[Chem. Pharm. Bull. 16(9)1816—1828(1968)] UDC 547.556.9.04 : 541.653

Stereochemical Studies. I. Elucidation of the Reaction Mechanism of the Base-induced Rearrangement of Ketone Trimethylhydrazonium Iodide using optically Active Compounds

SHUN-ICHI YAMADA and SHIRO TERASHIMA

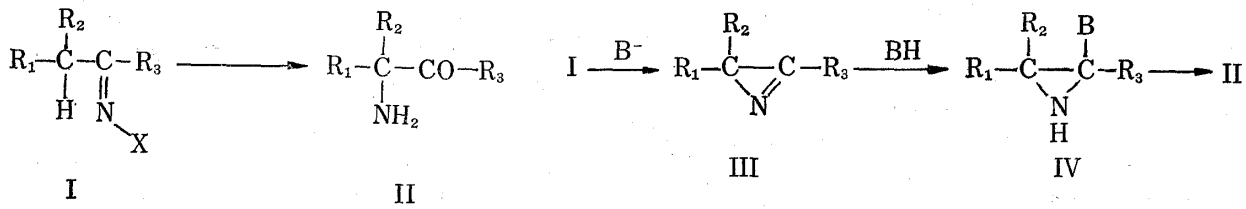
Faculty of Pharmaceutical Sciences, University of Tokyo[1]

(Received January 26, 1968)

The reaction mechanism of the base-induced rearrangement of ketone trimethylhydrazonium iodide (Ia) was studied using the optically active open chain compound, *S*(+)-3-methyl-4-phenyl-2-butanone trimethylhydrazonium iodide (*S*(+)-VIII). According to the nearly complete racemization of the rearrangement product (IXa) and little but evident optical retention of the recovered ketone (XIa), it appeared more probable that this rearrangement had proceeded through vinyl nitrene (V). Then, it became difficult to prepare the optically active α-amino ketone (II) from the ketone involving the optically active C–H bond at α-position with this rearrangement.

Preliminary examinations using racemic compounds were also reported.

The base-induced rearrangement of ketone trimethylhydrazonium iodide (Ia), discovered by Smith, *et al.*[2,3] as the modification of the so-called Neber rearrangement, is valuable for the introduction of amino group into the α-position of an aliphatic ketone.[4,5] However, an application of this rearrangement to the open chain ketone trimethylhydrazonium iodide (Ia) containing an optically active C–H bond at the α-position has never been attempted the same as in the case of the Neber rearrangement.[6] If it is possible using this rearrangement to prepare the optically active α-amino ketone (II) from Ia, the evaluation for this rearrangement can be much improved. It is evident that whether or not the rearrangement is applicable to the synthesis of the optically active II depends on its reaction mechanism, which has been considered as similar to that of the Neber rearrangement of ketoxime tosylate (Ib)[2,7] because the final product of this rearrangement, the α-amino ketone (II),[3–5] and the intermediates, azirine (III)[4,5] and aziridine (IV),[4] are the same as those of the Neber rearrangement.[2] Moreover,



a : X=$\overset{+}{N}(CH_3)_3\,I^-$

b : X=OTos

1) Location: *Hongo, Tokyo.*
2) C. O'Brien, *Chem. Rev.*, **64**, 81 (1964).
3) P.A.S. Smith and E.E. Most, Jr., *J. Org. Chem.*, **22**, 358 (1957).
4) R.F. Parcell, *Chem. Ind.*, **1963**, 1396.
5) D.F. Morrow, M.E. Butler, and E.C.Y. Huang, *J. Org. Chem.*, **30**, 579 (1956).
6) Morrow, *et al.* applied this base-induced rearrangement of ketone trimethylhydrazonium iodide to pregnenolone, and obtained 17β-amino steroid as the reaction product. They did not confirm the mechanism for this rearrangement, but suggested that steric repulsion of the two methyl group at C-18 and C-21 had caused the reaction to proceed stereoselectively through the lower energy transition state (see ref. 5).
7) D.J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, London, **1965**, p. 249.

the reaction conditions of these two rearrangements are nearly equal. The mechanism between Ia and III, which decides whether or not this rearrangement can proceed with retention of optical activity, has not yet been established, and several possibilities may be considered from the reaction mechanisms suggested for the Neber rearrangement.[2,5] As shown in Chart 1, one of them is through vinyl nitrene (V) (path A).[8] The others are through the concerted electron migration in the carbanion (VI) or the transition state (VII) (path B).[9] Racemization is inevitable in path A but path B may have some possibility for the retention of optical activity.

The authors undertook the base-induced rearrangement using optically active Ia containing an optically active C–H bond at the α-position, in order to study the reaction mechanism between Ia and III and to elucidate the applicability of this rearrangement for the preparation of the optically active α-amino ketone.

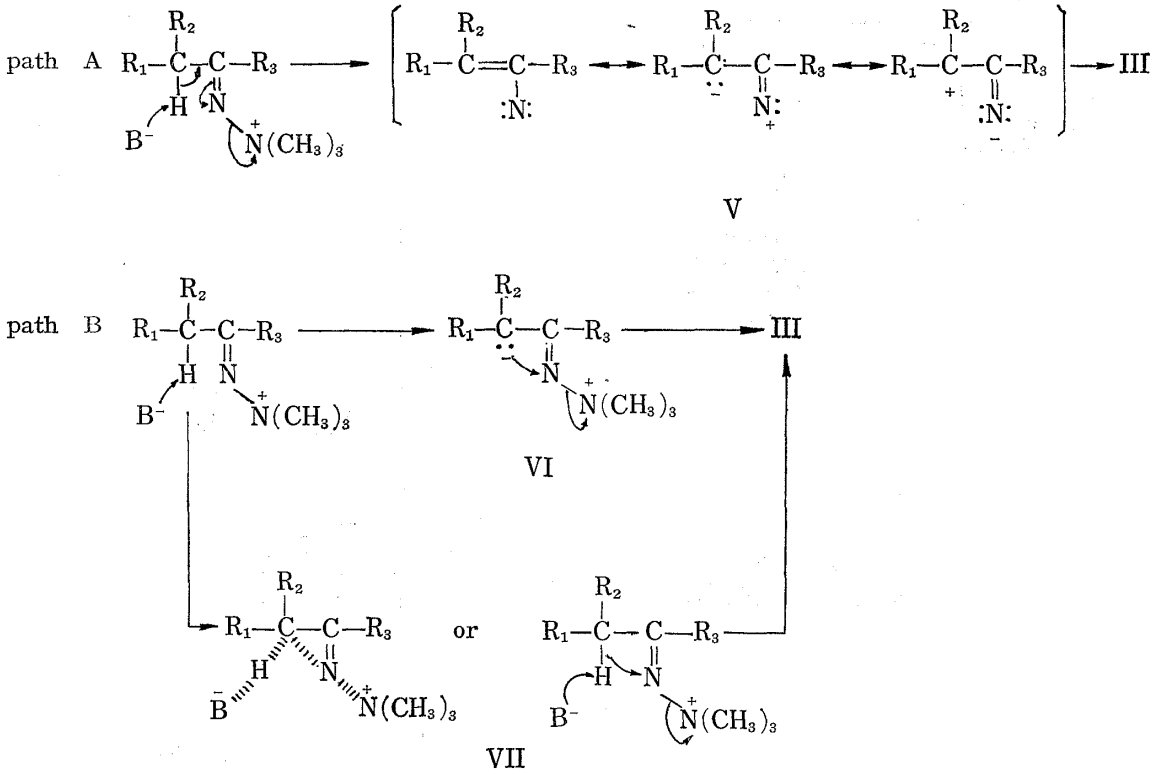


Chart 1

Results and Discussion

As starting material in the rearrangement 3-methyl-4-phenyl-2-butanone trimethylhydrazonium iodide (VIII) was selected for the following three reasons; 1) VIII has a very

8) In the Neber rearrangement, the mechanism through vinyl nitrene (V) is thought to be the most probable course (see ref. 2,7; D.J. Cram and M.J. Hatch, *J. Am. Chem. Soc.*, **75**, 33, 38 (1953); H.O. House and W.F. Berkowitz, *J. Org. Chem.*, **28**, 307, 2271 (1963)), and the mechanism by way of concerted electron migration of the carbanion (i) seems to be less likely because of the independence of the reaction course on the configration of the OTos group (H.O. House and W.F. Berkowitz, *J. Org. Chem.*, **28**, 2271 (1963)).

(i)

9) Transition states such as VII have never been taken up in the Neber rearrangement, but some differences found in the results obtained from the Neber rearrangement of Ib and from the base-induced rearrangement of Ia prompted us to assume that the latter rearrangement can proceed through such a synchronous transition state.

simple structure, 2) the optically active isomer of VIII is easily prepared, from 2-methyl-3-phenylpropionic acid (X), which absolute configuration has already been clearly established,[10] through 3-methyl-4-phenyl-2-butanone (XI), and 3) the absolute configuration and optical purity of 3-amino-3-methyl-4-phenyl-2-butanone (IX), which can be expected as the product from this rearrangement, can be easily established by independent synthesis from optically active α-methylphenylalanine (XII) whose absolute configuration and optical purity have been established by us.[11]

The chemical scheme we employed is shown in Chart 2. Before studying the rearrangement using the optically active compounds, experiments on racemic compounds were carried out in order to ascertain the best working conditions.

