[Chem. Pharm. Bull. 19(2)227—246(1971)]

UDC 547.233.3.04

Stereochemical Studies. VII.[1] Thermal Rearrangement of α-Hydroxyimines to α-Aminoketones using optically Active Open Chain Compounds[2,3]

Hatsuhiko Mizuno, Shiro Terashima and Shun-ichi Yamada

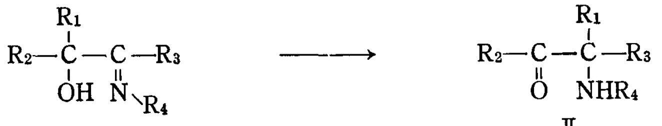
Faculty of Pharmaceutical Sciences, University of Tokyo[4]

(Received March 30, 1970)

Thermal rearrangements of three types of optically active open chain α-hydroxyimines (I) were attempted. In all cases two optically active isomeric α-aminoketones (II) were obtained with almost full retention of optical activity, regardless of the species of the migrated groups in the 38—53% total yield. Stereospecifically, this thermal rearrangement was assumed to proceed *via* the intramolecular cyclic mechanism. The presence of a fragmentation reaction was shown. Thus, the coexistence of cleavage in all carbon–carbon bonds attached to the carbon atom bearing the hydroxy group was demonstrated for the first time.

Preliminary experiments using racemic compounds were also described.

Thermal rearrangement of α-hydroxyimines (I) with tertiary carbinol skeletons to give α-aminoketones (II) is unique for carbon skeletal rearrangement. The first study of this rearrangement was performed by Shoppee and Prins[5] in the steroidal field. This reaction was later extended to become a general reaction in simpler alicyclic[6,7] and aliphatic systems,[7a,b] and is now recognized as a new method for the preparation of α-aminoketones.[7e-g] The mechanism of this rearrangement is thought to be an intramolecular concerted reaction, based on kinetic analysis, characterized by large negative activation entropies in the alicyclic system.[7e] This explanation has not, however, been confirmed by examinations on steroidal α-hydroxyimines.[8]



I

II

The results cited prompted us to investigate the rearrangement using optically active

---

1) Part VI: S. Terashima, M. Wagatsuma and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **18**, 1137 (1970).

2) Presented at the 87th and 89th Annual Meetings of the Pharmaceutical Society of Japan, Kyoto, April 1967, and Nagoya, April 1969.

3) Part of this work has been published as a communication. S. Yamada, H. Mizuno and S. Terashima, *Chem. Comm.*, **1967**, 1058.

4) Location: *Bunkyo-ku, Tokyo.*

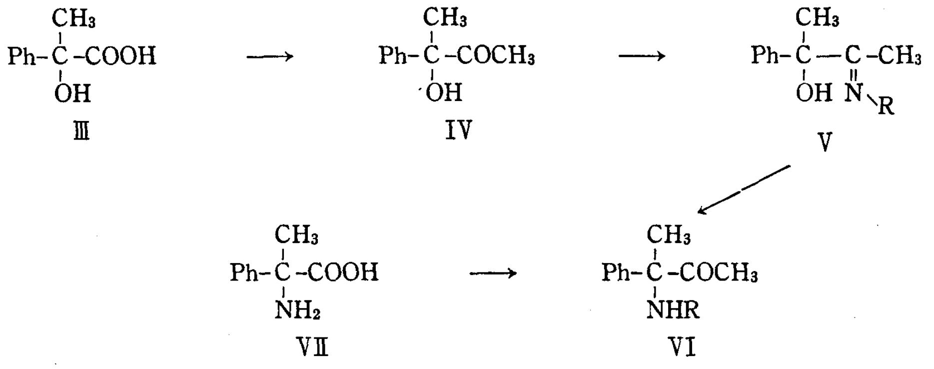
5) *a*) C.W. Shoppee and D.A. Prins, *Helv. Chim. Acta*, **26**, 185 (1943); *b*) *Idem*, *ibid.*, **26**, 201 (1943); *c*) M.W. Goldberg and R. Aeschbacher, *ibid.*, **22**, 1188 (1939); *d*) H.E. Stavely, *J. Am. Chem. Soc.*, **62**, 489 (1940).

6) I. Elphimoff-Felkin, *Bull. Soc. Chim. France*, **1962**, 653.

7) *a*) C.L. Stevens, R.D. Elliott, B.L. Winch and I.L. Klundt, *J. Am. Chem. Soc.*, **84**, 2272 (1962); *b*) C.L. Stevens, R.D. Elliott and B.L. Winch, *ibid.*, **85**, 1464 (1963); *c*) C.L. Stevens, A. Thuillier and F.A. Daniher, *J. Org. Chem.*, **30**, 2962 (1965); *d*) C.L. Stevens, I.L. Klundt, M.E. Munk and M.D. Pillai, *ibid.*, **30**, 2967 (1965); *e*) C.L. Stevens, H.T. Hanson and K.G. Taylor, *J. Am. Chem. Soc.*, **88**, 2769 (1966); *f*) C.L. Stevens, A.B. Ash, A. Thuillier, J.H. Amin, A. Balys, W.E. Dennis, J.P. Dicherson, R.P. Glinski, H.L. Hanson, M.D. Pillai and J.W. Stoddard, *J. Org. Chem.*, **31**, 2593 (1966); *g*) C.L. Stevens, A. Thuillier, K.G. Taylor, F.A. Daniher, J.P. Dickerson, H.T. Hanson, N.A. Nielsen, N.A. Tikotkar and R.M. Weier, *ibid.*, **31**, 2601 (1966).

8) D.F. Morrow, M.E. Brokke, G.W. Moersch, M.E. Butler, C.F. Klein, W.A. Neuklis and E.C.Y. Huang, *J. Org. Chem.*, **30**, 212 (1965).

open chain α-hydroxyimines with no ring system effect and with no asymmetric centers except for the reaction center. Based on the migratory aptitude by which the thermal rearrangement of I gave only a phenyl migrated α-aminoketone in the aliphatic system,[7b] optically active α-hydroxyimines of type V prepared from optically active atrolactic acid (III) whose absolute configuration[9] and optical purity are known, were selected as starting materials. The extent of retention of optical activity and the absolute configuration of α-aminoketone (VI) obtained as a rearrangement product, we compared with those of authentic VI, prepared independently from optically active α-methylphenylglycine (VII) whose absolute configuration had been previously determined.[10]



These examinations provide clear stereochemical evidence for the intramolecular concerted mechanism, even in an aliphatic system, and the applicability of this rearrangement for preparing optically active α-aminoketones.

Result and Discussion

The first substrate selected for thermal rearrangement was 3-benzylimino-2-phenyl-2-butanol (Va). Preliminary experiments on racemic compounds were examined to find the optimal working conditions described in detail in the experimental section. Rearrangement studies using optically active compounds were then carried out following the route shown in in Chart 1 and 2.

Reflux of an ether solution of methyl lithium with the lithium salt of (*S*) (+)-atrolactic acid ((*S*) (+)-III), $[\alpha]_D^{30}$ +45.2° (c=1.93, H_2O), optical purity 81%,[11] obtained from the resolution of (±)-III with (−)α-phenethylamine by the method of Smith,[12] gave (*S*) (+)-3-hydroxy-3-phenyl-2-butanone ((*S*) (+)-IV), $[\alpha]_D^{32.5}$+ 222° (C_6H_6), in a 47% yield. This was condensed with benzylamine to afford (*S*) (+)-3-benzylimino-2-phenyl-2-butanol ((*S*) (+)-Va), α_D^{32} +22.7° (l=0.1, neat), in a 87% yield (Chart 1). Thermal rearrangement of (*S*) (+)-Va was performed under reflux in decalin as shown in Chart 2, giving a mixture of two isomeric α-aminoketones, α_D^{26} −2.97° (l=0.1, neat), which consisted of a desired phenyl migrated product; *i.e.*, (−)-3-benzylamino-3-phenyl-2-butanone ((−)-VIa) and a methyl migrated product, 2-benzylamino-2-methylpropiophenone (VIIIa), in a combined yield of 38% from the basic fraction. Because of an unsuccessful attempt to separate (−)-VIa and VIIIa, the mixture was benzoylated with pyridine-benzoyl chloride to give (+)-N-benzoyl-3-benzylamino-3-

---

9) *a)* K. Freudenberg, J. Todd and R. Seidler, *Ann.*, **501**, 199 (1933); *b)* J.H. Brewster, *J. Am. Chem. Soc.*, **78**, 4061 (1956); D.J. Cram, K.R. Kopecky, F. Hauck and A. Langemann, *ibid.*, **81**, 5754 (1959).

10) H. Mizuno, S. Terashima, K. Achiwa and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 1749 (1967).

11) Maximum optical rotation is $[\alpha]_D^{18}$ +56.0° (c=1.591, H_2O) (see ref. 12), from values reported in the literature, and is assumed to be 100% optically pure. Some temperature differences and the concentration differences at which optical rotation measurements were carried out were neglected.

12) L. Smith, *J. Prakt. Chem.*, [2], **84**, 738 (1911).

phenyl-2-butanone ((+)-IXa), [α]$^{19}_{D}$ +9.19° (EtOH), and N-benzoyl-2-benzylamino-2-methylpropiophenone (Xa), which were isolated by silica gel column chromatography (Chart 2).

