68; H, 8.35; N, 8.52. IR and NMR spectra of this oil were superimposable on those of (±)-XXVIII.

(+)-2-(2-Phenyl)butyl Cyanide ((±)-XXIX)——An ethereal solution of (±)-acid chloride (5.3 g, 0.027 mole) prepared from (±)-XXX[24] (5.0 g, 0.028 mole) according to the established method, was gradually added to vigorously stirred aqueous ammonia (*ca.* 28%, 140 ml) in an ice-salt bath. After the whole had been stirred for 2 hr in an ice bath, the upper ethereal layer was separated. The lower aqueous phase was twice extracted with ether. The combined ethereal layers were successively washed with satd. $NaHCO_3$, satd. NaCl, 10% acetic acid, and satd. NaCl. After drying over anhyd. sodium sulfate, filtration and evaporation *in vacuo* gave the crude amide ((±)-XXXIII) as a pale yellow solid (3.6 g, 72%), mp 76—78.5°. Recrystallization from a mixture of chloroform and *n*-hexane gave pure (±)-XXXIII as colorless plates (2.4 g, 48%), mp 76—78°. *Anal.* Calcd. for $C_{11}H_{15}ON$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.32; H, 8.51; N, 8.29. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1679 (amide). NMR (in $CDCl_3$): 0.80 (3H, triplet, J=7.5 cps, $CH_2C\underline{H}_3$), 1.50 (3H, singlet, $C\underline{H}_3$), 2.00 (2H, quartet, J=7.5 cps, $-C\underline{H}_2CH_3$), 5.25, 6.31 (2H, broad two singlets, $CON\underline{H}_2$), 7.28 (5H, singlet, $C_6\underline{H}_5$).

An acetonitrile solution (5 ml) of phosphorus oxychloride (1.04 g, 6.8 mmole) was added to a stirred solution of the (±)-XXXIII (1.0 g, 5.6 mmole) prepared above in acetonitrile (15 ml) in an ice bath. After the addition, the cooling bath was removed, and the whole was stirred at 50° for 8.25 hr. An oily precipitate was removed by decantation, and the upper clear acetonitrile solution was evaporated *in vacuo*, giving a pale brown oil (*ca.* 1.0 g), which was purified by column chromatography using silica gel (50 g, solvent: petr. ether–ethyl acetate 10: 1), to afford crude (±)-XXIX as a pale yellow oil (0.7 g, 78%). Distillation *in vacuo* gave a pure sample as a colorless oil (0.57 g, 64%). *Anal.* Calcd. for $C_{12}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.92; H, 8.17; N, 8.90. IR ν_{max}^{neat} cm^{-1}: 2250 (CN). NMR (in CCl_4): 0.94 (3H, triplet, J=7.5 cps, $CH_2C\underline{H}_3$), 1.66 (3H, singlet, $C\underline{H}_3$), 1.92 (2H, quartet, J=7.5 cps, $C\underline{H}_2CH_3$), 7.26 (5H, singlet, $C_6\underline{H}_5$). Gas chromatographic analysis (15% SE-30 on Diasolid L, 2.25 m, 130°) of this oil showed a single peak whose retention time was 10.2 min.

***R*(+)-2-(2-Phenyl)butyl Cyanide (*R*(+)-XXIX)**——Treatment of *R*(−)-XXX ($[\alpha]_D^{15}$ −23.2° (c=1.838, benzene), 75.3% optically pure)[38] (7.2 g, 0.041 mole) similar to that of (±)-XXX gave crude *R*-XXXIII as a pale yellow viscous oil (7.4 g, quantitative yield) after evaporation of the ethereal extracts. The IR spectrum of this oil was identical with that of (±)-XXXIII. This oil was directly used for the next dehydration, under the same conditions employed for the prepation of (±)-XXIX, to afford crude *R*(+)-XXIX as a pale yellow oil (5.5 g, 86% based on *R*(−)-XXX) after chromatographic purification. Distillation *in vacuo* gave pure *R*(+)-XXIX as a colorless oil (5.3 g, 82% based on *R*(−)-XXX), bp 121—124° (25.5 mmHg). *Anal.* Calcd. for $C_{12}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.96; H, 8.18; N, 8.92. IR and NMR spectra of this oil were identical with those of (±)-XXIX. $[M]^{17}$ (c=1.214, benzene) (mμ): +5.7° (400), +47.7° (300). Gas chromatographic analysis (15% SE-30 on Diasolid L, 2.25 m, 130°) of this oil showed a single peak whose retention time was identical with that of the racemic compound.