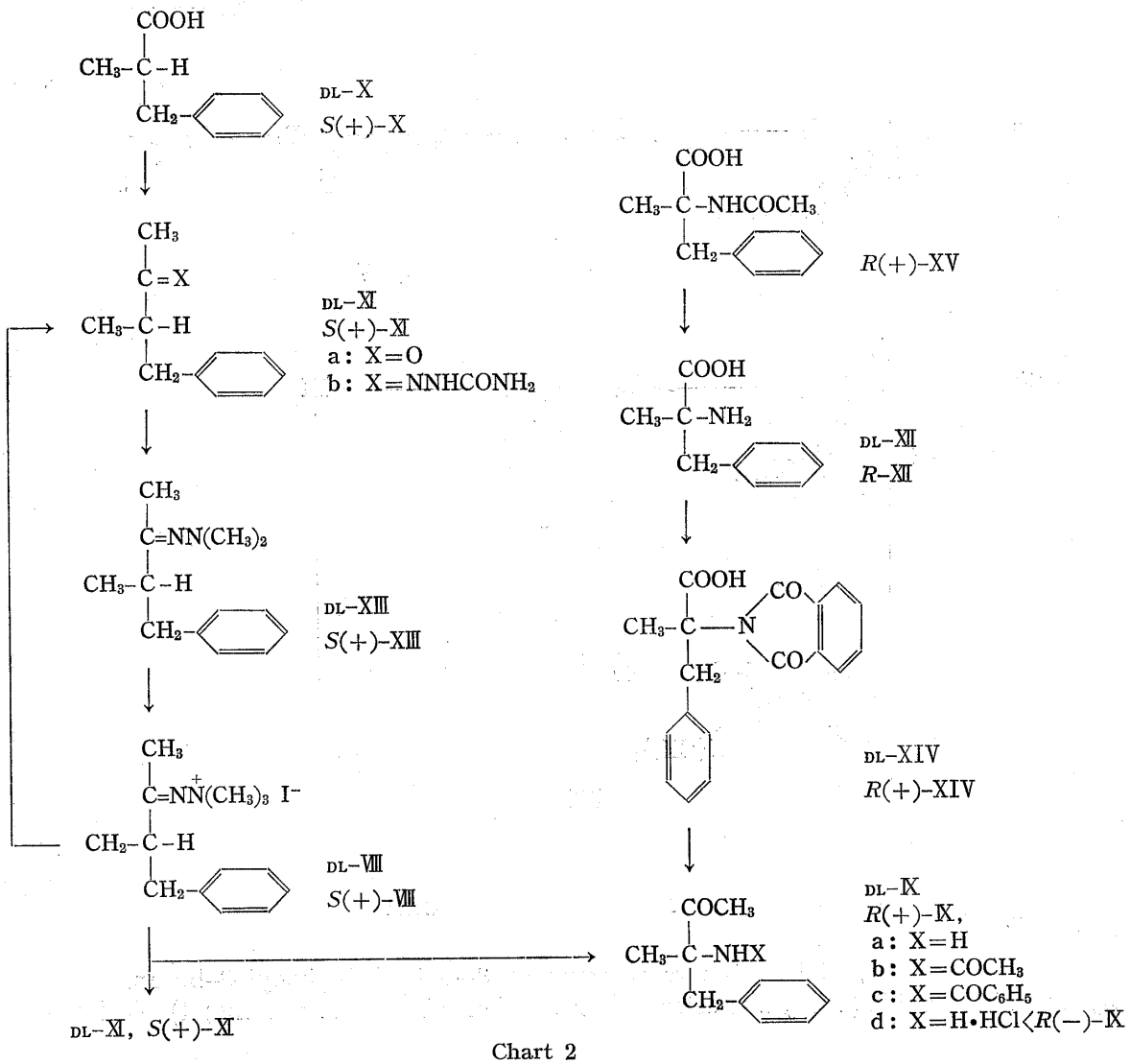


Chart 2

Acid chloride, obtained from DL-X[10,12-15] on reflux with thionyl chloride, was treated with magnesium diethylmalonate ethoxide to give the keto ester which was hydrolysed and

10) A.W. Schrecker, *J. Org. Chem.*, **22**, 33 (1957).
11) S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 1138 (1966).
12) L.W. Jones and E.S. Wallis, *J. Am. Chem. Soc.*, **48**, 169 (1926).
13) M. Conrad and C.A. Bischoff, *Ann.*, **204**, 177 (1880).
14) M. Conrad, *Ber.*, **11**, 1055 (1878).
15) F.S. Kipping and A.E. Hunter, *J. Biol. Chem.*, **83**, 1005 (1903).

decarboxylated on reflux with a mixture of acetic acid and 47% hydrobromic acid to afford DL–3–methyl–4–phenyl–2–butanone[16–19] (DL–XIa) in a 76% yield. The DL–XIa obtained was refluxed with dimethylhydrazine in a sealed tube for 6 hr[3,5] to give DL–3–methyl–4–phenyl–2–butanone dimethylhydrazone (DL–XIII)[20] in a 93% yield, and was identified from spectral data. Treatment of DL–XIII, with an excess of methyl iodide at room temperature,[5] gave crude DL–VIII as an amorphous yellow powder in a 89% yield, which did not show a sharp melting point and the purification of which, using the recrystallization method, was difficult.[21] But DL–VIII was confirmed from the spectral data and the result of acidic hydrolysis which gave DL–XIa in a good yield.

The base–induced rearrangement of DL–VIII, under the several conditions as shown in Table 1, was undertaken in order to find out the best working conditions.

The procedure for the rearrangement is described below.[22] After the reaction was over, the reaction mixture was evaporated to a small volume, to which was added a mixture of benzene and ether. The aqueous layer (fraction A) obtained was refluxed, after the addition of conc. hydrochloric acid, and a neutral fraction extracted, which gave a very small amount of DL–Xla, except in the case where triethylamine was used as the base. The benzene–ether layer was evaporated *in vacuo*, and a mixture of ethanol and conc. hydrochloric acid was added to the residue which was refluxed. The neutral (fraction B) and basic fractions (fraction C) were obtained from this reaction mixture. Fraction B was purified using silica gel column chromatography to give DL–XIa, which was identified by its semicarbazone (DL–XIb). DL–XIa, isolated from fraction B, seems to be obtained from the ethanolysis product of DL–VIII, which was produced during the rearrangement. DL–IXa, isolated from fraction C, was acetylated with pyridine–acetic anhydride to afford DL–3–acetamido–3–methyl–4–phenyl–2–butanone (DL–IXb) which was identified by comparison with the authentic DL–IXb prepared from DL–α–methylphenylalanine (DL–XII) by mixed melting point measurement and infrared and nuclear magnetic resonance (NMR) spectra. The yield of DL–IXa, on the base–induced rearrangement of DL–VIII, can be calculated from the yield of DL–IXb, since the yield of DL–IXb when prepared from the pure DL–IXa is 77%.

Next, independent synthesis of the authentic DL–IXb, from DL–XII, was undertaken. As shown in Chart 2, N–phthaloyl–DL–α–methylphenylalanine (DL–XIV), obtained by the treatment of DL–XII[11] with phthalic anhydride,[23] was converted in the usual way to its acid chloride, which was treated in the same manner as DL–XIa to give DL–IXa in a 54% yield.[24] DL–IXa afforded DL–IXb and DL–3–benzamido–3–methy–4–phenyl–2–butanone (DL–IXc) in a usual manner. Both the DL–IXb and DL–IXc obtained were identified from elemental analyses and spectral data.

The results summarized in Table 1 clearly disclose that this base–induced rearrangement of DL–VIII can be accomplished not only with sodium hydride as an added base but also with the strong basic ion exchange resin, Amberlite IRA–400 (OH^- form). The best yield was

16) H. Rupe and H. Müller, *Helv. Chim. Acta*, **4**, 841 (1921).
17) M. Montagne, *Compt. rend.*, **218**, 679 (1944).
18) A.L. Seales and R.J. Kelley, *J. Am. Chem. Soc.*, **78**, 2242 (1956).
19) L.H. Briggs, G.C. De Ath, and S.R. Ellis, *J. Chem. Soc.*, **1942**, 61.
20) In DL–XIII two geometrical isomers, *syn* or *anti* isomer, may be possible. But comparison of the bulkiness of the 1–methyl–2–phenylethyl group with that of the methyl group shows that the structure which invloves N $(CH_3)_2$ group *syn* to CH_3 group must be predominant. Gas chromatographic analysis of crude DL–XIII showed no existence of the two isomers (see experimental).
21) Attempted purifications of crude DL–VIII by converting it into other quarternary ammonium salts were all unsuccessful.
22) This procedure was devised after a report by Morrow, *et al.* (see ref. 5).
23) S. D, Uphan and O. C. Dermer, *J. Org. Chem.*, **22**, 799 (1957).
24) After standing at room temperature for a long time, DL–IXa gradually converted to its dihydropyrazine derivative (see experimental).