To estimate the optical purity of IXa and to establish its absolute configuration, IXa was prepared independently from α-methylphenylglycine (VII) as shown in Chart 3. Esterification of (*R*)(−)-α-methylphenylglycine ((*R*)(−)-VII),[10] [α]$^{19}_{D}$ −89.8° (1N HCl), optical

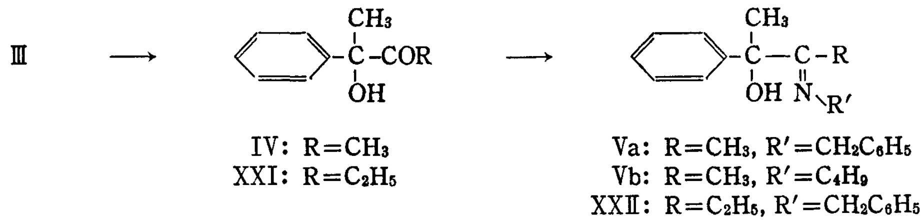
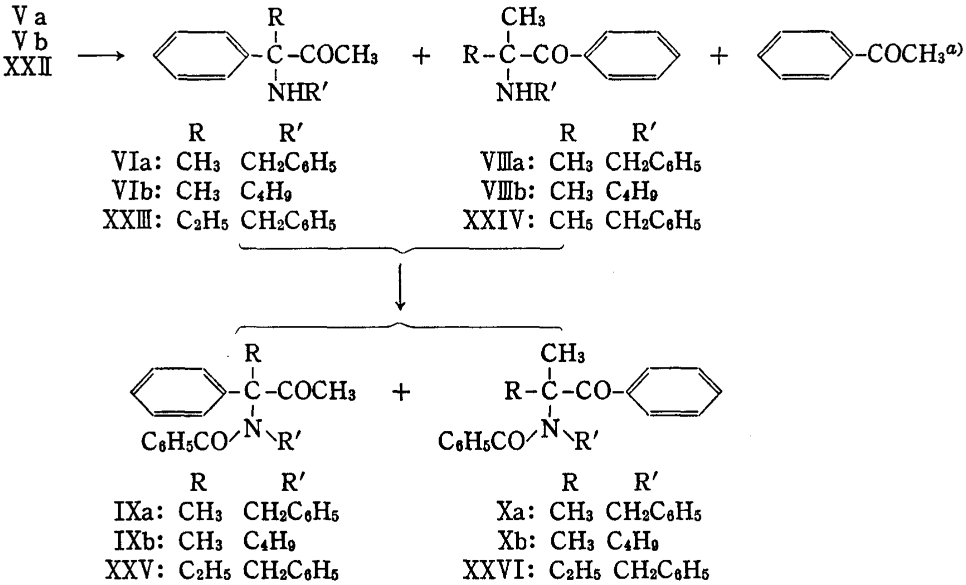


Chart 1



a) Isolation of acetophenone as semicarbazone was examined only in the cases of thermolyses of (±)-Va, (±)-XXII and (*S*)(+)-XXII.

Chart 2

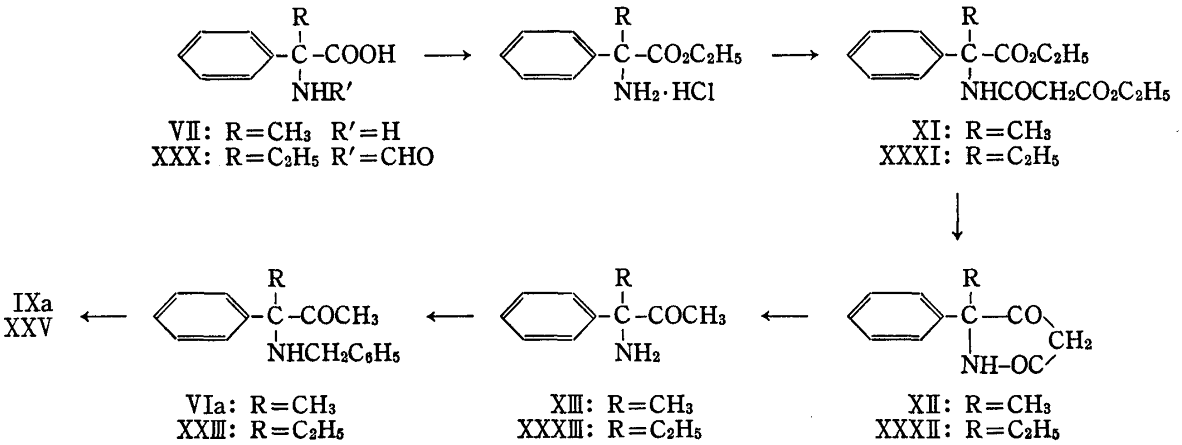


Chart 3

purity 99%,[13] obtained from the resolution of (±)-VII,[14] gave ethyl ester hydrochloride, which was converted to (*R*)(−)-ethyl N-ethoxycarbonylacetyl-α-methylphenylglycinate ((*R*)-(−)-XI), $[\alpha]^{28}_{D}$ −13.1° (EtOH) in a 87% yield based on (*R*)(−)-VII by treatment with triethylamine and ethoxycarbonylacetylchloride. (*R*)(−)-XI was submitted to Dieckman cyclization with sodium methoxide in refluxed benzene and followed by hydrolysis and decarboxylation with KOH in aqueous ethanol giving (*R*)(+)-5-methyl-5-phenylpyrrolidin-2,4-dione ((*R*)(+)-XII), $[\alpha]^{26}_{D}$ +29.8° (C_6H_6), in a 88% yield. Hydrolysis of (*R*)(+)-XII with conc. hydrochloric acid gave (*R*)(−)-3-amino-3-phenyl-2-butanone ((*R*)(−)-XIII), α^{27}_{D} −5.56° (l=0.1, neat), in a 72% yield. This was condensed with benzaldehyde, followed by catalytic hydrogenation on Pd–C affording (*R*)(−)-3-benzylamino-3-phenyl-2-butanone ((*R*)(−)-VIa), α^{24}_{D} −3.73° (l=0.1, neat), in a 57% yield. Benzoylation of (*R*)(−)-VIa gave (*R*)(+)-N-benzoyl-3-benzylamino-3-phenyl-2-butanone ((*R*)(+)-IXa), $[\alpha]^{11}_{D}$ +11.2° (EtOH). The (*R*)(+)-IXa obtained was identified with (+)-IXa, prepared by thermal rearrangement, from its infrared (IR) and nuclear magnetic resonance (NMR) spectra, by elemental analysis and by thin–layer chromatography.

Thus, the absolute configuration (+)-IXa obtained from thermal rearrangement was demonstrated to have (*R*)-configuration. Comparing optical purity of the authentic (*R*)(+)-IXa prepared from (*R*)(−)-VII with that of (*R*)(+)-IXa obtained by thermal rearrangement followed by benzoylation, we concluded that in this phenyl migration reaction (*R*)(−)-VIa was obtained from (*S*)(+)-Va with 100% retention of optical activity, based on the optical purities of (*S*)(+)-III and (*R*)(−)-VII, since purification of each compound through these reaction sequences was performed by column chromatography or distillation, not by recrystallization.

Next, independent sysnthesis of authentic N-benzoyl-2-benzylamino-2-methylpropiophenone (Xa), methyl migrated product, from α-aminoisobutyric acid (XIV) was undertaken as shown in Chart 4. From α-phthalimido isobutyric acid (XV) obtained in a 63% yield by the treatment of XIV with phthalic anhydride, 2-amino-2-methylpropiophenone (XVI) was prepared in a 25% yield according to the reported method.[15] XVI was treated as the same as (*R*)(−)-XIII to afford 2-benzylamino-2-methylpropiophenone (VIIIa) in a 50% yield. Authentic N-benzoyl-2-benzylamino-2-methylpropiophenone (Xa) prepared by benzoylation of VIIIa was identified with Xa obtained by rearrangement of (*S*)(+)-Va followed by benzoylation, from its mixed melting point, IR and NMR spectra, and by gas chromatography.

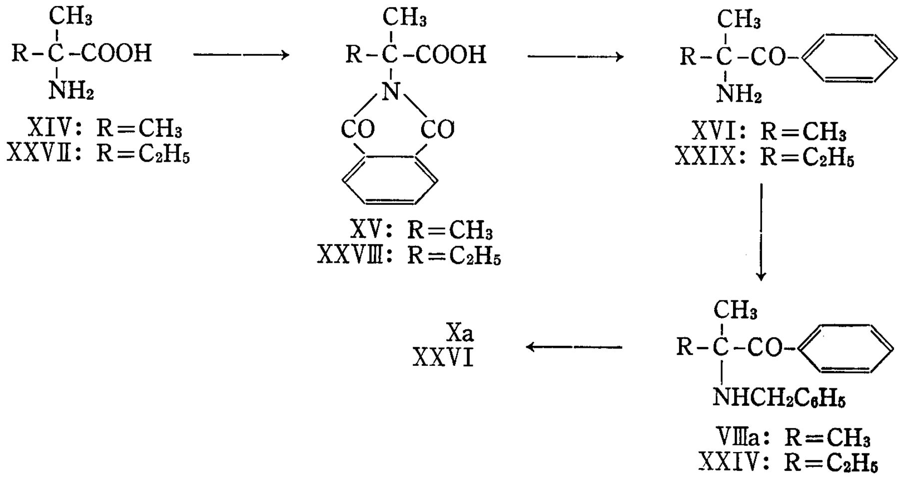


Chart 4

---

[13] (*R*)(−)-VII showing $[\alpha]^{19}_{D}$ −90.3° (1N HCl) (see ref. 14) was the maximum optical rotation. This was assumed to be optically pure.

[14] A. Mckenzie and G.W. Clough, *J. Chem. Soc.*, **101**, 390 (1912).

[15] S. Gabriel, *Chem. Ber.*, **44**, 57 (1911).

The generality of thermal rearrangement of α-hydroxyimines was further demonstrated using the same reaction with α-hydroxyimines, such as Vb, containing alkylimino skeletons as shown in Chart 1 and 2.

Thermal rearrangement of (*R*)(—)-Vb, α_D^{29} —15.5° (l=0.1, neat), prepared from (*R*)(—)-atrolactic acid ((*R*)(—)-III), $[\alpha]_D^{20}$ —41.9° (c=2.01, H_2O), optical purity 75%,16) as shown in Chart 1 was done under reflux in decalin giving a mixture, $[\alpha]_D^{28.5}$ +83.3° (EtOH), of (+)-3-butylamino-3-phenyl-2-butanone ((+)-VIb) and 2-butylamino-2-metylpropiophenone (VIIIb), in a combined yield of 46% from the basic fraction. Here, too, the mixture was benzoylated without separation of (+)-VIb and VIIIb and was followed by the purification described above, to isolate (—)-N-benzoyl-3-butylamino-3-phenyl-2-butanone ((—)-IXb), $[\alpha]_D^{14.5}$ —12.5° (EtOH), and N-benzoyl-2-butylamino-2-methylpropiophenone (Xb) respectively.