Preparation of *cis*- and *trans*-2-Phenyl-2-butene (XXXIV and XXXV) and 2-Phenyl-1-butene (XXXVI)——A mixture of these three olefins was prepared by dehydration of (±)-2-phenylbutan-2-ol with 4N sulfuric acid using the procedure reported by Cram,[27] then they were separated with a Nester/Faust Auto-Annular Teflon Sprinning Band Distillation Instrument. The three isolated olefins were confirmed by their NMR spectra and were used as authentic sample for thermal rearrangement.

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[38] *R*(−)-XXX showing $[\alpha]_D^{14}$ −30.8° (c=1.140, benzene) (see reference 25) was assumed to be 100% optically pure.

cis-2-Phenyl-2-butene (XXXIV): bp 127—128° (114 mmHg) (lit.[27] bp 194 (760 mmHg)). IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 1650, 833 (olefin). NMR (in CCl_4): 1.76 (3H, doublet, J=7.0 cps, $-CH-C\underline{H}_3$), 1.99 (3H, singlet, $C\underline{H}_3-C(C_6H_5)=$), 5.75 (1H, quartet, J=7.0 cps, $=C\underline{H}-CH_3$), 7.15 (5H, singlet, $C_6\underline{H}_5$).

trans-2-Phenyl-2-butene (XXXV): bp 109—110° (115 mmHg) (lit.[27] bp 174° (176 mmHg)). IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 1605, 820 (olefin). NMR (in CCl_4): 1.57 (3H, doublet, J=7.5 cps, $=CH-C\underline{H}_3$), 2.00 (3H, singlet, $C\underline{H}_3-C(C_6H_5)=$), 5.30 (1H, quartet, J=7.5 cps, $=C\underline{H}-CH_3$), 7.13 (5H, singlet, $C_6\underline{H}_5$).

2-Phenyl-1-butene (XXXVI)[39]: bp 118—120° (116 mmHg). IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 1603, 895 (terminal olefin). NMR (in CCl_4): 1.05 (3H, triplet, J=7.5 cps, $CH_2C\underline{H}_3$), 2.47 (2H, quartet, J=7.5 cps, $C\underline{H}_2CH_3$), 4.99 (1H, multiplet, $_{\text{Et}}{>}C{=}C{<}^{H}_{\underline{H}}$), 5.17 (1H, doublet, J=1.5 cps, $^{C_6H_5}_{\text{Et}}{>}C{=}C{<}^{\underline{H}}_{H}$), 7.18 (5H, singlet, C_6H_5).

When these olefins underwent gas chromatography (15% SE-30 on Diasolid L, 2.25 m, 130°), they showed the following retention times: XXXIV (4.6 min); XXXV (1.9 min); XXXVI (2.7 min).

Thermal Rearrangement of (±)- and *R*(+)-2-(2-Phenyl)butyl Isocyanide ((±)- and *R*(+)-XXVIII)—— Run 1: A diphenyl ether solution (20 ml) of (±)-XXVIII (1.89 g, 0.012 mole) was refluxed (bath temperature 280°) under a nitrogen atmosphere for 3 hr. The IR spectrum of the reaction mixture showed a complete absence of the starting material (IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2140 (N≡C)). Quantitative analysis of the reaction mixture with gas chromatography using naphthalene as the internal standard (15% SE-30, on Diasolid L, 2.25 m, 130°) showed the formation of (±)-XXIX in 19% yield (naphthalene retention time 6.8 min, (±)-XXIX retention time 10.2 min). No quantitative analysis of the three different olefins (XXXIV, XXXV, XXXVI) was attempted at this stage.