TABLE I. Rearrangements of DL–3–Methyl–4–phenyl–2–butanone Trimethylhydrazonium Iodide (DL–VIII) under Several Conditions

Run	Base (added) nature	eq.[a]	Solvent (v/v ratio)	Reflux time (hr)	Reaction products: DL–3–Amino–3–methyl–4–phenyl–2–butanone (DL–IXa) isolated as DL–IXb: Crude DL–IXb Yield (%)	Crude DL–IXb mp (°C)	Pure DL–IXb[b] Yield (%)	Pure DL–IXb[b] mp (°C)	DL–3–Methyl–4–phenyl–2–butanone (DL–XIa) recovered: DL–XIa from fraction B Yield (%)	DL–XIa from fraction B mp of DL–XIb (°C)	DL–XIa from fraction A Yield (%)	DL–XIa from fraction A mp of DL–XIb (°C)
1	NaH[c]	1	EtOH–DMSO[d] (10 : 1)	6	23	130—134.5	13	137.5—138.5[e]	32[f]	112—113[e]	3	110—113[e]
2	NaH[c]	5.3	EtOH–DMSO[d] (10 : 1)	6	25	134—137.5	21	138.5—139.5[e]	32[g]	114—115[e]	trace[h]	—
3	NaH[c]	1	*t*–BuOH	6	<2[i]	—	—	—	21[f]	110.5—112[e]	trace[h]	—
4	HaN[c]	1	dioxane–EtOH (30 : 1)	6	<4[i]	—	—	—	25[f]	113—114.5[e]	trace[h]	—
5	NaH[c]	1	EtOH	6⅓	16[i]	—	7	138—138.5[e]	26[f]	112.5—114.5[e]	—	—
6	Et_3N	6	EtOH–DMSO[d] (10 : 1)	6	0	—	—	—	10[j]	109.5—111[e]	10[i]	—
7	Amberlite IRA–400[k]	12	EtOH–DMSO[d] (10 : 1)	6	19	132.5—137.5	13	138.5—139.5[e]	—	—	trace[h]	—
8	Amberlite IRA–400[k]	12	EtOH–DMSO[d] (10 : 1)	6	20	135.5—137.5	12	138.5—139.5[e]	43[g]	114—116[e]	—	—

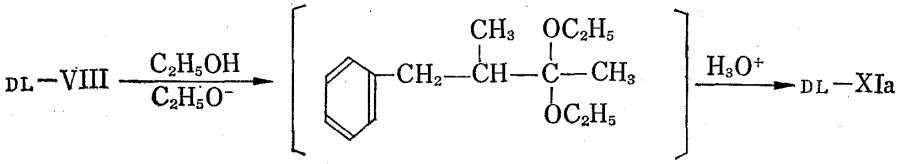
a) equivalent; *b*) one recrystallization from hexane–EtOAc; *c*) a 50% sodium hydride oil dispersion; *d*) dimethy lsulfoxide; *e*) Mixed melting point with the authentic sample showed no depression; *f*) Purified with silica gel column chromatography (solvent: hexane–$CHCl_3$ 1:1); *g*) purified with silica gel column chromatography (solvent: hexane–EtOAc 96:4); *h*) Identified with thin-layer chromatography (see experimental); *i*) Identified using thin-layer chromatography and infrared spectrum (see experimental); *j*) Purified with silica gel column chromatography (solvent: benzene); *k*) OH^- form

TABLE II. Rearrangements of *S*(+)–3–Methyl–4–phenyl–2–butanone Trimethylhydrazonium Iodide (*S*(+)–VIII) under Several Conditions

Run	Base (added) nature	eq.[a]	Optical purity of *S*(+)–VIII (%)	Solvent (v/v ratio)	Reflux time (hr)	Reaction products: 3–Amino–3–methyl–4–phenyl–2–butanone (IXa) isolated as IXb: Crude IXb Yield (%)	Crude IXb mp (°C)	Pure IXb[b] Yield (%)	Pure IXb[b] mp (°C)	Pure IXb[b] $[M]_{350}$[c] (max.)	Retention of confign[d] (%) (max.)	3–Methyl–4–phenyl–2–butanone (XIa) recovered: XIa from fraction B Yield (%)	XIa from fraction B $[M]_{350}$[c]	XIa from fraction B Optical purity (%)[e]	XIa from fraction B Retention of confign. (%)[f]	XIa from Fraction A Yield (%)
9	NaH[g]	1	46	EtOH–DMSO[h] (10 : 1)	6	28[i]	132.5—138	13	139—140	0	0	27[i,j]	15.4	3.0	7.0	trace[k]
10	Amberlite[l] IRA–400	12	46	EtOH–DMSO[h] (10 : 1)	6	18[i]	132—136.5	15	137.5—138.5	2.0	0.27	27[i,j]	11.2	2.2	5.0	trace[k]

a) equivalent; *b*) Purified with silica gel column chromatography (solvent:hexane–AcOEt 1:1); *c*) Measured from the optical rotatory dispersion chart; *d*) Calculated from the following equation: [retention of confign. (%)] $= \frac{[M]_{350}}{1590 \times 0.46} \times 100$; *e*) Calculated from the following equation: [optical purity (%)] $= \frac{[M]_{350} \times 84}{426}$, (*S*(+)–XIa showing $[M]_{350}$ 426° is optical purity of 84%); *f*) Corrected for racemization expected in the isolation procedure; *g*) a 50% sodium hydride oil dispersion; *h*) dimethylsulfoxide; *i*) Identified with infrared spectra; *j*) Identified as semicarbazone (XIb); *k*) Identified from thin-layer chromatography (see experimental); *l*) OH^- form

obtained when a mixture of ethanol and dimethyl sulfoxide (10:1)[25] was used as the reaction solvent, and in *t*-butanol, or in a mixture of dioxane and ethanol (30:1), only a trace of DL-IXa was formed. DL-XIa, recovered from the benzene-ether soluble fraction (fraction B), was considered to be produced from the acid hydrolysis of the ketal (DL-XVI),[26] which seemed



DL-XVI

to be prepared from the ethanolysis of DL-VIII during the rearrangement. If the C=N double bond of DL-VIII were not cleaved completely, the product soluble in benzene-ether could not be expected to be obtained.

Then, in order to examine the rearrangement using optically active compounds, synthesis of optically active 3-methyl-4-phenyl-2-butanone trimethylhydrazonium iodide (VIII) was attempted. *S*(+)-X, α_D^{21} +1.939° (*l*=0.1, neat), $[\alpha]_D^{11}$ +22.2° (*c*=4.946, benzene) (optical purity 74%)[27] obtained from the resolution [10,12-15] of DL-X with quinine[15] was treated in the same way as DL-X to afford the acid chloride, which, without isolation, was treated with dimethyl cadmium in ether to give crude *S*(+)-XIa. Purification using column chromatography yielding pure *S*(+)-XIa, α_D^{13} +2.442° (*l*=0.1, neat), $[\alpha]_D^{14}$ +32.9° (benzene) in a 26% yield,[28-30] which was identified as semicarbazone (*S*(+)-XIb), $[\alpha]_D^{20}$ +31.4° (ethanol). The *S*(+)-XIa thus obtained was treated in the same way as DL-XIa to give *S*(+)-XIII, α_D^{17} +2.728° (*l*=0.1, neat) in a 92% yield, which afforded *S*(+)-VIII, $[\alpha]_D^{17}$ +16.1° (methanol) as an amorphous pale yellow powder after the same treatment as in the case of DL-XIII. When the *S*(+)-VIII prepared above was dissolved in 10% hydrochloric acid and the acidic solution was extracted with ether, the ether layer afforded *S*(+)-XIa showing $[\alpha]_D^{15}$ +19.0° (benzene), and optical purity of 43%. On the other hand, when *S*(+)-XIa was treated with the same conditions[31] as those used in the hydrolysis of *S*(+)-VIII, *S*(+)-XIa could be recovered with 94% retention of its optical activity. From this control experiment the optical purity of

25) This solveut system was used originally by Mollow, *et al.* for the preparation of the *α*-amino ketone by this rearrangement (see ref. 5).

26) Isolation of DL-XVI from the reaction mixture was not attempted.

27) The maximum reported optical rotation of optically active X, $[\alpha]_D^{22}$ −24.56° (*l*=1, neat), d_4^{22} 1.065 (see ref. 10), was assumed to have an optical purity of 100%. Several rotation values, $[\alpha]_D$ +27.06° (*c*=3.733, benzene), $[\alpha]_D$ +27.72° (*c*=3.283, chloroform) measured in solution, seemed to have optical purities below 100%, as the same sample showed $[\alpha]_D$ +22.65° (*l*=1, neat), d_4^{20} 1.065 in an undiluted state (*cf.* R.H. Pickard and J. Yates, *J. Chem. Soc.*, **95**, 1011 (1909)).

28) No racemization was observed in the treatment of *S*(+)-X with thionyl chloride (ref. 12 and E.S. Wallis and S.C. Nagel, *J. Am. Chem. Soc.*, **53**, 2787 (1931)), and Kenyon, *et al.* (A. Campbell and J. Kenyon, *J. Chem. Soc.*, **1946**, 25) reported that the methyl ketone prepared from dimethyl cadmium and the chloride of optically pure (+)-hydratropic acid gave optically pure (−)-N-acetyl-*α*-phenethylamine under the same conditions as the Curtius and Schmidt rearrangement. Summarizing the above results, the authors expected no racemization in the process from *S*(+)-X to *S*(+)-XIa.