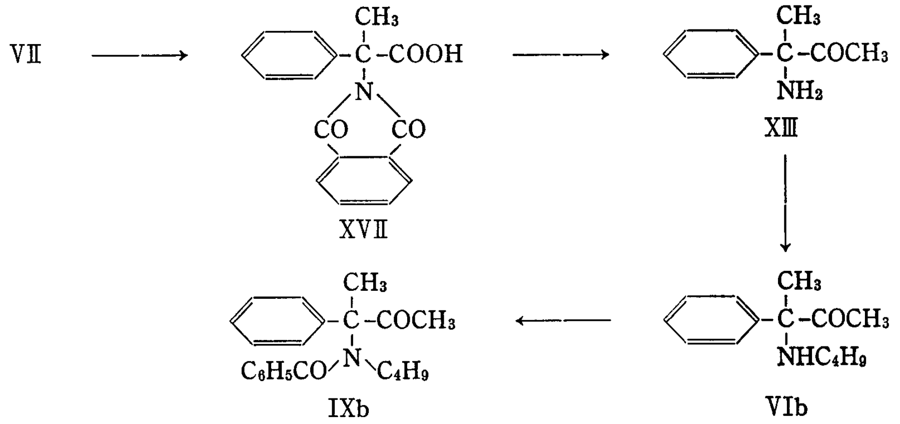


Chart 5

The preparation of authentic IXb is shown in Chart 5. (*S*)(+)-α-methylphenylglycine ((*S*)(+)-VII), $[\alpha]_D$ +85.8° (N–HCl), optical purity 95%,13) was treated by a previously reported method10) to afford (*S*)(+)-3-amino-3-phenyl-2-butanone ((*S*)(+)-XIII), α_D^{27} +5.57° (l=0.1, neat), optical purity 99%,17) by way of (*S*)(+)-N-phthanoyl-α-methylphenylglycine ((*S*)(+)-XVII), $[\alpha]_D^{31.5}$ +16.0 (EtOH). Condensation of (*S*)(+)-XIII with *n*-butylaldehyde, followed by catalytic hydrogenation on PtO_2, without purification of Schiff's base, gave (*S*)(+)-3-butylamino-3-phenyl-2-butanone ((*S*)(+)-VIb), $[\alpha]_D^{28.5}$ +114° (EtOH) which was benzoylated with pyridine-benzoyl chloride to afford (*S*)(—)-N-benzoyl-3-butylamino-3-phenyl-2-butanone ((*S*)(—)-IXb), $[\alpha]_D^{15}$ —15.7° (EtOH). The (*S*)(—)-IXb obtained was identified with (—)-IXb, prepared by phenyl migration on the thermal rearrangement of (*R*)(—)-Vb, from elemental analysis, from its IR and NMR spectra, by thin layer chromatography, and from its mixed melting point.

These results revealed that the absolute configuration of (—)-IXb and that of (+)-VIb, obtained by the rearrangement, were the same (*S*)-configuration. It was also evident that phenyl migration in the thermal rearrangement of (*R*)(—)-Vb gave (*S*)(+)-VIb with 105% retention of optical activity based on the optical purities of (*R*)(—)-III and (*S*)(+)-XIII.

Xb, the methyl migrated product, was confirmed from its IR spectrum and by elemental analysis.

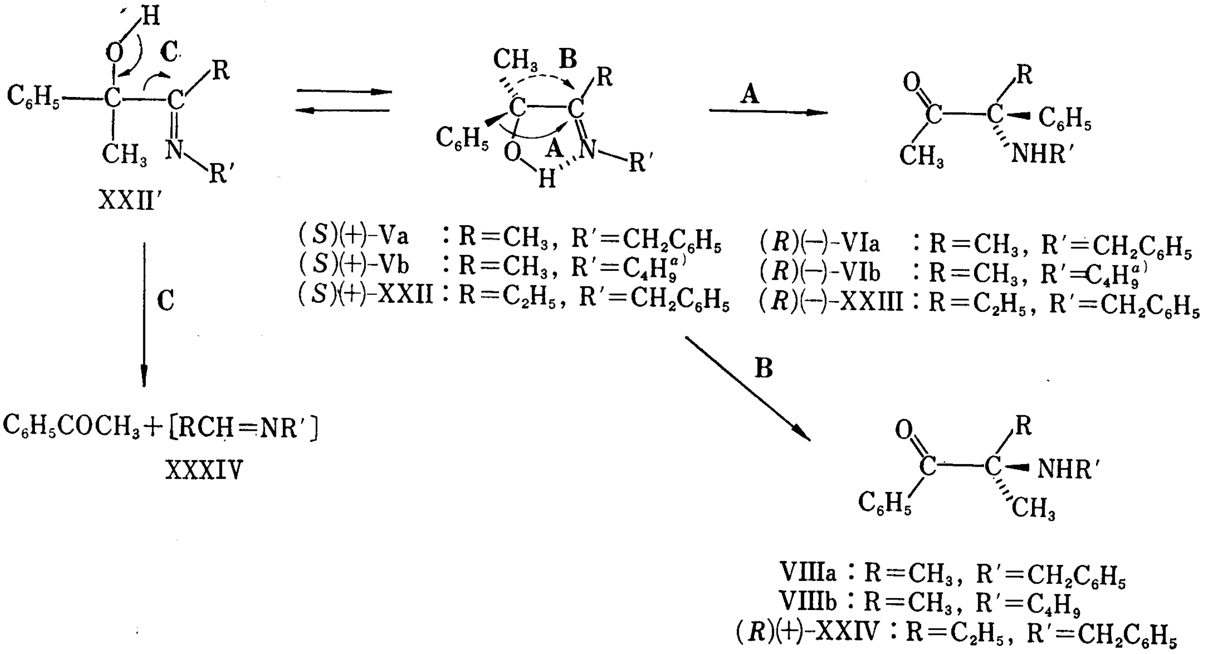
Thermal rearrangement of (*S*)(+)-Va and (*R*)(—)-Vb gave (*R*)(—)-VIa and (*S*)(+)-VIb, respectively, under phenyl migration with almost full retention of optical activity. These findings are in agreement with the intramolecular concerted mechanism by which the phenyl

---

16) *cf.* ref. 11.

17) Based on the assumption that (*R*)(—)-XIII, prepared from (*R*)(—)-VII according to the scheme shown in Chart 1, showing α_D^{27} —5.56° (l=0.1, neat), was 99% optically pure. The optical purity of (*S*)(+)-XIII described here became 99%.

group of intramolecular hydrogen-bonded α-hydroxyimine migrates exclusively *via* route A. Therefore, α-hydroxyimine with (*S*)-configuration gives α-aminoketone with (*R*)-configuration, as shown in Chart 6. The IR spectrum of (±)-Va in CCl_4 suggested the existence of an intramolecular hydrogen bonded hydroxy group, which was shown at 3314 cm^{-1}. It was not affected by concentration changes. Methyl migration may also be assumed to proceed *via* route **B**. The coexistence of two migration courses was a first example in the open chain system, though in the alicyclic system the coexistence of two reaction routes was observed only where the reaction proceeded from XVIII to XIX and XX.



XXII'

(*S*)(+)-Va : $R=CH_3$, $R'=CH_2C_6H_5$
(*S*)(+)-Vb : $R=CH_3$, $R'=C_4H_9$[a]
(*S*)(+)-XXII : $R=C_2H_5$, $R'=CH_2C_6H_5$

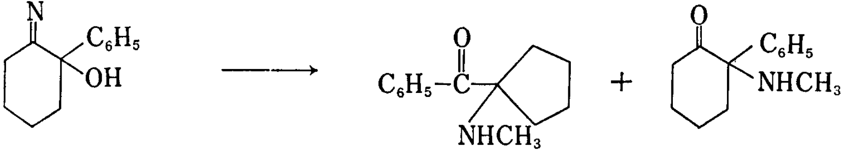
(*R*)(−)-VIa : $R=CH_3$, $R'=CH_2C_6H_5$
(*R*)(−)-VIb : $R=CH_3$, $R'=C_4H_9$[a]
(*R*)(−)-XXIII : $R=C_2H_5$, $R'=CH_2C_6H_5$

$C_6H_5COCH_3+[RCH{=}NR']$
XXXIV

VIIIa : $R=CH_3$, $R'=CH_2C_6H_5$
VIIIb : $R=CH_3$, $R'=C_4H_9$
(*R*)(+)-XXIV : $R=C_2H_5$, $R'=CH_2C_6H_5$

a) Rearrangement of optically active Vb was carried out with (*R*)(−)-Vb. (*S*)(+)-VIb was obtained.

Chart 6



XVIII XIX XX

Investigation of the ratio of phenyl migration to methyl migration (**A**/**B** in Chart 6), suggested a system for migratory aptitude. This system has the advantage of negligibility in the conformational factor, which is unavoidable in the open chain system, since this compound has a symmetrical plane containing a hydrogen bonding ring system. In the former instance, the ratio of **A**/**B** in the rearrangement of (*S*)(+)-Va was calculated as 9, based on the comparison of the optical rotation of authentic (*R*)(−)-VIa obtained from (*R*)(−)-VII with that of the mixture of (*R*)(−)-VIa and VIIIa, prepared by rearrangement of (*S*)(+)-Va. The ratio of **A**/**B** in the case of (*R*)(−)-Vb was also calculated as 9 by the procedures used for (*S*)(+)-Va. Moreover, comparison of the intensity of the tertiary methyl signal in the NMR spectrum of a mixture of VIa and VIIIa showed the ratio of **A**/**B** to be 7—15 on three repeated examinations. The **A**/**B** ratios from optical rotation and from NMR method are acceptable.

To investigate stereospecificity in methyl migration, we carried out the rearrangement of optically active 3-benzylimino-2-phenyl-2-pentanol (XXII), since the methyl migrated terminus in this rearrangement should also be an asymmetric carbon. The chemical scheme used is illustrated in Chart 1, 2, 3 and 4.