To isolate these olefins, the whole was submitted to silica gel column chromatography (200 g). Elution of the column with petr. ether, followed by evaporation *in vacuo* gave a mixture of diphenyl ether and the olefins. This was further purified by fractional distillation to afford an oil (*ca.* 0.5 g), bp 78—130° (17 mm Hg). Gas chromatographic analysis of this oil (15% SE-30 on Diasolid L, 2.25 m, 130°) clearly showed that it mainly consisted of the olefinic mixture (retention time: diphenyl ether (17.8 min), olefins (1.9, 2.7, 4.6 min)). Further purification of this oil with silica gel column chromatography (solvent: petr. ether) gave almost pure XXXIV (*ca.* 0.1 g) and XXXV (0.01 g). These two olefins were identified with authentic samples by comparison of their NMR spectra and retention times on gas chromatography with those of authentic samples: XXXIV retention time, 4.6 min and XXXV retention time, 1.9 min (15% SE-30 on Diasolid L, 2.25 m, 130°). Although isolation of XXXVI in the pure state was unsuccessful, confirmation of XXXVI was achieved with gas chromatography by comparing its retention time with that of authentic XXXVI. Column A: 15% SE-30 on Diasolid L, 2.25 m, 130°, retention time 2.7 min; Column B: 15% PEGA on Diasolid L, 2.25 m, 130°, retention time 3.2 min.

Run 2: Treatment of the diphenyl ether solution (16 ml) of *R*(+)-XXVIII (α_{D}^{20} −0.090° (l=0.1, neat), 80.8% optically pure) (1.66 g, 0.010 mole) with the same procedure as used in run 1, completed the thermal rearrangement of *R*(+)-XXVIII. Quantitative analysis of the products formed was done by gas chromatography using naphthalene as the internal standard (15% SE-30 on Diasolid L, 2.25 m, 130°): *R*(+)-XXIX (21%, retention time 10.2 min), XXXIV (35%, retention time 4.6 min), XXXV (4%, retention time 1.9 min), XXXVI (28%, retention time 2.7 min). Identification of the four peaks which formed was made by comparisons of their retention times with those of authentic samples.

To measure the optical rotation of *R*(+)-XXIX, the reaction mixture was purified with silica gel column chromatography (170 g). The column was first eluted with petr. ether to remove the olefins and diphenyl ether, then with a mixture of petr. ether and ethyl acetate (10: 1). to afford crude *R*(+)-XXIX as a pale yellow oil (0.33 g, 20%). Further purification by fractional distillation gave pure *R*(+)-XXIX as a colorless oil (0.06 g, 4%), bp 131—132° (10 mmHg) (bath temperature). $[M]^{20}$ (c=0.462, benzene) (mμ): 0° (400). +9.5° (300). The IR spectrum of this oil measured in a neat state was identical with that of authentic *R*(+)-XXIX. Gas chromatographic analysis (15% SE-30 on Diasolid L, 2.25 m, 130°) of this oil showed a single peak whose retention time was identical with that of authentic *R*(+)-XXIX. The optical purity of the *R*(+)-XXIX obtained was calculated as 15.0% since *R*(+)-XXIX showing $[M]_{300}^{17}$ +47.7° (c=1.214, benzene) was 57.3% optically pure. Thus, the degree of retention of configuration in this reaction was 19%.

Run 3: (±)-Cyanide ((±)-XXVIII) (2.15 g, 0.014 mole) was heated at 260° (bath temperature) under a nitrogen atmosphere without solvent for 5 hr. The IR spectrum of the reaction mixture showed the complete disappearance of the starting (±)-XXVIII. Quantitative analysis of the reaction mixture using gas chromatography (run 1) showed formation of (±)-XXIX in a 52% yield. No quantitative analysis of the olefins formed was attempted here either. The whole was purified with silica gel column chromatography (200 g, solvent: petr. ether–ethyl acetate 10: 1), to give crude (±)-XXIX as a colorless oil (1.10 g, 51%). Fractional distillation of this oil afforded pure (±)-XXIX as a colorless oil (1.06 g, 49%), bp 85—90° (7 mmHg). The IR spectrum of this oil measured in a neat state was identical with that of the authentic (±)-XXIX.

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39) No Formation of XXXVI was reported in reference 27.