29) In asymmetric synthesis Arcus, *et al.* (C.L. Arcus, L.A. Cort, T.J. Howard, and LeBeloc, *J. Chem. Soc.*, **1960**, 1195) obtained two lots of (−)-XIa showing α_D^{25}-1.76° (*l*=0.5, neat) and α_D^{25} −1.42° (*l*=0.5, neat) respectively. The optical purities of these samples were measured from gas chromatographic analyses as 21.5% and 17.3%. Optical rotation of optically pure (−)-XIa can then be calculated as α_D^{25} −1.64° (*l*=0.1, neat). However in these cases, incomplete resolution of the starting material must be considered.

30) Nearly complete racemization was observed when synthesis of *S*(+)-XIa from *S*(+)-X, using the same method as used in the preparation of DL-XIa, was attempted.

31) After *S*(+)-XIa was dissolved in ether and the ether layer washed four times with 10% hydrochloric acid, *S*(+)-XIa was again recovered from the ether layer (see experimetal).

S(+)–VIII, prepared from *S*(+)–XIa, was calculated to be 46%. Racemization may have occurred during the process from *S*(+)–XIa to *S*(+)–XIII.

Preparation of optically active 3–amino–3–methyl–4–phenyl–2–butanone (IXa), which could be expected to be obtained if the rearrangement proceeded with the retention of optical activity, was undertaken. Crude *R*–α–methylphenylalanine (*R*–XII) prepared from (+)–N–acetyl–*R*–α–methylphenylalanine (*R*(+)–XV),[11] $[\alpha]_D^{12}$ +86.8° (methanol), optical purity 100%,[11] was treated in a way similar to DL–XII[23] to afford *R*(+)–XIV in a 63% yield, from *R*(+)–XV. *R*(+)–XIV was coverted to *R*(+)–IXa, α_D^{12} +0.194° (*l*=0.1, neat), in a 51% yield the same as DL–XIV. *R*(+)–IXa was identified as hydrochloride (*R*(−)–IXd), $[\alpha]_D^{8}$ −53.5° (methanol). Similar to DL–IXa, *R*(+)–IXa gave N–acetyl derivative (*R*(+)–IXb), $[\alpha]_D^{21}$ +164° (methanol), and N–benzoyl one (*R*(+)–IXc), $[\alpha]_D^{12}$ +167° (methanol) in good yields. *R*(+)–IXb and *R*(+)–IXc were identified from elemental analyses and spectral data. On the optical rotatory dispersion measurement *R*(+)–IXb showed a positive plain curve.

The rearrangement of *S*(+)–VIII was attempted under the conditions described in Table 2. Crude IXb which was obtained after the same treatment as in the case of DL–VIII was purified, thoroughly, with silica gel column chromatography to give pure IXb, which showed $[M]_D^{15}=0$, $[M]_{350}^{15}=0$ in run 9 and $[M]_D^{15}=0$, $[M]_{350}^{15}<+2.0°$ in run 10 on the optical rotatory dispersion curve measurements. Owing to the absolute configuration and optical purity of the starting material, the retention percent of the configuration of IXb, obtained from the above rearrangement, was calculated to be 0% (run 9) and less than 0.27% (run 10). On the other hand, XIa, considered to be obtained from the ethanolysis product of *S*(+)–VIII, disclosed a small optical activity on the optical rotatory dispersion curve measurements, $[M]_{350}^{16.5}$ +15.4° (benzene) in run 9 and $[M]_{350}^{18}$ +11.2° (benzene) in run 10. These optical rotations did not seem to be due to impurities because the semicarbazones (*S*(+)–XIb) prepared from *S*(+)–XIa with small optical rotations clearly showed optical activity even after one recrystallization from aqueous ethanol. So it is evident that the retention percent of the configuration of *S*(+)–XIa is at least eighteen times that of *R*(+)–IXb.

These results clearly demonstrated that racemization had occurred during the process affording α–amino ketone (IXa) from *S*(+)–VIII, since it was not considered that *S*(+)–VIII had racemized completel before the rearrangement started. Nearly complete racemization of IXa may be most adequately interpreted by assuming the intervention of vinyl nitrene (V) during the rearrangement. However, possibilities of racemization by the other mechanism except through vinyl nitrene (V) can not be completely excluded. The mechanisms involving carbanion (VI) or the concerted transition state (VII) would give less probable reasons than that through vinyl nitrene (V) for the nearly complete racemization of IXa obtained.

Considerable racemization of the *S*(+)–XIa recovered seems to have occurred, not only in the starting material *S*(+)–VIII, but in the ketal (XVI) prepared during the rearrangement.

Summing up the results obtained above, the base–induced rearrangement of Ia can be assumed to proceed through path A, as shown in Chart 1. That is, it is clear that the introduction of the optically active amino group into the α position of the ketone, containing the optically active α–C–H bond with the retention of optical activity, is difficult using this rearrangement.

Experimental[32]

DL-and *S*(+)-2-Methyl-3-phenylpropionic Acid (DL-X and *S*(+)-X)——DL–X was prepared from ethyl acetate according to the method reported,[12–15] bp 137—137.5° (5.5 mmHg), mp 36—38° (lit.,[12] bp 144°

32) All melting points and boiling points were uncorrected. IR spectra measurements were performed with a Spectrometer, Model DS–402 and IR–S, Japan Spectroscopic Co., Ltd. NMR spectra were determined with a Spectrometer, Model 3H–60, Japan Electron Optics Lab. Optical activities were measured with a Yanagimoto Photo Direct Reading Polarimeter, Model OR–20. ORD curve measurements were carried on with a Spectrometer Model ORD/UV–5, Japan Spectroscopic Co., Ltd. Gas chromatographic analyses were performed using Yanagimoto Gas Chromatograph, Model GCG–3D.

(9 mmHg), mp 36.5°; lit.,[13] bp 272°, mp 37°; lit.,[15] bp160° (12mmHg); lit.,[10] bp 148—149° (9 mmHg), mp 36.6—37.5°, DL–X was resolved with quinine to afford *S*(+)–X, bp 146° (8.5 mmHg), α_D^{21} +1.939° (*l*=0.1, neat), $[\alpha]_D^{21}$ +22.2° (*c*=4.946, benzene), optical purity 74%[27] (lit.,[10] bp 111° (0.2 mmHg), $[\alpha]_D^{22}$ −24.56° (*l*=1, neat), d_4^{22} 1.065). IR γ_{max}^{cap} cm^{-1}: 1710, 1606, 740, 697. This infrared spectrum was identical with that of DL–X in the same state.

DL-3-Methyl-4-phenyl-2-butanone (**DL-XIa**)——A mixture of DL–X (16.4 g, 0.100 mole) and $SOCl_2$ (35.7 g, 0.300 mole) was refluxed for 30 min and evaporated to dryness *in vacuo*. Benzene (25 ml) was added to the residue and evaporated to dryness to afford a reddish brown oil. This procedure was repeated five times to remove $SOCl_2$ completely.

On other the hand, Mg (2.9 g, 0.12 atom) was added to a mixture of ethanol (100 ml) and CCl_4 (5 ml), and the whole was refluxed under stirring for 2 hr. The solvent was removed from the reaction mixture on a distillation and benzene (50 ml) was added to the residue. Benzene solution was again distilled off. Addition of benzene (50 ml) and evaporation to dryness were repeated to give white residue, which was dissolved in ether (60 ml). Ether solution (60 ml) containing diethyl malonate (19.4 g, 0.120 mole) was added to the above ether solution and the whole was refluxed under stirring for 3 hr, to which was added benzene solution (70 ml) dissolving the reddish brown oil prepared above. After reflux and stirring continued for 8 hr the reaction mixture was washed with 1N H_2SO_4(100 ml×2) and satd. NaCl (50 ml×3) successively, and dried over anhyd. Na_2SO_4. Filtration and evaporation gave a brown oil, to which was added a mixture of AcOH (80 ml) and 47% HBr (80 ml). The whole was refluxed for 5 hr. and then cooled in an ice bath. H_2O(200 ml) was added to the reaction mixture and extracted with ether (100 ml, 50 ml×2). Ether layer was washed with 5% NaOH (100 ml×3) and satd. NaCl (100 ml×3) successively, and dried over anhyd. Na_2SO_4. After filtration and evaporation *in vacuo*, a brown oil (14.5 g) obtained was submitted to the fractional distillation to give DL–XIa as a colorless oil (12.3 g, 76%), bp 118—120 (17.5 mmHg)(lit.,[16] bp 118—120° (14 mmHg); lit.,[17] bp 115° (14 mmHg); lit.,[18] bp 135—137° (15 mmHg); lit.,[19] bp 111° (10 mmHg)). IR ν_{max}^{Cap} cm^{-1}: 1716, 1605, 753, 735, ,699.

Semicarbazone (DL–XIb) prepared as colorless small needles as usual showed mp114—115° (lit.,[16] mp 112°; lit.,[17] mp 115°. IR ν_{max}^{KBr} cm^{-1}: 3460, 1694, 1649, 1586, 763, 743, 699. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540, 3400, 3380, 1693, 1603, 1563.