Treatment of the lithium salt of (*S*)(+)-atrolactic acid ((*S*)(+)-III), $[\alpha]_D^{22}$ +47.8° (c= 1.49, H_2O), optical purity 85%,[11] with ethyl lithium in anhydrous ether gave (*S*)(+)-2-hydroxy-2-phenyl-3-pentanone ((*S*)(+)-XXI), $[\alpha]_D^{22}$ +211° (C_6H_6), in a 75% yield. This was condensed with benzylamine to afford (*S*)(+)-3-benzylimino-2-phenyl-2-pentanol ((*S*)(+)-XXII), $[\alpha]_D^{27}$ +218° (C_6H_6), in a 95% yield (Chart 1). Thermolysis of (*S*)(+)-XXII, followed by extraction with aqueous hydrochloric acid, afforded a basic fraction. This gave a mixture of (−)-3-benzylamino-3-phenyl-2-pentanone ((−)-XXIII) and (−)-2-benzylamino-2-methylbutyrophenone ((−)-XXIV) in a combined yield of 53%, $[\alpha]_D^{26.5}$ −24.2° (C_6H_6). The neutral fraction of the reaction mixture contained acetophenone in a 25% yield, it was identified by its semicarbazone. Two isomeric α-aminoketones ((−)-XXIII and (−)-XXIV) were isolated by column chromatography using silica gel. However, to identify them as crystal derivatives the mixture of these α-aminoketones was benzoylated immediately without separation. (+)-N-Benzoyl-3-benzylamino-3-phenyl-2-pentanone ((+)-XXV), $[\alpha]_D^{19}$ +92.4° (EtOH), and (+)-N-benzoyl-2-benzylamino-2-methylbutyrophenone ((+)-XXVI), $[\alpha]_{342}^{25.5}$ +63.1° ($CHCl_3$),[18] were isolated by the same purification method used in previous examinations (Chart 2).

Absolute configuration and optical purity of (+)-XXVI were shown by independently synthesizing it from (*R*)(−)-isovaline ((*R*)(−)-XXVII) whose absolute configuration[19] and optical purity[20] had already been determined according to the same route as the synthesis of Xa as shown in Chart 4. In preparing (*R*)(−)-XXIV, a mixture of two lots of (*R*)(−)-XXVII showing $[\alpha]_D^{27}$ −11.8° (H_2O) and $[\alpha]_D^{27}$ −12.7° (H_2O) respectively, both practically optically pure,[21] was used for phthaloylation. Benzoylation of (*R*)(−)-XXIV gave authentic (*R*) (+)-N-benzoyl-2-benzylamino-2-methylbutyrophenone ((*R*) (+)-XXVI), $[\alpha]_{342}^{26.5}$ + 68.9° ($CHCl_3$),[18] which was identified with (+)-XXVI, prepared by the thermal rearrangement of (*S*) (+)-XXII followed by benzoylation, from its elemental analysis, from its mixed melting point, its IR and NMR spectra, thin-layer chromatography, and its optical rotatory dispersion curves.

The conclusion is that methyl migration in the rearrangement of (*S*)(+)-XXII afforded (*R*)(−)-XXIV with full retention of optical activity.

Stereochemistry of the phenyl migration was further demonstrated by correlating the other α-amino ketone ((+)-XXIII) and its N-benzoyl derivative ((+)-XXV) to optically active α-ethylphenylglycine, whose absolute configuration we had determined.[22] To establish the absolute configuration and to estimate the extent of retention of optical activity, independent sysnthesis of XXV from (*S*)(+)-N-formyl-α-ethylphenylglycine ((*S*)(+)-XXX)[22] was carried out as shown in Chart 3.

(*S*)(+)-N-Formyl-α-ethylphenylglycine ((*S*)(+)-XXX), $[\alpha]_D^{26}$ +126° (N–NaOH), optical purity 100%,[23] prepared from the resolution of (±)-XXX with quinine, according to Sobotka's

---

[18] This optical rotation was calculated from the optical rotatory dispersion Chart.

[19] K. Achiwa and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 537 (1966).

[20] S. Terashima, K. Achiwa and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 1399 (1965).

[21] The value of $[\alpha]_D^{21}$ −11.9° (H_2O) (see ref. 20) was the highest value among those reported in the literatures for optically active XXVII. Thus, the two lots of (*R*)(−)-XXVII used as starting material may be considered optically pure. The difference in optical rotations between the two lots of (*R*)(−)-XXVII was assumed to be due to experimental error.

[22] The absolute configuration of some derivatives of α-ethylphenylglycine; *i.e.* (+)-N-formyl-α-ethylphenylglycine ((+)-XXX) and (+)-3-amino-3-phenyl-2-pentanone ((+)-XXV), was determined as S series (see ref. 26). (+)-XXX had already been correlated to (+)-α-ethylphenylglycine (see ref. 24).

[23] Maximum optical rotation, $[\alpha]_D$ +126° (aq. alkali) (see ref. 25). In the resolution of DL-XXX with (−)quinine, we obtained (+)-XXX and (−)-XXX, whose optical rotations were $[\alpha]_D^{26}$ +126° (1N NaOH) and $[\alpha]_D^{27}$ −124° (1N NaOH), respectively.

[24] H. Sobotka, M.F. Holzman and J. Kahm, *J. Am. Chem. Soc.*, **54**, 4697 (1932).

method,[24)] was hydrolyzed with 10% HCl. This was led to (*S*)(+)-ethyl N-ethoxycarbonylacetyl-α-ethylphenylglycinate ((*S*)(+)-XXXI), $[\alpha]_D^{25}$ +42.2° (C_6H_6), in a 80% yield based on (*S*)(+)-XXX. (*S*)(+)-XXXI was converted to (*S*)(+)-3-benzylamino-3-phenyl-2-pentanone ((*S*)(+)-XXIII), $[\alpha]_D^{23}$ +37.0° (C_6H_6), by way of (*S*)(+)-5-ethyl-5-phenylpyrrolidin-2,4-dione ((*S*)(+)-XXXII), $[\alpha]_D^{23.5}$ +85.3° (EtOH), and (*S*)(+)-3-amino-3-phenyl-2-pentanone ((*S*)(+)-XXXIII), $[\alpha]_D^{26}$ +32.6°(C_6H_6), by treatments the same as those used in the synthesis of (*R*)(−)-VIa from (*R*)(−)-VII. This (*S*)(+)-XXIII was benzoylated to afford authentic (*S*)(−)-N-benzoyl-3-benzylamino-3-phenyl-2-pentanone ((*S*)(−)-XXV), $[\alpha]_D^{18.5}$ −101° (EtOH), which was identified with (+)-XXV, prepared by rearrangement of (*S*)(+)-XXII followed by the benzoylation, except for its optical rotation.

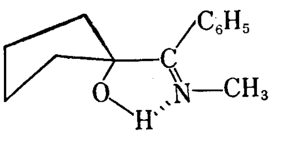
Comparison of the optical rotations of the XXV, showed that phenyl migration in the rearrangement of (*S*)(+)-XXII proceeded with 108% retention of optical activity. The absolute configuration of (+)-XXV from (*S*)(+)-XXII was shown to be (*R*)-configuration.

These findings also show that phenyl migration proceeded stereospecifically *via* route **A**, as shown in the thermolyses of (*S*)(+)-Va and (*R*)(−)-Vb (Chart 6). Formation of (*R*)(−)-XXIV from (*S*)(+)-XXII with full retention of optical activity clearly demonstrates that the methyl group migrated exclusively *via* route **B**, which is opposite to route **A** on a quasi hetero ring (Chart 6). This methyl migration is also explainable by the intramolecular concerted mechanism.

The ratio of A/B was calculated from the NMR chart, as 8—16 by comparison of the intensity of the acetyl methyl signal (8.13 τ) in XXIII with the tertiary methyl signal (8.5 τ) in XXIV.

Formation of acetophenone observed in the thermolysis of (±)-Va, (±)-XXII and (*S*)-(+)-XXII suggests the presence of a fragmentation reaction course, *i.e.*, route C in chart 6. Therefore, the formation N-benzylimine derivatives of aceto- or propion-aldehyde (XXXIV) should be deducible from the experiments reported by Stevens, *et al.*[7f,g)] but isolation of these compounds, *i.e.*, XXXIV was not examined. The presence of reaction routes A, B and C in this thermal reaction shows the coexistence of cleavage in all the carbon–carbon bonds attached to the carbon atom bearing the hydroxy group.

Of these three reaction products, phenyl and methyl migration products proceed streospecifically by route A and B on the hydrogen bonded α-hydroxyimines. The route for the formation of ketone is not as obvious as routes A and B, and it is not clear whether ketone is formed from the hydrogen bonded ring system or not. However, since ketone formation does not require orientation of the OH bond and the C=N double bond in the same plane, it is possible that a fragmentation reaction would occur under non-hydrogen bonded α-hydroxyimines at the reaction temperature, *i.e.* the boiling point of decalin (*ca.* 190°). Even though the absorption band of the free hydrogen group in the IR spectrum of (±)-Va at room temperature was not recognized, the presence of non-hydrogen bonded conformation was observed by IR[25)] and circular dichroism (CD)[26)] in α-hydroxyketones at room temperature. Hence, non-hydrogen bonded conformation of α-hydroxyimine might be present at the boiling point of decalin. This speculation is supported by the report of Stevens, *et al.*[7e)] that the fragmentation reaction did not occur in the thermolysis of 1-(α-methyliminobenzyl)-cyclopentanol (XXXV), whose IR spectrum in $CHCl_3$ revealed a strongly hydrogen bonded hydroxy absorption at 2135 cm^{-1}.



XXXV

Product yields and the percents of retention of optical activities observed in the thermal rearrangement of the three types of optically active α-hydroxyimines, in decalin, are summarized in Table I.

---

25) L. Joris and R. von R. Schleyer, *J. Am. Chem. Soc.*, **90**, 4599 (1968).
26) H. Mizuno and S. Yamada, in preparation.