Run 4: Treatment of *R*(+)-XXVIII (α_D^{20} +0.090° (l=0.1, neat), 80.8% optically pure) (2.17 g, 0.014 mole) with the procedure used in run 3 completed the thermal rearrangement. Quantitative gas chromatography of the reaction mixture (run 2) showed the formation of the cyanide and olefins in the following yields: cyanide (XXIX) (61%, retention time 10.2 min), XXXIV (10%, retention time 4.6 min), XXXV (1% retention time 1.9 min), XXXVI (11% retention time 2.7 min). To separate the cyanide, the reaction mixture was submitted to silica gel column chromatography, as in run 3, to give crude cyanide (XXIX) as a pale yellow oil (1.20 g, 55%). Purification by fractional distillation gave pure cyanide as a colorless oil (0.62 g, 29%), bp 88—90° (3.5 mmHg), $[M]^{19}$ (c=1.012, benzene) (mμ): 0° (400), 0° (300). The IR spectrum of this oil was identical with that of authentic (±)-XXIX. Gas chromatographic analysis (run 2) of this oil showed a single peak whose retention time was identical with that of authentic (±)-XXIX.

Thermal Stability of *R*(+)-2-(2-Phenyl)butyl Cyanide (*R*(+)-XXIX)——*R*(+)-Cyanide (*R*(+)-XXIX) ($[M]_{300}^{17}$ +47.7° (c=1.214, benzene), 75.3% optically pure) (0.48 g, 3.0 mmole) was heated at 250° (bath temperature) under a nitrogen atmosphere for 5 hr. Distillation of the remaining oil recovered *R*(+)-XXIX as a colorless oil (0.23 g, 48% recovery), bp 88—90° (9 mmHg), $[M]^{21}$ (c=1.332, benzene) (mμ): +6.7° (400), +51.5° (300). The IR spectrum of this oil measured in a neat state was identical with that of the starting *R*(+)-XXIX. This clearly showed that no recemization of *R*(+)-XXIX occurred during the thermal reaction.

Thermal Stability of *R*(+)-2-(2-Phenyl)butyl Isocyanide (*R*(+)-XXVIII)——*R*(+)-Cyanide (*R*(+)-XXVIII) (α_D^{20} +0.090° (l=0.1, neat), 80.8% optically pure) (1.78 g, 0.011 mole) was heated at 260° under a nitrogen atmosphere without solvent for 0.25 hr. IR ν_{max}^{neat} cm^{-1}: 2140 (N≡C), 2250 (C≡N). This oily mixture was dissolved in a mixture of 10% HCl and ethanol (1 : 1) (18 ml), and the aqueous solution was refluxed for 0.5 hr. Ethanol was distilled off *in vacuo*, then the neutral products, *i.e.* the rearranged cyanide and olefins, were removed by extraction with ether. The residual acidic aqueous phase was made alkaline with 10% NaOH (pH>10) under ice-cooling, and the liberated oil was extracted with ether. Organic layers were combined and washed with satd. NaCl, then were dried over anhyd. potassium carbonate. Filtration and evaporation *in vacuo* gave crude *R*(+)-XXXI as a pale yellow oil. This was purified by fractional distillation to afford pure *R*(+)-XXXI as a colorless oil (0.23 g, 14%), bp 83—84° (7.5 mmHg), $\alpha_D^{9.5}$ +1.176° (l=0.1, neat), The IR spectrum of this oil measured in a neat state was identical with that of the authentic *R*(+)-XXXI.

Thermal Rearrangement of (±)-2-(2-Phenyl)butyl Isocyanide ((±)-XXVIII)in the Presence of Tri-*n*-butyltin Hydride as a Radical Scavenger——A mixture of (±)-XXVIII (0.50 g, 3.1 mmole) and tri-*n*-butyltin hydride (0.91 g, 3.1 mmole) in diphenyl ether (5 ml) was refluxed under a nitrogen atmosphere for 1 hr (bath temperature 280°). Quantitative gas chromatographic analysis of the reaction mixture using *m*-xylene as the internal standard, showed no formation of olefins (XXXIV, XXXV, and XXXVI) and exclusive formation of *sec*-butylbenzene (61%), which was identified with a commercially available authentic sample by comparison of their retention times on gas chromatography: 15% SE-30 on Diasolid L, 2.25 m, 130°, retention time 2.8 min; 70°, retention time 14.6 min; 15% PEGA on Diasolid L, 2.25 m, 130°, retention time 3.2 min.

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