S*(+)-3-Methyl-4-phenyl-2-butanone**(S*(+)-XIa**)——*S*(+)–X(bp 146° (8.5 mmHg), α_D^{21} +1.939° (*l*=0.1, neat), optical purity 74%[27]) (11.5 g, 0.070 mole) was treated with $SOCl_2$ (16.7 g, 0.140 mole) as same as DL–X to give crude acid chloride as a pale yellow oil (12.5 g). On the other hand, to a suspension of Mg (2.2 g, 0.091 atom) in ether (50 ml) was added an ether solution (30 ml) containing MeI (12.9 g, 0.091 mole) dropwise during 20 min under stirring in ice bath. After stirring was contineued for 2 hr at room temperature, $CdCl_2$ (8.3 g, 0.045 mole) was added to the reaction mixture and the whole was stirred at room temperature for another 2 hr. Solution of the acid chloride prepared above in ether (40 ml) was added to the solution of dimethyl cadmium for 12 min under ice cooling. The reaction was stirred and refluxed for 3 hr and then kept standing overnight at room temperature. 2N H_2SO_4 (80 ml) was added to the reaction mixture and the organic layer was isolated. Aqueous layer was further extracted with ether (40 ml), and the combined ether layers were washed with satd. NaCl (50 ml×4), 5% Na_2CO_3 (50 ml), and then satd. NaCl (50 ml ×4) successively and dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave a yellow oil (9.8 g), which was submitted to the fractional distillation to afford a colorless oil (4.7 g), bp ~98° (7 mmHg), $[\alpha]_D^{15}$ +2.206° (*l*=0.1, neat). This oil was purified using silica gel column chromatography (100 g, solvent; hexane–AcOEt 96:4) to give crude *S*(+)–XIa as a colorless oil, fractionation of which afforded pure *S*(+)–XIa as a colorless oil (2.9 g, 26%), bp 108—110° (11.5 mmHg), α_D^{13}+2.442° (*l*=0.1, neat), $[\alpha]_D^{14}$ +32.9° (*c*=4.990, benzene). IR ν_{max}^{Cap} cm^{-1}: 1712, 1603, 752, 735, 699. This infrared spectrum was identical with that of DL–XIa in the same state. Optical rotatory dispersion measurements were performed on the speciman of *S*(+)–XIa showing bp 103—104° (13 mmHg), α_D^{30} +2.850° (*l*=0.1, neat), $[\alpha]_D^{30}$ +38.9° (*c*=4.238, benzene), prepared from *S*(+)–X, bp 144—146.5° (7.5 mmHg), α_D^{24} +2.209° (*l*=0.1, neat), optical purity 84%.[27]

$[M]^{29.5}$ (*c*=0.230, MeOH) (mμ): +40.8° (700), +63.5° (589), +98.6° (500), +138° (450), +212° (400), +450° (350), +1550° (305, positive max.), +1370° (300), 0° (286), −1980° (264, negative max.), −1620° (240, positive max.), −2820° (220).

$[M]^{34.5}$ (*c*=0.346, benzene) (mμ): +39.8° (700), +61.0° (589), +98.3° (500), +136° (450), +206° (400), +426° (350), +1240° (317, positive max.), +1170° (312 ,negative max.), +1240° (308, positive max.), +679° (300), 0° (293), −796° (282).

Semicarbazone (*S*(+)–XIb) was prepared as colorless plates from *S*(+)–XIa showing α_D^{13} +2.442° (*l*=0.1, neat), mp 97—102.5° (recrystallized from hexane–AcOEt), $[\alpha]_D^{20}$ +31.4° (*c*=0.726, EtOH). *Anal.* Calcd. for $C_{12}H_{17}ON_3$: C, 65.79; H, 7.80; N, 19.31. Found: C, 65.72; H, 7.81; N, 19.16. IR ν_{max}^{KBr}cm^{-1}: 3460, 1696, 1586, 764, 741, 699. This infrared spectrum was different from that of DL–XIb in a solid state. IR $\nu_{max}^{CHCl_3}$ cm^{-1}; 3530, 3410, 3380, 1692, 1603, 1562. This infrared spectrum was superimposable with that of DL–XIb in $CHCl_3$ solution. Optical rotatory dispersion measurement: $[M]_D^{20}$ (*c*=0.200, EtOH) (*mμ*): +37.3° (700), +61.3° (589), +98.5° (500), +129° (450), +184° (400), +305° (350), +603° (300), +3840° (249).

DL-3-Methyl-4-phenyl-2-butanone Dimethylhydrazone (**DL-XIII**)——A mixture of DL–XIa (3.0 g, 0.019 mole) and N,N–dimethylhydrazine (5.6 g, 0.093 mole) was refluxed for 6 hr in a sealed tube.[3] Addition

of benzene (25 ml) to the reaction mixture and evaporation to dryness was repeated three times to give a yellow oil, which was submitted to the fractional distillation to afford DL-XIII as a pale yellow oil (3.5 g, 91%), bp 105—106.5° (5 mmHg). Redistillation gave DL-XIII as pale yellow oil, bp 100° (4 mmHg). *Anal.* Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.58; H, 9.70; N, 13.71. IR ν_{max}^{Cap} cm^{-1}: 2810, 2770, 1630, 1605, 739, 699. NMR (60 Mc, in CCl_4, TMS internal standard): 9.00 τ (3H, multiplet, $\underline{CH_3}$–CH–C(=N)–$\underline{CH_3}$) 8.24 τ (3H, singlet, –C(=N)–$\underline{CH_3}$), 7.74 τ (6H, singlet, –N($\underline{HC_3}$)$_2$), 7.62—7.06 τ (3H, multiplet, C_6H_5–$\underline{HC_2}$–$\underline{HC}$–), 2.91 τ (5H, singlet, benzene ring). Gas chromatographic analysis was performed on crude DL-XIII and only two peaks (retention time: 2.2 min and 3.6 min) were identified. The former peak was confirmed to be DL-XIa and the latter DL-XIII (10% SE-30 on Diasolide L, 2 m, 163°).

***S*(+)-3-Methyl-4-phenyl-2-butanone Dimethylhydrazone(*S*(+)-XIII)**——*S*(+)-XIa (bp 108—110° (11.5 mmHg), α_D^{13} +2.442° (l=0.1, neat)) (2.5 g, 0.016 mole) was treated similarly to the case of DL-XIa to give a yellow oil, but in this case the reflux with N,N-dimethylhydrazine in a sealed tube was repeated again. The yellow oil obtained was submitted to the fractional distillation to afford *S*(+)-XIII as a nearly colorless oil (2.9 g, 92%), bp 105—106° (6 mmHg), α_D^{17} +2.728 °(l=0.1, neat). *Anal.* Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 75.78; H, 9.74; N, 13.45. IR ν_{max}^{Cap} cm^{-1}: 2810, 2770, 1630, 1603, 738, 698. No absorbtion was observed at near 1715 cm^{-1}. This infrared spectrum was nearly identical with that of DL-XIII in the same state.

DL-3-Methyl-4-phenyl-2-butanone Trimethylhydrazoium Iodide (DL-VIII)——Methyl iodide (35.0 g, 0.25 mole) containing DL-XIII (3.5 g, 0.017 mole) was kept standing at room temperature for 3 days,[3] and then evaporated to dryness *in vacuo* to give a yellowish brown oil, which was triturated with ether (20 ml) to afford crude DL-VIII as an amorphous pale yellow powder (5.3 g, 89%), mp 99.5—103.5° (partial decomp.) (sintered at *ca.* 75°). IR ν_{max}^{KBr} cm^{-1}: 1642, 1603, 1455, 742, 734, 699. All recrystallizations attempted under various conditions were unsuccessful.[21]

To crude DL-VIII thus obtained (1.0 g, 0.0029 mole) was added a mixture of conc. HCl and H_2O (1:2) (60 ml), and the whole was refluxed for 30 min to afford DL-XIa in a 72% yield. On the other hand, when a mixture of 10% HCl and EtOH (1:4) (50 ml) was used as solvent and the reflux was continued for 4 hr, DL-XIa was recovered in a 98% yield. And then dissolving DL-VIII (0.50 g, 0.0015 mole) in 10% aqueous HCl (20 ml) and extracting the aqueous layer with ether (20 ml×4) gave DL-XIa in a 89% yield. DL-XIa obtained in several hydrolytic experiments was identified respectively with the infrared spectra and as its semicarbazone.

***S*(+)-3-Methyl-4-phenyl-2-butanone Trimethylhydrazonium Iodide (*S*(+)-VIII)**——*S*(+)-XIII (bp 105—106° (6 mmHg), α_D^{17} +2.728° (l=0.1, neat) (2.8 g, 0.014 mole) was treated as same as DL-XIII to afford crude *S*(+)-VIII as an amorphous yellow powder (4.3 g, 91%), mp 93—108° (partial decomp.), $[\alpha]_D^{18}$ +16.1° (c=1.120, MeOH), $[\alpha]_D^{15}$ +14.5° (c=1.242, EtOH). IR ν_{max}^{KBr} cm^{-1}: 1641, 1603, 741, 733, 699. This infrared spectrum was nearly equal to that of DL-VIII in a solid state. This sample was used immediately for the next base-induced rearrangement.