TABLE I. Thermal Rearrangements of Optically Active α-Hydroxyimines in Decalin

Starting material	Products	Yield (%)	Ratio of phenyl migration to methyl migration	Retention of optical purity (%)
(*S*)(+)-Va	(*R*)(−)-VIa VIIIa	38	9, 7∼15	100
	acetophenone	—		
(*R*)(−)-Vb	(*S*)(+)-VIb VIIIb	46	9	105
	acetophenone	—		
(*S*)(+)-XXII	(*R*)(−)-XXIII	53	8∼16	108
	(*R*)(−)-XXIV			100
	acetophenone	25		

Experimental27)

Resolution of Atrolactic Acid (III)——Using Smith's method,12) (±)-atrolactic acid·1/2 H_2O ((±)-III·1/2 H_2O)23) was resolved with (−)-phenethylamine29) to give (*S*)(+)-atrolactic acid ((*S*)(+)-III), mp 104—110°, $[\alpha]_D^{30}$ +45.2° (c=1.93, H_2O) (lit.12) mp 116.5—117°, $[\alpha]_D^{18}$+56.0° (c=1.591, H_2O)). All filtrates in the resolution of the diastereomeric salts were concentrated and were acidified to pH 2 to separate the (±)-III·1/2 H_2O. (±)-III·1/2 H_2O was filtered off. Extractions with ether from the filtrate, followed by evaporation gave (*R*)(−)-atrolactic acid ((*R*)(−)-III), mp 106—110°, $[\alpha]_D^{20}$ −41.9° (c=2.01, H_2O) (lit.12) mp 116°, $[\alpha]_D^{20}$ −52.0° (c=2.001, H_2O)).

(±)-3-Hydroxy-3-phenyl-2-butanone ((±)-IV)——(±)-Atrolactic acid·1/2 H_2O ((±)-III·1/2 H_2O) (10.2 g, 0.058 mole) was added to an MeOH (50 ml) solution of the metal Li (0.44 g, 0.058 mole). The mixture was triturated to make a solidic lithium salt. Ether solution (220 ml) of CH_3Li30) prepared from Li (2.22 g, 0.320 mole) and CH_3I (20.7 g, 0.146 mole) was added to the suspension of the dried lithium (±)-atrolactate in anhyd. ether (80 ml) under stirring. The whole was refluxed with stirring for 17 hr under an N_2 atmosphere, then treated with H_2O (100 ml) with stirring in an ice bath. The organic layer was washed with sat. NaCl, 5% HCl and sat. NaCl, dried over anhyd. Na_2SO_4 and evaporated to dryness to give a yellow oil, which was distilled under reduced pressure. The volatile fraction (bp 99—103.5° (4.5 mmHg)) was purified with column chromatography using silica gel (solv. $CHCl_3$) and distilled fractionally under reduced pressure to give (±)-IV as a pale yellow oil (4.90 g, 51%), bp 97.5—98.5° (4 mmHg) (lit.31) bp 126—127° (12 mmHg)). IR ν_{max}^{cap} cm^{-1}: 3460, 1716, 1358, 1135, 759, 701. NMR32) (10% solution in CCl_4) τ: 8.35 (3H, singlet, $-\overset{|}{\underset{|}{C}}-CH_3$), 8.00 (3H, singlet, $-COCH_3$), 5.67 (1H, singlet, −OH), *ca.* 2.7 (5H, multiplet, benzene proton). Semicarbazone, colorless needles, mp 179—180.5° (recrystallized from aq. EtOH) (lit.,31) mp 183—184°). IR ν_{max}^{KBr} cm^{-1}: 3468, 3305, 3195, 1666, 1588, 1580.

(*S*)(+)-3-Hydroxy-3-phenyl-2-butanone ((*S*)(+)-IV——(*S*)(+)-Atrolactic acid ((*S*)(+)-III) ($[\alpha]_D^{30}$ +45.2 (c=1.93, H_2O), optical purity 81%11)) (9.0 g, 0.053 mole) was treated the same as (±)-III·1/2 H_2O to give (*S*)(+)-IV as a slightly yellow oil (4.07 g, 47%), bp 100—104° (5.5 mmHg), $[\alpha]_D^{32.5}$ +222° (c=1.27, C_6H_6). IR ν_{max}^{cap} cm^{-1}: 3460, 1713, 1359, 1136, 758, 702. Semicarbazone, colorless needles, mp 143.5—162°33) (recrystallized from aq. EtOH). *Anal.* Calcd. for $C_{11}H_{15}O_2N_3$: C, 59.71; H, 6.81; N, 18.99. Found: C, 60.00; H, 6.73; N, 19.13. IR ν_{max}^{KBr} cm^{-1}: 3473, 3304, 3225, 3203, 1669, 1580.

Thermal Rearrangement of (±)-3-Benzylimine-2-phenyl-2-butanol ((±)-Va)——i) Synthesis of (±)-Va: A mixture of benzylamine (3.07 g, 0.0287 mole) and a trace of *p*-toluenesulfonic acid·H_2O in anhyd. benzene

---

27) All melting points and boiling points were uncorrected. IR spectra measurements were performed with spectrometers, Models-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 and CD curve measurements were carried out with a spectrometer Model ORD/UV-5, Japan Spectroscopic Co., Ltd. Gas chromatographic analyses were performed using a Shimazu Gas Chromatograph, Model GC-1B.

28) E.L. Eliel and J.P. Freeman, "Organic Syntheses," Coll. Vol. IV, ed. by N. Rabjohn, John Wiley and Sons, Inc., New York, 1963, p. 58.

29) W. Theilacker and H.G. Winkler, *Chem. Ber.*, **87**, 690 (1954).

30) C. Tegner, *Acta Chem. Scand.*, **6**, 782 (1952).

31) K. von Auwers and H. Mauss, *Biochem. Z.*, **192**, 221 (1928).

32) Tetramethylsilane was used as internal standard.

33) This broad melting point range was due to partially resolved starting material (III).

(30 ml) was azeotroped to remove H_2O, then (±)-IV (3.13 g, 0.0191 mole) was added. The whole was refluxed for 17 hr in a flask equipped with a Dean–Stark trap, then evaporated to dryness *in vacuo* under an N_2 atmosphere to give a residual oil. This was fractionally distilled under an N_2 atomosphere to afford (±)-Va as a pale yellow oil (4.6 g, 95%), bp 153—161° (0.3 mmHg). IR $\nu_{\max}^{\mathrm{cap}}$ $\mathrm{cm^{-1}}$: 3392, 1712 (weak), 1667.

ii) Thermal Rearrangement of (±)-Va: A mixture of the (±)-Va (1.82 g, 0.00718 mole) and freshly distilled decalin (18 ml) was refluxed for 11 hr. The reaction mixture was extracted with 18% HCl (10 ml) and 10% HCl (10 ml, 5 ml), then washed with sat. NaCl, 10% Na_2CO_3 and sat. NaCl. The decalin layer was dried over anhyd. Na_2SO_4 and filtered. The filtrate was submitted to column chromatography using silica gel. Decalin was eluted from the column using *n*-hexane. The eluting solvent was then changed to AcOEt–hexane (1:1). All eluting oil with this solvent (0.25 g) contained acetophenone from its IR spectrum and a thin-layer chromatogram. This oil was converted to semicarbazone (0.08 g), mp 191—193°, mixed mp with authentic sample (mp 195—197°), 191—193°.

Acid extracts of the reaction mixture were warmed for a while, then washed with benzene. The aqueous layer was made alkaline with 40% NaOH, then extracted with benzene (10 ml × 2, 5 ml). Combined extracts were washed with sat. NaCl, dried over anhyd. K_2CO_3 and evaporated to dryness to give a brown oil. This was submitted to column chromatography using silica gel (hexane:AcOEt=3:2) and distilled fractionally under an N_2 atmosphere to afford a mixture of (±)-VIa and VIIIa as a pale yellow viscous oil (0.63 g, 35%), bp 164—170° (0.09 mmHg). IR $\nu_{\max}^{\mathrm{cap}}$ $\mathrm{cm^{-1}}$: 3338, 1714, 1683 (shoulder), 1603, 760, 737, 700.

Thermal Rearrangement of (*S*)(+)-3-Benzylimino-2-phenyl-2-butanol ((*S*)(+)-Va)——i) Synthesis of (*S*)(+)-Va: The same treatment of (*S*)(+)-IV ($[\alpha]_D^{32.5}$ +222° (c=1.27, C_6H_6)) (3.20 g, 0.0195 mole) as with (±)-IV gave (*S*)(+)-Va as a yellow viscous oil (4.11 g, 83%), bp 161—165° (0.04 mmHg), α_D^{33} +22.7° (l=0.1, neat). IR $\nu_{\max}^{\mathrm{cap}}$ $\mathrm{cm^{-1}}$: 3377, 1713 (weak), 1666, 762, 739, 699.

ii) Thermal Rearrangement of (*S*)(+)-Va: (*S*)(+)-Va (α_D^{33} +22.7° (l=0.1, neat)) (4.00 g, 0.0158 mole) was treated similarly to (±)-Va to give a mixture of (−)-VIa and VIIIa as a pale yellow viscous oil (1.50 g, 38%), bp 146—148° (0.06 mmHg), α_D^{32} −2.98° (l=0.1, neat), α_D^{26} −2.97° (l=0.1, neat). IR $\nu_{\max}^{\mathrm{cap}}$ $\mathrm{cm^{-1}}$: 3332, 1713, 1681 (weak), 1602, 760, 735, 701. NMR (10% solution in CCl_4) τ: 8.55 (0.3H, singlet, $(CH_3)_2\text{-}\underset{|}{C}\text{-}CO\text{-}C_6H_5$), 8.40 (3H, singlet, $-\overset{|}{\underset{|}{C}}-CH_3$), 8.10 (3H, singlet, $-COCH_3$), 7.95 (*ca.* 1H, singlet, NH), 6.54 (2H, singlet, $C_6H_5CH_2-$), *ca.* 2.75 (12H, multiplet, benzene proton).

Isolation of acetophenone as the semicarbazone was not examined in the case of optically active compound.

Benzoylation of a Mixture of (±)-3-Benzylamino-3-phenyl-2-butanone ((±)-VIa) and 2-Benzylamino-2-methylpropiophenone (VIIIa) prepared by Thermal Rearrangement——A solution of a mixture of (±)-VIa and VIIIa (0.490 mg, 0.00193 mole), from the thermal rearrangement, and benzoyl chloride (0.410 g, 0.0029 mole) in pyridine (5 ml) was warmed at *ca.* 80° for 3 hr and kept at room temperature for 3 hr. Ice and water (25 ml) were added to this reaction mixture. The mixture was made alkaline with 40% NaOH, then extracted with benzene (10 ml × 3). Combined extracts were washed with sat. NaCl, 10% HCl and sat. NaCl, dried over anhyd. Na_2SO_4, then evaporated to dryness to give a brown viscous oil. This oil was submitted to column chromatography using silica gel (solv. CH_2Cl_2:*n*-hexane=3:1), purified by trituration with IPE (isopropyl ether) to solidify it. Then it was recrystallized from benzene–IPE–*n*-hexane, five times, to give (±)-IXa as colorless prisms (210 mg); mp 122—123°, mixed melting point with the authentic sample (cited later) showed no depression. *Anal.* Calcd. for $C_{24}H_{23}O_2N$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.55; H, 6.32; N, 4.13. IR $\nu_{\max}^{\mathrm{KBr}}$ $\mathrm{cm^{-1}}$: 1701, 1632. NMR (10% solution in $CDCl_3$) τ: 8.17 (3H, singlet, $-\overset{|}{\underset{|}{C}}-CH_3$), 7.82 (3H, singlet, $-COCH_3$), 5.50 (2H, quartet, J_{AB}=16 cps, $-CH_2C_6H_5$), 2.5—3.2 (15H, multiplet, benzene proton).

Isolation of N-benzoyl-2-benzylamino-2-methylpropiophenone (Xa) was not attempted.

Benzoylation of a Mixture of (−)-3-Benzylamino-3-phenyl-2-butanone ((−)-VIa) and 2-Benzylamino-2-methylpropiophenone (VIIIa) prepared by Thermal Rearrangement——A mixture of (−)-VIa and VIIIa (α_D^{26} −2.97° (l=0.1, neat)) (1.25 g, 0.00494 mole) was treated similar to the racemate to afford a brown viscous oil as the neutral fraction. Silica gel column chromatography gave a yellow viscous oil (1.40 g). Part (400 mg) of this oil was distilled fractionally. The distilled fraction (bp ~204° (0.05 mmHg)) was submitted to column chromatography using silica gel (solv. IPE:*n*-hexane=1:1, silica gel 120 g). Fractions from 1200 ml to 1300 ml gave Xa (10 mg), mp 166—180°. IR $\nu_{\max}^{\mathrm{KBr}}$ $\mathrm{cm^{-1}}$: 1687, 1618. NMR (2% solution in $CDCl_3$) τ: 8.38 (6H, singlet, $-CO-\underset{\substack{|\\ N}}{C}-(CH_3)_2$), 5.13 (2H, singlet, $-CH_2C_6H_5$), *ca.* 2—3 (15H, multiplet, benzene proton). This spectrum was superimposable on that of the authentic sample (cited later). Gas chromatographic analysis of this sample showed a single peak with a retention time the same as that of the authentic Xa (5% SE-30 on Diasolid, 0.75 m, 221°; retention time 9.7 min). Recrystallization from benzene–IPE gave pale brown needles, mp 189—190°, mixed mp with authentic Xa showed no depression. IR $\nu_{\max}^{\mathrm{KBr}}$ $\mathrm{cm^{-1}}$; 1689, 1619, this spectrum was superimposable on that of authentic Xa.

Fractions from 1525 ml to 1700 ml afforded (+)-IXa (280 mg), mp 98—109°, $[\alpha]_D^{10}$ +9.19° (c=2.13, EtOH). IR $\nu_{\max}^{\mathrm{KBr}}$: 1712, 1621. NMR (10% solution in $CDCl_3$) τ: 8.18 (3H, singlet, $-\overset{|}{\underset{|}{C}}-CH_3$), 7.80 (3H, singlet, $-COCH_3$), 5.53 (2H, quartet, $J_{AB}=1.6$ cps, $C_6H_5-CH_2-$), 2.5—3.2 (15H, multiplet, benzene proton). Three recrystallizations from EtOH–*n*-hexane gave colorless prisms, mp 110—120°,[33] $[\alpha]_D^{13}$ +6.87° ($c=0.846$, EtOH). *Anal.* Calcd. for $C_{24}H_{23}O_2N$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.89; H, 6.36; N, 3.93. IR ν_{max}^{KBr} cm^{-1}: 1713, 1622. This IR spectrum was superimposable on that of (+)-IXa at the purification step with column chromatography.

(±)-Ethyl N-Ethoxycarbonylacetyl-α-methylphenylglycinate ((±)-XI)——A solution of ethoxycarbonylacetyl chloride (3.02 g, 0.0201 mole) in $CHCl_3$ (25 ml) was added to a mixture of ethyl (±)-α-methylphenylglycinate (3.87 g, 0.0201 mole), prepared by the general method, and triethylamine (2.24 g, 0.0221 mole) in $CHCl_3$ (70 ml) with stirring on an ice bath below 10°. After stirring overnight at room temperature the reaction mixture was washed with 5% Na_2CO_3, sat. NaCl, 5% HCl and sat. NaCl dried over Na_2SO_4. Filtration and evaporation gave (±)-XI as a pale yellow viscous oil (5.00 g, 81%). This crude (±)-XI was used without purification for the following experiment.

(*R*)(−)-Ethyl N-Ethoxycarbonylacetyl-α-methylphenylglycinate ((*R*)(−)-XI)——$SOCl_2$ (5.73 g, 0.0480 mole) was added to the suspension of (*R*)(−)-α-methylphenylglycine ((*R*)(−)-VII) ($[\alpha]_D^{19}$ −89.8° ($c=2.71$, NHCl), optical purity 99%[13]) (3.97 g, 0.0240 mole), resolved with quinine[34] through its N-formyl derivative, in abs. EtOH (40 ml) under cooling. The mixture was refluxed for 4 hr and evaporated to dryness to give a residual oil, to which $CHCl_3$ was added. The solvent was evaporated to dryness. Addition and evaporation of $CHCl_3$ was repeated five times to separate (*R*)(−)-VII·HCl as a powder. Filtered (*R*)(−)-VII·HCl was similarly treated to give a solution of ester hydrochloride in $CHCl_3$. Combined $CHCl_3$ layers were evaporated to dryness *in vacuo* to give ethyl (*R*)-α-methylphenylglycinate hydrochloride as a yellow viscous oil (6.00 g). This oil was dissolved in $CHCl_3$ (30 ml), and triethylamine (6.57 g, 0.0636 mole), and a solution of ethoxycarbonylacetyl chloride (5.43 g, 0.0360 mole) in $CHCl_3$ were added successively with stirring on an ice bath. The reaction mixture was washed with 5% HCl, sat. NaCl, 5% Na_2CO_3 and sat. NaCl, dried over anhyd. Na_2SO_4 and evaporated to give a pale brown oil. Purification with column chromatography using silica gel (solv. *n*-hexane:IPE:CH_2Cl_2=2:1:1) gave (*R*)(−)-XI as a pale brown oil (6.42 g, 87%), $[\alpha]_D^{23}$ −13.1° ($c=$ 1.13, EtOH). This crude (*R*)(−)-XI was used for further experiments.

(±)-5-Methyl-5-phenylpyrrolidin-2,4-dione ((±)-XII)——Anhyd. benzene (40 ml) and a solution of (±)-XI (5.00 g, 0.0163 moles) in anhyd. benzene (60 ml) were added successively with stirring to the solution of Na (0.49 g, 0.0213 g atom) in abs. MeOH (7 ml). The whole was refluxed with stirring for 16 hr under an N_2 atmosphere and treated with H_2O (40 ml) under cooling. The aqueous layer which separated was acidified to pH 1 with conc. HCl to a separate solid, which was collected by decantation and dissolved in MeOH. The aqueous layer was extracted with AcOEt containing 20% of MeOH (20 ml) and benzene (20 ml × 2). Organic layers containing MeOH were made a single layer by an addition of AcOEt. This organic layer was washed with sat. NaCl, then dried over anhyd. Na_2SO_4 and evaporated to dryness to give a pale brown solid. The mixture of this solid (2.8 g, 0.0107 mole as a ketoester) and KOH (1.8 g, 0.0321 mole) in 50% aqueous EtOH (60 ml) was refluxed for 3.5 hr, and concentrated to *ca.* 30 ml. The residual solution was acidified with conc.HCl to separate solids, which were extracted with AcOEt (20 ml × 2, 10 ml). Combined AcOEt layers were washed with sat. NaCl, then dried over anhyd. Na_2SO_4 and evaporated to dryness to afford pale brown solids. Purification on column chromatography using silica gel (solv. AcOEt: CH_2Cl_2=1:1) gave (±)-XII as brown crystals (2.06 g, 67%), mp 132—136°. An analytical sample was obtained as colorless prisms after column chromatography followed by recrystallization from IPE–EtOH, mp 136—137°. *Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.72; H, 5..94; N, 7.58. IR ν_{max}^{KBr} cm^{-1}: 3305, 1775, 1702, 1680. IR $\nu_{max}^{CHCl_3}$ 3413, 3229, 3081, 1778, 1706.

(*R*)(+)-5-Methyl-5-phenylpyrrolidin-2,4-dione ((*R*)(+)-XII)——(*R*)(−)-XI ($[\alpha]_D^{23}$ −13.1° ($c=1.13$, EtOH)) (6.36 g, 0.0207 mole) was treated similar to (±)-XI, except a 7 hr reflux was performed for Diekmann condensation to give (*R*)(+)-XII as a yellow viscous oil (3.46 g, 88%), $[\alpha]_D^{26}$ +29.8° ($c=1.05$, benzene). Fractional distillation (bp 144—154° (0.055 mmHg)) followed by twice recrystallizations from EtOH–IPE–*n*-hexane gave (*R*)(+)-XII as colorless prisms, mp 102.5—103.5°, $[\alpha]_D^{27}$ +42.1° ($c=1.11$, benzene). *Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.96; H, 5.70; N, 7.19. IR ν_{max}^{KBr}: 3313, 1770, 1691. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3404, 3189, 3097, 1772, 1694. NMR (10% solution in $CDCl_3$) τ: 8.25 (3H, singlet, $-\overset{|}{\underset{|}{C}}-CH_3$), 6.97 (2H, singlet, $-COCH_2-CO-$), *ca.* 2.6 (5H, multiplet, benzene proton), 1.85 (1H, singlet, NH).