Hydrolysis of *S*(+)-3-Methyl-4-phenyl-2-butanone Trimetylhydrazoium Iodide(*S*(+)-VIII)—— 10% HCl (20 ml) containing *S*(+)-VIII (mp 93—108° (partial decomp.), $[\alpha]_D^{18}$+16.1° (c=1.120, MeOH), (0.50 g, 0.0015 mole) was extracted with ether (20 ml×4). The combined ether layer was washed with dil. $Na_2S_2O_3$ solution (20 ml×2), satd. NaCl (20 ml×3) and dried with anhyd. Na_2SO_4. Filtration and evaporation gave crude *S*(+)-XIa as a pale yellow oil (0.18 g, 77%), which was purified with silica gel column chromatography (10 g, solvent: hexane–AcOEt 96:4) to afford *S*(+)-XIa as a nearly colorless oil (0.09 g, 38%), $[\alpha]_D^{15}$ +19.0° (c=1.380, benzene). Infrared spectrum of *S*(+)-XIa thus obtained measured in capillary was superimposable with that of the authentic DL-XIa. *S*(+)-XIa whose optical purity is 74% showed $[\alpha]_D^{14}$ +32.9° (c=4.990, benzene), so the optical purity of *S*(+)-XIa recovered from *S*(+)-VIII could be calculated to be 43%. Since next experiment disclosed that *S*(+)-XIa could be recovered with 94% retention of the optical activity, the optical purity of *S*(+)-VIII showing $[\alpha]_D^{15}$ +16.1° (MeOH) was assumed to be 46%.

Semicarbazone (*S*(+)-XIb) was obtained as a colorless powder from *S*(+)-XIa prepared above, mp 112—114.5°, $[\alpha]_D^{20}$ +5.7° (c=0.14, EtOH).[33] Infrared spectrum of this *S*(+)-XIb was identical with that of DL-XIb in a solid state.

Racemization of *S*(+)-3-Methyl-4-phenyl-2-butanone(*S*(+)-XIa)——*S*(+)-XIa (bp 103—104.5° (13 mmHg), α_D^{30} +2.850° (l=0.1, neat), $[\alpha]_D^{30}$ +38.9° (c=4.238, benzene)) (0.50 g. 0.0031 mole) was dissolved in ether (20 ml) and the ether layer was extracted with 10% HCl (20 ml×4), washed with satd. NaCl (20 ml×3), and dried over anhyd. Na_2SO_4. Filtration and evaporation gave *S*(+)-XIa as a colorless oil (0.45 g, 95%), $[\alpha]_D^{28}$ +36.6° (c=6.148, benzene). From the result obtained, the racemization which occurred in this procedure can be calculated to be 6%. Semicarbazone(*S*(+)-XIb) was prepared from this sample, mp 98.5—101°,

33) This optical activity was calculated from the optical rotatory dispersion chart.

$[\alpha]_D^{23}$ +35.5° (c=1.088, EtOH). Mixed melting point with the authentic $S(+)$–XIb (mp 97.5—100°) showed no depression (mp 97.5—100°). Infrared spectrum of this sample was superimposable with that of the authentic $S(+)$–XIb in a solid state.

N-Phthaloyl-DL-α-methylphenylalanine (DL-XIV)——A mixture of DL–XII (3.0 g, 0.017 mole) and phthalic anhydride (3.0 g, 0.020 mole) was heated at 180—200° on an oil bath for 30 min.[23] Additional amount of phthalic anhydride (0.50 g) was added to the reaction mixture after 10 min heating. After cooled, MeOH (20 ml) was added to the reaction mixture and the whole was refluxed for a short time. Undissolved materials were filtered off and washed with MeOH (3 ml). The combined filtrate and washings were concentrated to *ca.* 20 ml *in vacuo*. H_2O (15 ml) was added to the methanolic solution, and the whole was kept standing at room temperature for 2 days after seeded. Additional H_2O (5 ml) was added to the methanolic solution, which was kept standing in an ice bath for 4 hr. Colorless crystals precipitated was collected and dried (2.9 g, 56%), mp 157—163°. Successive recrystallizations from MeOH–H_2O, AcOH–Ac_2O, and MeOH–H_2O (×2) afforded pure DL–XIV as colorless crystals, mp 168.5—170.5°. *Anal.* Calcd. for $C_{18}H_{15}O_4N$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.16; H, 4.82; N, 4.75. IR ν_{max}^{KBr} cm^{-1}: 1770, 1739, 1691, 1604, 779, 716.

(+)-N-Phthaloyl-*R*-α-methylphenylalanine(*R*(+)-XIV)——*R*(+)–XV[11] (mp 200.5—201.5°, $[\alpha]_D^{12}$ +86.8° (c=0.922, MeOH)) (7.2 g, 0.033 mole) was added to 10% HCl (144 ml) and the mixture was refluxed for 3 hr. The aqueous solution was evaporated to dryness. To the residue was added H_2O (30 ml) and the evaporation was repeated again. Crude *R*–α–methylphenylalanine hydrochloride obtained as white solid was converted to free *R*–α–methylphenylalanine (*R*–XII) using ion exchange resin, Amberlite IR–120 (H^+ form, 300 ml), as usual. *R*–XII (5.3 g, 0.030 mole) obtained above was treated similarly to the case of DL–XII[23] to give crude *R*(+)–XIV (6.3 g, 63% from *R*(+)–XV), mp 191.5—193.5°, $[\alpha]_D^{13}$ +178° (c=0.586, MeOH). After treated with charcoal, crude *R*(+)–XIV was recrystallized several times from MeOH–H_2O (×4) to give pure *R*(+)–XIV as colorless prisms, mp 194.5—195°, $[\alpha]_D^{13}$+182° (c=0.626, MeOH). *Anal.* Calcd. for C_{18}-$H_{15}O_4N$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.91; H, 4.92; N, 4.53. IR $\nu_{max}^{KBr}$$cm^{-1}$: 1767, 1745, 1695, 775, 715, 703. This infrared spectrum was different from that of DL–XIV in a solid state.

DL-3-Amino-3-methyl-4-phenyl-2-butanone (DL-IXa)——A mixture of $SOCl_2$ (23.8 g, 0.200 mole) and DL–XIV (12.3 g, 0.040 mole) was refluxed for 30 min and evaporated to dryness *in vacuo*. To the residue was added benzene (30 ml) and evaporated to dryness to give a pale yellow oil. This procedure was repeated five times to remove $SOCl_2$ completely. To ether solution (30 ml) of magnesium ethoxide prepared from Mg (1.2 g, 0.048 atom) and ethanol (50 ml) as same as in the case of DL–XIa was added ether solution (30 ml)of diethyl malonate (7.7 g, 0.048 mole), and the whole was refluxed under stirring fof 3 hr, to which was added the benzene solution (60 ml) of the pale yellow oil obtained above. Reflux and stirring was continued for 8 hr, and 1N H_2SO_4(60 ml) was added to the reaction mixture. The organic layer was separated, washed with satd. NaCl (50 ml×3), and evaporated to dryness *in vacuo* to afford a pale yellow viscous oil, to which were added AcOH (60 ml) and 47% HBr (60 ml). The whole was refluxed for 4 hr and concentrated to *ca.* 60 ml. After cooled, the precipitates were filtered off and washed with H_2O (60 ml). Combined filtrate and washings were extracted with ether (60 ml×3), made alkaline with conc. NaOH solution, and then extracted with ether (60 ml×3). Ether layer was washed with satd. NaCl (60 ml×3) and dried over anhyd. K_2CO_3. Filtration and evaporation under N_2 atmosphere gave a pale brown oil (4.4 g), which was submitted to the fractional distillation under N_2 atmosphere to afford DL–IXa as a colorless oil (3.8 g, 54%), bp 121—122° (6.5 mmHg). IR ν_{max}^{Cap} cm^{-1}: 3365, 3300, 1711, 1605, 1596, 749, 702. After kept standing at room temperature for several months, this oil solidified gradually. Several recrystallizations from ethyl acetate gave colorless prisms showing mp 175—177°, which seemed to be 2,5–dimethyl–2,5–(1–methyl–2–phenylethyl)–2,5–dihydropyrazine from the elemental analyses and spectral data. *Anal.* Calcd. for $C_{22}H_{26}N_2$: C, 82.97; H, 8.23; N, 8.80. Found: C, 83.07; H, 8.14; N, 8.57. IR ν_{max}^{KBr} cm^{-1}: 1662, 1603, 769, 731, 700.

DL–IXa was identified as hydrochloride (DL–IXd), colorless crystals, mp 211.5—213.5° (from EtOH–ether). *Anal.* Calcd. for $C_{11}H_{15}ON$–HCl: C, 61.82; H, 7.55; N, 6.55. Found: C, 61.65; H, 7.62; N, 6.70. IR ν_{max}^{KBr} cm^{-1}: 3400, 2850, 1720, 1588, 1510, 752, 705.

***R*(+)-3-Amino-3-methyl-4-phenyl-2-butanone(*R*(+)-IXa)**——*R*(+)–XIV (mp 193.5—194.5°, $[\alpha]_D^{13}$ +178° (c=0.586, MeOH)) (5.5 g, 0.018 mole) was treated in the same manner as DL–XIV to give *R*(+)–IXa as a colorless oil (1.5 g, 51%), bp 123—127° (8.5 mmHg), α_D^{12} +0.194° (l=0.1, neat). IR ν_{max}^{Cap} cm^{-1}: 3370, 3300, 1712, 1605, 1496, 750, 703. This infrared spectrum was identical with that of DL–IXa. Hydrochloride (*R*(−)–IXd) was prepared as usual, colorless crystals, mp 188—190° (partial decomp.), $[\alpha]_D^5$ −53.5° (c=0.568, EtOH). *Anal.* Calcd. for $C_{11}H_{15}ON$–HCl: C, 61.82; H, 7.55; N, 6.55. Found: C, 61.65; H, 7.56; N, 6.65. IR ν_{max}^{KBr} cm^{-1}: 3130, 2860, 1723, 1605, 1513, 756, 704. This infrared spectrum was different from that of DL–IXd in the same state.

DL-3-Acetamido-3-methyl-4-phenyl-2-butanone(DL-IXb)——A mixture of DL–IXa (1.0 g, 0.0057 mole) and Ac_2O (10 ml) in pyridine (10 ml) was kept standing at room temperature for 2 days, and poured onto a mixture of ice and water. After kept standing at room temperature for 5 hr, the whole was extracted with ether (50 ml×4). Ether layer was washed successively with 10% HCl (50 ml×1), satd. NaCl (50 ml ×3), 10% Na_2CO_3 (50 ml×2), and satd. NaCl (50 ml×2), and dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave crude DL–IXb as a white solid (0.96 g, 77%), mp 138—139°. Several recrystal-

lizations from AcOEt–hexane afforded pure DL–IXb as colorless needles, mp 138.5—139.5°. *Anal.* Calcd. for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.82; N, 6.39. Found: C, 70.94; H, 7.92; N, 6.33. IR ν_{max}^{KBr} cm^{-1}: 3250, 1750, 1640, 1549, 728, 706. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 3380, 1714, 1665, 1498, NMR (60 Mc, solvent $CDCl_3$, TMS internal standard): 8.69 τ (3H, singlet, $-\underset{|}{\overset{|}{C}}-\underline{CH_3}$), 8.11 τ (3H, singlet, $-NH-CO-\underline{HC_3}$),[34] 7.84 τ (3H, singlet, $-\underset{|}{\overset{|}{C}}-CO-\underline{CH_3}$),[34] 6.80 τ (2H, singlet, $C_6H_5-\underline{CH_2}-\underset{|}{\overset{|}{C}}-$), 3.34 τ (1H, singlet, $-\underline{NH}-$), 2.62 τ (5H, multiplet, benzene ring).

***R*(+)-3-Acetamido-3)-methyl-4-phenyl-2-butanone(*R*(+)-IXb)**——*R*(+)–IXa (bp 123—127° (8.5 mmHg), α_D^{12} +0.194° (l=0.1, neat)), (0.90 g, 0.0051 mole) was treated as same as DL–IXa to afford crude *R*(+)–IXb as white solid (0.84 g, 76%), mp 126.5—128.5°, $[\alpha]_D^{17}$ +162° (c=0.764, MeOH). Several recrystallizations from AcOEt–hexane gave pure *R*(+)–IXb as colorless needles, mp 127—128.5°, $[\alpha]_D^{21}$ +164° (c=0.708, MeOH). *Anal.* Calcd. for $C_{13}H_{17}O_2N$: C, 7.120; H, 7.82; N, 6.39. Found: C, 71.22; H, 7.88; N, 6.46. IR ν_{max}^{KBr} cm^{-1}: 3270, 1722, 1637, 1550, 723, 697.

This spectrum was different from that of DL–IXb in a solid state. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430, 3390, 1717, 1668, 1503. This infrared spectrum was identical with that of DL–IXb in $CHCl_3$ solution. Optical rotatory dispersion measurement; $[M]^{11}$ (c=0.146, MeOH) (mμ): +300° (700), +390° (589), +571° (500), +780° (450), +1020° (400), +1590° (350), +2740° (300), +4800° (270).

DL-3-Benzamido-3-methyl-4-phenyl-2-butanone(DL-IXc)——A mixture of DL–IXa (2.0 g, 0.011 mole) and benzoyl chloride (2.4 g, 0.017 mole) in pyridine (20 ml) was treated similarly to the case of DL–IXb to give crude DL–IXc as a pale yellow solid (3.0 g, 94%), mp 139—140.5°. Several recrystallizations from AcOEt–hexane afforded pure DL–IXc as colorless needles, mp 140.5—142°. *Anal.* Calcd. for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.80; H, 6.98; N, 4.97. IR ν_{max}^{KBr} cm^{-1}: 3340, 1716, 1631, 1603, 1577, 1533, 724, 715, 702, 690. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 3390, 1716, 1658, 1603, 1581, 1510. NMR (60 Mc, solvent $CDCl_3$, TMS internal standard): 8.48 τ (3H, singlet, $-\underset{|}{\overset{|}{C}}-\underline{HC_3}$), 7.74 τ (3H, singlet, $-CO-\underline{CH}$), 6.62 τ (2H, quartet, J_{AB}=13.8 cps, $C_6H_5-\underline{CH_2}-\underset{|}{\overset{|}{C}}-$), 3.13—2.19 τ (11H, multiplet, 2 benzene rings and $-N\underline{H}-$).

***R*(+)-3-Benzamido-3-methyl-4-phenyl-2-butanone(*R*(+)-IXc)**——*R*(+)–IXa (bp 123—127° (8.5 mmHg), α_D^{12} +0.194° (l=0.1, neat)) (0.30 g, 0.0017 mole) was treated in the same way as DL–IXa to give crude *R*(+)–IXc as yellow solid (0.43 g, 91%), mp 129—132°, $[\alpha]_D^{18}$ +152° (c=0.968, MeOH). Several recrystallizations from EtOAc–hexane afforded pure *R*(+)–IXc as colorless pillars, mp 132.5—133.5°, $[\alpha]_D^{12}$ +167° (c=0.444, MeOH). *Anal.* Calcd. for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.87; H, 6.79; N, 4.73. IR ν_{max}^{KBr} cm^{-1}: 3400, 1728, 1649, 1603, 1579, 1522, 717. This infrared spectrum was different from that of DL–IXc in a solid state. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425, 3380, 1718, 1660, 1604, 1581, 1510. This infrared spectrum was superimposable with that of DL–IXc in $CHCl_3$ solution.

Base-induced Rearrangement of DL-3-Methyl-4-phenyl-2-butanone Trimethylhydrazonium Iodide (DL-VIII)——a) (Table 1, run 2) A mixture of DL–VIII (2.0 g, 0.0058 mole) and NaH (a 50% NaH oil dispersion) (1.5 g, 0.031 mole) in EtOH (150 ml) and dimethyl sulfoxide (15 ml) was refluxed for 6 hr, and concentrated to *ca.* 20 ml under reduced pressure after kept standing overnight at room temperature. H_2O (100 ml) was added to the residual solution and extracted with a mixture of ether and benzene (1:1) (50 ml×3). Aqueous layer was named (fraction A).

Organic layer was washed with H_2O (50 ml×3) and then evaporated to dryness *in vacuo* to give pale yellow oil, to which was added EtOH (40 ml) and conc. HCl (12 ml). The whole was refluxed for 30 min, and H_2O (150 ml) was added to the reaction mixture, which was extracted with ether (50 ml×3). Ether layer was washed with satd. NaCl (50 ml×3) and dried over anhyd. Na_2SO_4. Filtration and evaporation to dryness gave a yellow oil (1.07 g), which was named (fraction B).

Aqueous layer giving (fraction B) was made alkaline with 50 w/w% NaOH and extracted with ether (50 ml×3). Ether layer was washed with satd. NaCl (50 ml×3) and dried over andyd. K_2CO_3. Filtration and evaporation *in vacuo* under N_2 atmosphere gave a pale yellow oil (0.40 g), which was named (fraction C).

(Fraction A) Conc. HCl (20 ml) was added to the aqueous solution and the whole was refluxed for 30 min, and extracted with ether (30 ml×3). The ether layer was washed with *ca.* 10% $Na_2S_2O_3$ (30 ml×3) and satd. NaCl (30 ml×3), and dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave a trace oil, which showed the presence of a small amount of DL–XIa on the thin-layer chromatography (silica gel, solvent hexane–AcOEt 4 ml: 10 drops, *Rf* value 0.25).

(Fraction B) Yellow oil was submitted to the silica gel column chromatography (30 g, solvent hexane–AcOEt 96:4) to afford DL–XIa as a nearly colorless oil (0.30 g, 32%), which was identified with the infrared spectrum and as its semicarbazone (DL–XIb), mp 114—115°.

34) These assignments could be attainable by the comparison of the NMR spectrum of DL–IXb with that of DL–IXc. However, the possibility of the interconversion of the assignments for the signal 8.11τ and 7.84τ can not be excluded.

(Fraction C) Pale yellow oil was acetylated using pyridine (4 ml) and Ac_2O (4 ml) similarly to the case of DL–IXb to afford crude DL–IXb as a white solid (0.32 g, 25%), mp 134—137.5°. The infrared spectrum of this sample was identical with that of the authentic DL–IXb in a solid state. One recrystallization from AcOEt–hexane gave pure DL–IXb as colorless needles (0.26 g, 21%), mp 138—139.5°. Mixed melting point with the authentic DL–IXb (mp 138.5—139.5°) showed no depression (mp 138.5—139.5°). The infrared and NMR spectra of this sample were identical with those of the authentic DL–IXb measured in the same states.

b) (Table 1, run 4) A mixture of DL–VIII (2.0 g, 0.0058 mole) and NaH (a 50% NaH oil dispersion) (0.28 g, 0.0058 mole) in dioxane (150 ml) and EtOH (5 ml) was refluxed for 6 hr, and then treated similarly to the case of a) to give three fractions:

(Fraction A) Aqueous layer was treated as same as in the case of a) to give a trace brown oil. Thin-layer chromatography (silica gel, solvent:hexane–$CHCl_3$ 1:1, *Rf* value 0.35) of this oil showed that this oil contained very small amount of DL–XIa.