(±)-3-Amino-3-phenyl-2-butanone ((±)-XIII)——A mixture of (±)-XII (2.03 g, 0.0107 mole) and conc.HCl (20 ml) was refluxed for 5 hr to afford a clear solution, which was washed with AcOEt (20 ml) and benzene (20 ml), made alkaline with 40% NaOH under cooling. It was then extracted with benzene (20 ml × 2, 10 ml). Combined extracts were washed with sat. NaCl and dried over anhyd. K_2CO_3. Filtration, followed by evaporation under an N_2 atmosphere, gave a pale yellow oil. This was sumbitted to fractional distillation to afford (±)-XIII as a colorless oil (1.51 g, 86%), bp 115—115.5 (5 mmHg) (lit.[10] bp 123—124° (11.5 mmHg)). IR ν_{max}^{cap} cm^{-1}: 3370, 3304, 1713, 761, 702. Hydrochloride: colorless prisms, mp 237—238° (de-

---

34) (*R*)(−)-VII was obtained from more soluble fractions of optically resolutional recrystallizations as reported by Mckenzie and Clough (lit. 14).

comp.) (from H_2O–EtOH–ether). *Anal.* Calcd. for $C_{10}H_{14}ONCl$: C, 60.15; H, 7.07; N, 7.02. Found: C, 60.22; H, 7.06; N, 7.09. IR ν_{max}^{KBr} cm^{-1}: 3217, 3158, 1714, 764, 706.

(*R*)(−)-3-Amino-3-phenyl-2-butanone ((*R*)(−)-XIII)——(*R*)(+)-XII ($[\alpha]_D^{26}$ +29.8° (c=1.05, benzene)) (2.40 g, 0.00127 mole) (purified with column chromatography) was treated the same as (±)-XII to give (*R*)(−)-XIII as a colorless oil (1.49 g, 72%), bp 96—97° (4 mmHg), $[\alpha]_D^{27}$ −5.56° (l=0.1, neat), $[\alpha]_D^{26}$ −59.8° (c=1.17, benzene) (lit.[10] bp 94—97° (4 mmHg), $[\alpha]_D^{10}$ +5.104° (l=0.1, neat)). IR ν_{max}^{cap} cm^{-1}: 3360, 3295, 1712, 1603, 764, 704. Hydrochloride: colorless fine prisms, mp 254.5° (decomp.) (from H_2O–EtOH–ether), $[\alpha]_D^{31}$ −241° (c=1.12, EtOH). *Anal.* Calcd. for $C_{10}H_{14}ONCl$: C, 60.15; H, 7.07; N, 7.02. Found: C, 60.38; H, 7.31; N, 7.08. IR ν_{max}^{KBr} cm^{-1}: 3214, 3156, 1712, 754, 705.

(±)-3-Benzylamino-3-phenyl-2-butanone ((±)-VIa)——Freshly distilled benzaldehyde (3.5 g, 0.033 mole), a trace of *p*-toluenesulfonic acid·H_2O and anhyd.benzene (30 ml) were placed in a 100 ml flask equipped with a Dean–Stark trap. The mixture was azeotroped to remove water. A solution of (±)-XIII (1.8 g, 0.011 mole) in anhyd. benzene (20 ml) was added. The whole was heated under reflux for 9 hr and evaporated to dryness to give a residual oil, which was fractionally distilled under an N_2 atmosphere to afford (±)-3-benzylimino-3-phenyl-2-butanone (2.47 g, 89%), bp 150—160° (0.08 mmHg). IR ν_{max}^{cap} cm^{-1}: 1716, 1643, 754, 694. (±)-Schiff's base was hydrogenated on 5% Pd–C (560 mg) in EtOH (25 ml) at room temperature and atmospheric pressure. After the theoretical amount of H_2 was absorbed, catalyst was filtered and washed with EtOH. Filtrate and washings were evaporated to dryness under an N_2 atmosphere to give a residual oil, which was dissolved in benzene (25 ml). The benzene layer was extracted with 10% HCl (10 ml). (±)-VIa·HCl was separated from the aqueous layer as a colorless solid. The filtered solid was recrystallized twice from EtOH–IPE–*n*-hexane to give colorless prisms (2.06 g), mp 180—183° (decomp.). The mixture of (±)-VIa·HCl and 10% NaOH (20 ml) was refluxed for 1 hr to separate a colorless oil, which was extracted with ether (20 ml × 2, 10 ml). Combined ether layers were washed with sat. NaCl, dried over anhyd. K_2CO_3 and evaporated to dryness. This residue was distilled fractionally to give (±)-VIa as a colorless oil (1.34 g, 52%), bp 160—162° (0.23 mmHg). IR ν_{max}^{cap} cm^{-1}: 3331, 1712, 1602, 760, 736, 700. NMR (10% solution in CCl_4) τ: 8.38 (3H, singlet, $-\overset{|}{\underset{|}{C}}-CH_3$), 8.09 (3H, singlet, $-CO\ CH_3$), 7.90 (1H, singlet, NH), 6.50 (2H, singlet. $C_6H_5CH_2-$), *ca.* 2.75 (10H, multiplet, benzene proton).

(*R*)(−)-3-Benzylamino-3-phenyl-2-butanone ((*R*)(−)-VIa)——(*R*)(−)-XIII ($[\alpha]_D^{27}$ −5.56° (l=0.1, neat)) (1.11 g, 0.00681 mole) was treated similar to (±)-XIII to give (*R*)-Schiff's base as a slightly yellow oil, which solidified on standing. IR ν_{max}^{KBr} cm^{-1}: 1717, 1648. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1711, 1643. This Schiff's base was hydrogenated on 5% Pd–C as was the racemic compound. A basic fraction extracted by aqueous HCl, followed by the usual general procedure, was submitted to column chromatography using silica gel (solv. CH_2Cl_2: IPE=10:1) and fractionally distilled under an N_2 atmosphere to give (*R*)(−)-VIa as a colorless oil (990 mg, 57%), bp 147—148°, (0.05 mmHg) $[\alpha]_D^{25}$ −44.0° (c=1.36, benzene), $[\alpha]_D^{24}$ −3.73° (l=0.1, neat). IR ν_{max}^{cap} cm^{-1}: 3329, 1705, 1603.

(±)-N-Benzoyl-3-benzylamino-3-phenyl-2-butanone ((±)-IXa)——A mixture of (±)-VIa (540 mg, 0.00213 mole), benzoyl chloride (450 mg, 0.00319 mole) and anhyd. pyridine (6 ml) was warmed at *ca.* 80° for 3 hr. It was kept for 3 hr at room temperature then poured onto a mixture of ice and water (25 ml). After standing overnight at room temperature the mixture was made alkaline with 40% NaOH and extracted with benzene (10 ml × 3). The combined benzene layers were washed with sat. NaCl, 10% HCl and sat. NaCl. Drying over anhyd. Na_2SO_4 and evaporation gave a yellow viscous oil, which was purified with column chromatography using silica gel (solv. IPE:*n*-hexane=3:2) to give (±)-IXa as pale brown crystals (600 mg, 79%). Six recrystallizations from benzene–IPE–*n*-hexane or benzene–*n*-hexane gave colorless prisms, mp 122—122.5°. *Anal.* Calcd. for $C_{23}H_{23}O_2N$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.62; H, 6.47; N, 4.08. IR ν_{max}^{KBr} cm^{-1}: 1701, 1642. This spectrum was superimposable on that of (±)-IXa obtained by thermal rearrangement followed by benzoylation.

(*R*)(+)-N-Benzoyl-3-benzylamino-3-phenyl-2-butanone ((*R*)(+)-IXa)——A solution of (*R*)(−)-VIa ($[\alpha]_D^{24}$ −3.73° (l=0.1, neat)) (990 mg, 0.00391 mole) and benzoyl chloride (830 mg, 0.00576 mole) in anhyd. pyridine (10 ml) was warmed at 80° for 3 hr, then benzoyl chloride (550 mg, 0.00391 mole) was added. The whole was warmed at 80° for 7 hr, then poured onto ice and water (40 ml), and kept at room temperature for 2 days. The mixture was treated as usual to give a yellow viscous oil as a neutral fraction. This oil was submitted to column chromatography using silica gel twice (first solvent, *n*-hexane:IPE:CH_2Cl_2=2:1:1, second solvent, CH_2Cl_2:IPE=10:1) to afford (*R*)(+)-IXa as yellow crystals (1.09 g), mp 105—107.5°, $[\alpha]_D^{11}$ +11.2° (c=2.04, EtOH). IR and NMR spectra of this sample were identical with those of (*R*)(+)-IXa prepared by thermal rearrangement followed by benzoylation of (*S*)(+)-Va. The percent of retention of optical activity in the migration of the phenyl group was calculated as 100%, based on optical purities of the respective starting materials, ((*S*)(+)-III and (*R*)(−)-VII). Three recrystallizations from EtOH–IPE–*n*-hexane gave colorless prisms, mp 108—110°, $[\alpha]_D^{30}$ +4.7° (c=2.00, EtOH). *Anal.* Calcd. for $C_{23}H_{23}O_2N$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.90; H, 6.44; N, 4.01. IR ν_{max}^{KBr} cm^{-1}: 1709, 1620. NMR (10% solution in $CDCl_3$) τ: 8.16 (3H, singlet, $-\overset{|}{\underset{|}{C}}-CH_3$), 7.81 (3H, singlet, $-COCH_3$), 5.52 (2H, quartet, J_{AB}=16 cps, $-CH_2C_6H_5$), 2.5—3.2 (15H, multiplet, benzene proton). These spectra were identical with those of (*R*)(+)-IXa when purified with column chromatography.