(Fraction B) Reddish brown oil (0.70 g) obtained was purified with the silica gel column chromatography (30 g, solvent:hexane–$CHCl_3$ 1:1) to afford DL–XIa as an orange oil (0.23 g, 25%), which was identified using infrared spectrum and as its semicarbazone (DL–XIb), mp 113—114.5°.

(Fraction C) Orange oil (0.24 g) was acetylated with pyridine and acetic anhydride similarly to the case of a) and the neutral fraction extracted gave an orange oil (0.20 g). This oil showed several spots on thin-layer chromatography (silica gel, solvent:hexane–AcOEt 1:1), one of which seemed to be DL–IXb judging from its *Rf* value (0.25). The column chromatography of this oil using silica gel (20 g, solvent:hexane–AcOEt 1:1) gave crude DL–IXb as a pale yellow solid (0.05 g, $<4\%$), which was identified from the infrared spectrum and thin-layer chromatography (silica gel, solvent:hexane–AcOEt 1:1, *Rf* value 0.2).

c) (Table 2, run 6) A mixture of DL–VIII (2.0 g, 0.0058 mole) and Et_3N (3.5 g, 0.035 mole) in EtOH (150 ml) and dimethyl sulfoxide (15 ml) was refluxed for 6 hr, and then treated similarly to the case of a) to give three fractions:

(Fraction A) To the aqueous layer was added conc. HCl (20 ml) and the whole was refluxed for 30 min. The same treatment as in the case of a) gave a reddish brown oil (0.86 g), which was purified with the silica gel column chromatography (30 g, solvent: benzene) to give crude DL–XIa as a pale yellow oil (0.09 g, 10%), DL–XIa thus obtained was identified with the infrared spectrum and the thin-layer chromatography (silica gel, solvent:benzene, *Rf* value 0.4).

(Fraction B) The thin-layer chromatography (silica gel, solvent:hexane–AcOEt 4 ml: 8 drops, *Rf* value 0.25) of the residual oil (0.09 g, 10%) showed that it contained DL–XIa mainly, which was identified as its seimcarbazone (DL–XIb), mp 109.5—111°.

(Fraction C) This fraction was too little to study further.

Base-induced Rearrangement of *S*(+)-3-Methyl-4-phenyl-2-butanone Trimethylhydrazonium Iodide (*S*(+)-VIII)——a) (Table 2, run 9) A mixture of *S*(+)–VIII (mp 93—108°, $[\alpha]_D^{18}$ +16.1° (*c*=1.120, MeOH)) (1.8 g, 0.0052 mole) and NaH (a 50% NaH oil dispersion) (0.25 g, 0.0052 mole) in EtOH (135 ml) and dimethyl sulfoxide (13.5 ml) was refluxed for 6 hr. After kept standing overnight at room temperature, the reaction mixture was concentrated to *ca.* 20 ml. H_2O (100 ml) was added to the residual oil and the whole was extracted with a mixture of benzene and ether (1:1) (50 ml×3). Aqueous layer was named (fraction A).

Organic layer was washed with H_2O (50 ml×3), and then extracted with 10% HCl (50 ml×4).[35] Ether layer was washed with satd. NaCl (50 ml×3), and dried with anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave an orange oil (0.50 g), which was named (fraction B).

Combined 10% HCl extracts were made alkaline (pH>11) with 50 w/w% NaOH and extracted with ether (50 ml×3). Ether extract was washed with satd. NaCl (50 ml×3) and dried over anhyd. K_2CO_3. Filtration and evaporation under N_2 atmosphere to give a pale yellow oil (0.34 g), which was named (fraction C).

(Fraction A) Conc. HCl (30 ml) was added to the aqueous layer and the whole was extracted with ether (50 ml×4). The ether layer was washed successively with satd. NaCl (50 ml×1), diluted. $Na_2S_2O_3$ (50 ml×1) and satd. NaCl (50 ml×3), and dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* afforded very small amount of yellow oil, which appeared to contain a small amount of XIa from its thin-layer chromatography (silica gel, solvent: hexane–AcOEt 4 ml: 8 drops, *Rf* value 0.2).

(Fraction B) This oil was purified using silica gel column chromatography (30 g, solvent:hexane–AcOEt 96:4) to afford *S*(+)–XIa as a colorless oil (0.23 g, 27%), whose infrared spectrum was identical with that of the authentic DL–XIa. Optical rotatory dispersion measurement: $[M]^{16.5}$ (*c*=2.866, benzene) (*mμ*): +1.3° (700), +2.3° (589), +3.6° (500), +5.0° (450), +7.8° (400), +15.4° (350), +37.4° (320), +56.5° (307). Semicarbazone(*S*(+)–XIb) obtained as colorless crystals after one recrystallization from H_2O–EtOH showed mp 113.5—114.5°. The infrared spectrum of this sample was superimposable with that of the authentic

35) Racemization considered to occur in this procedure seems to be 6% from the control experiment (*loc. cit.*).

DL–XIb in a solid state. Optical rotatory dispersion measurement: $[M]^{17.5}$ (c=1.730, EtOH) (mμ): +2.0° (700), +2.6° (589), 3.5° (500), +4.6° (450), +6.8° (400), +9.6° (350), +11.6° (338).

(Fraction C) This oil was treated as same as in the case of run 2 to give crude IXb as a pale yellow solid (0.32 g, 28%), mp 132.5—138°, which was purified twice using the silica gel column chromatography (solvent:hexane–AcOEt 1: 1) to afford pure IXb as a pale yellow solid (0.14 g, 13%), mp 138—139.5.° Infrared spectrum of this sample was identical with that of the authentic DL–IXb in a solid state. Optical rotatory dispersion measurement: $[M]^{15}$ (c=1.422, MeOH) (mμ): 0° (700—310). Recrystallization from hexane–AcOEt gave DL–IXb as colorless needles, mp 139—140°, which showed no depression (mp 139—140°) on the mixed melting point measurement with the authentic DL–IXb (mp 139—139.5). Infrared spectrum of this sample was superimposable with that of the authentic DL–IXb in a solid state.

b) (Table 2, run 10) A mixture of $S(+)$–VIII (mp 93—108°, $[\alpha]_D^{18}$ +16.1° (c=1.120, MeOH) (1.8 g, 0.0052 mole) and Amberlite IRA–400 (OH^- form) (18.9 g, 0.0624 mole) in EtOH (135 ml) and dimethyl sulfoxide (13.5 ml) was refluxed for 6 hr, and after the resin was filered, the reacton mixture was treated similarly to the case of run 9 to give three fractions.

(Fraction A) The aqueous layer was treated in the same manner as in the case of run 9 to give a trace oil, which showed the presence of a small amount of XIa on the thin layer chromatography (silica gel, solvent: hexane–AcOEt 4 ml: 8drops, Rf value 0.25).

(Fraction B) This oil (0.41 g) was purified by the silica gel column chromatography (30 g, solvent:hexane–AcOEt 96: 4) to afford pure $S(+)$–XIa as pale yellow oil (0.23 g, 27%), which showed the same infrared spectrum as that of the authentic DL–XIa in the same state. Optical rotatory dispersion measurement: $[M]^{18}$ (c=3.530, benzene) (mμ): +1.1° (700), +1.6° (589), +2.6° (500), +3.7 (450) +5.5° (400), +11.2° (350), +13.6° (342). Semicarbazone ($S(+)$–XIb) was obtained as white crytsals after one recrystallization from H_2O–EtOH, mp 115—116°. The infrared spectrum of this sample was superimposable with that of the authentic DL–XIa. Optical rotatory dispersion measurement: $[M]^{16}$ (c=1.22, EtOH): 0° (700), 0° (589), +2.5° (500), +2.5° (450), +3.1° (400), +6.5° (350), +10.3° (320).

(Fraction C) Pale yellow oil (0.24 g) was treated as same as in the case of run 9 to give crude IXb as a pale yellow solid (0.20 g, 18%), which was purified using the silica gel column chromatography (solvent:hexane–AcOEt 1:1) to give pure IXb as nearly colorless solid (0.14 g, 12%), mp 137.5—138.5°. Infrared spectrum of this IXb in a solid state was identical with that of the authentic DL–IXb in the same state. Optical rotatory dispersion measurement: $[M]^{15}$ (c=1.298, MeOH) (mμ): 0° (700—400), $<$+2.0° (400—320). One recrystallizaiton from hexane and AcOEt gave DL–IXb as colorless needles, mp 138.5—139°, which showed no depression (mp 138.5—139°) on the mixed melting point measurement with the authentic DL–IXb (mp 138.5—139°) and the same infrared spectrum as that of the authentic DL–XIb in a solid state.

Acknowledgement The authors are grateful to the members of the Central Analysis Room of this Faculty for elemental analyses and spectral data.