2-Amino-2-methylpropionic Acid (XIV)——NH_4Cl (55 g, 1.03 mole) conc. NH_4OH (62 g, 1 mole), acetone (58 g, 1.0 mole) in EtOH (300 ml) was successively added to a solution of KCN (65 g, 1.03 moles) in H_2O (240 ml). The whole was warmed at 50—60° with stirring, and poured onto conc. HCl (800 ml) in an ice bath, which was saturated with HCl gas under cooling and left overnight at room temperature. The reaction mixture was diluted with H_2O (1 liter), refluxed for 2.5 hr and evaporated to dryness. Addition of H_2O (300 ml) followed by evaporation, was repeated twice leaving a residue, which was extracted with MeOH (400 ml). This filtered MeOH layer was adjusted to pH 5 with pyridine with warming, then more pyridine (80 ml) was added. The solution was left overnight in refrigerator and precipitated XIV as colorless minute prisms. Filtered XIV was successively washed with MeOH and ether and dried in a desicator (52.8 g, 51%).

N-Phthalyl-2-amino-2-methylpropionic Acid (XV)——A mixture of XIV (15.5 g, 0.150 mole), and phthalic anhydride (33.4 g, 0.225 mole) was heated to *ca.* 180° and became molten. The melt kept at this temperature for half an hour. The water produced was evaporated at slightly reduced pressure. The cooled reaction mixture was triturated with MeOH (60 ml), then filtered and washed with MeOH (20 ml). H_2O (200 ml) was added to the warm filtrate and the whole was left overnight at room temperature, then cooled in ice and salt for 30 minutes. Precipitated crystals were filtered and recrystallized from H_2O–acetic acid (3:1) to give XV as colorless pillars (22.0 g, 63%), mp 148—150° (lit.35) mp 152—153°, 76%, lit.15) mp 153—154°). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1782, 1742, 1711, 728.

2-Amino-2-methylpropiophenone (XVI)——Using Gabriel's method15) XV (10.0 g, 0.0429 mole) was converted to XVI by way of the acid chloride, the Friedel–Craft reaction and dephthaloylation (1.72 g, 25%), bp 94° (5 mmHg) (lit.15) bp 254—255° (732 mmHg)). IR $\nu_{\max}^{\text{cap}}$ cm^{-1}: 3366, 3301, 1679, 1600, 707. Hydrochloride: colorless minute prisms (from EtOH–ether), mp 184—186° (lit.15) mp 187—188° (soften from 137°), lit.36) mp 186—188°).

2-Benzylamino-2-methylpropiophenone (VIIIa)——XVI (1.69 g, 0.0103 mole) was treated similar to the synthesis of (±)-VIa from (±)-XIII to give VIIIa as a pale yellow oil (1.32 g, 50%) by way of 2-benzylimino-2-methylpropiophenone (bp 147—149° (0.1 mmHg)). In this case column chromatography using alumina (solv. CH_2Cl_2:*n*-hexane=1:2) was used as the purification method before fractional distillation, bp 141—145° (0.045 mmHg). IR $\nu_{\max}^{\text{cap}}$ cm^{-1}: 3315, 1677, 1597, 716, 700. NMR (10% solution in CCl_4) τ: 8.55 (6H, singlet, $-\underset{\substack{| \\ \text{N}}}{\text{C}}-(CH_3)_2$), 6.45 (2H, singlet, $C_6H_5CH_2-$), 1.7 and 2.6—2.9 (10H, multiplet, benzene proton).

N-Benzoyl-2-benzylamino-2-methylpropiophenone (Xa)——VIIIa (1.23 g, 0.00486 mole) was benzoylated according to the method cited previously to give a neutral fraction, which was recrystallized from benzene–EtOH to afford Xa as colorless fine needles (1.34 g, 77%), mp 188—189.5°. An analytical sample was obtained by repeated recrystallizations from benzene–EtOH and benzene, successively, as colorless needles, mp 188—189°. *Anal.* Calcd. for $C_{23}H_{23}O_2N$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.84; H, 6.44; N, 4.11. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1689, 1620. NMR (10% solution in $CDCl_3$) τ: 8.40 (6H, singlet, $-\underset{\substack{| \\ \text{N}}}{\text{C}}-(CH_3)_2$), 5.14 (2H, singlet, $C_6H_5CH_2-$), 2.0—2.8 (15H, multiplet, benzene proton).

Thermal Rearrangement of (±)-3-Butylimino-2-phenyl-2-butanol ((±)-Vb)——i) Synthesis of (±)-Vb: (±)-IV (1.00 g, 0.00609 mole) was condensed with *n*-butylamine (1.34 g, 0.0183 mole) as in the synthesis of (±)-Va, to give (±)-Vb as a slightly yellow oil (1.18 g, 88%), bp 124—125° (3 mmHg). IR $\nu_{\max}^{\text{cap}}$ cm^{-1}: 3266, 1733 (weak), 1667, 761, 699.

ii) Thermal Rearrangement of (±)-Vb: A solution of (±)-Vb (1.17 g, 0.00534 mole) in freshly distilled decalin (15 ml) was refluxed for 18 hr, then extracted with 18% HCl (10 ml) and 10% HCl (5 ml × 2). Combined acid extracts were refluxed for 15 minutes, washed with benzene (5 ml × 2), made alkaline with 40% NaOH under cooling, and extracted with benzene (10 ml × 3). Combined benzene layers were washed with sat. NaCl, dried over anhyd. K_2CO_3, evaporated under an N_2 atmosphere to give a residual oil, which was distilled under an N_2 atmosphere. The volatile fraction (bp 114° (3 mmHg), a yellow oil, 680 mg) was purified by two column chromatographies using silica gel (first solvent, acetone:*n*-hexane=1:3; second solvent, acetone:*n*-hexane=1:6) and fractional distillation to give a mixture of (±)-VIb and a slight amount of VIIIb as a pale yellow oil (550 mg, 47%), bp 119.5—120° (3.5 mmHg). IR $\nu_{\max}^{\text{cap}}$ cm^{-1}: 3333, 1711, 1682 (weak), 1601, 758, 700. NMR (10% solution in CCl_4) τ: 8.60 (6H, singlet, $-\underset{\substack{| \\ \text{N}}}{\text{C}}-(CH_3)_2$), 8.45 (3H, singlet, $-\overset{|}{\underset{|}{\text{C}}}-CH_3$), 8.25 (1H, singlet, NH), 8.13 (3H, singlet, $-COCH_3$), *ca.* 2.7 (5H, multiplet, benzene proton), no other peaks were assigned.

Thermal Rearrangement of (*R*)(−)-3-Butylimino-2-phenyl-2-butanol ((*R*)(−)-Vb)——i) Synthesis of (*R*)(−)-Vb: (*R*)(−)-IV ($[\alpha]_{\text{D}}^{30}$ −198° (c=0.960, C_6H_6), prepared from (*R*)(−)-III ($[\alpha]_{\text{D}}^{20}$ −41.9° (c=2.01, H_2O) which was 75% optically pure11)) (1.65 g, 0.0101 mole) was treated the same as (±)-IV to give (*R*)(−)-Vb as a slightly pink oil (2.07 g, 94%), $[\alpha]_{\text{D}}^{29}$ −15.5° (l=0.1, neat), bp 121—123° (2.5 mmHg). IR $\nu_{\max}^{\text{cpa}}$ cm^{-1}: 3360, 1667, 760, 699.

---

35) S.D. Upham and O.C. Dermer, *J. Org. Chem.*, **22**, 799 (1957).
36) H.E. Baumgarten, *J. Org. Chem.*, **28**, 2369 (1963).

ii) Thermal Rearrangement of (*R*)(−)-Vb: Thermolysis of (*R*)(−)-Vb (2.07 g, 0.00944 mole) was performed as for (±)-Vb, except that only one column chromatography using silica gel was done (solv. acetone:*n*-hexane=1:6). It gave (+)-VIb containing a small amount of VIIIb as a pale yellow oil (960 mg, 44%), $[\alpha]_D^{23.5}$ +83.3° (c=0.938, EtOH), bp 112.5—113° (2.5 mmHg). IR ν_{max}^{cap} cm^{-1}: 3343, 1713, 1678 (weak), 1601.

Benzoylation of a Mixture of (±)-3-Butylamino-3-phenyl-2-butanone ((±)-VIb) and 2-Butylamino-2-methylpropiophenone (VIIIb) prepared by Thermal Rearrangement——A mixture of (±)-VIb and VIIIb (1.00 g, 0.00456 mole) prepared by thermolysis of (±)-Vb was benzoylated and worked up as for the mixture of (±)-VIa and VIIIa to give a reddish brown viscous oil as a neutral fraction. This oil was distilled fractionally to afford a yellow viscous oil (1.42 g), bp 175—180° (0.1 mmHg). This oil was chromatographed over silica gel (150 g, solv. IPE:*n*-hexane=3:1). The fraction from 600 ml to 675 ml gave Xb as yellow crystals (130 mg), mp 105—111°. These were twice recrystallized from EtOH–*n*-hexane to give colorless needles, mp 113—114°. *Anal.* Calcd. for $C_{21}H_{25}O_2N$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.73; H, 7.81; N, 4.07. IR ν_{max}^{KBr} cm^{-1}: 1688, 1608. A pale yellow viscous oil obtained from the fraction from 775 ml to 1000 ml was submitted to column chromatography using silica gel (solv. CH_2Cl_2:IPE=4:1). This was followed by fractional distillation (bp 168—173° (0.04 mmHg)) to give (±)-IXb as pale yellow crystals (1.01 g), mp 86—89°. IR ν_{max}^{KBr} cm^{-1}: 1712, 1630. NMR (10% solution in $CDCl_3$) τ: 7.98 (3H, singlet, $-\overset{|}{\underset{|}{C}}-CH_3$), 7.88 (3H, singlet, $-COCH_3$), *ca.* 2.6 (10H, multiplet, benzene proton). Assignment of other peaks was difficult. IR-and NMR-spectra were superimposable on those of an authentic sample (cited later). Three recrystallizations from EtOH–*n*-hexane– pet.ether gave colorless prisms, mp 90—91.5°. *Anal.* Calcd. for $C_{21}H_{25}O_2N$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.37; H, 7.74; N, 4.59. IR ν_{max}^{KBr} cm^{-1}: 1712, 1631. This spectrum was superimposable on that of (±)-IXb obtained after the second column chromatography.

Benzoylation of a Mixture of (+)-3-Butylamino-3-phenyl-2-butanone ((+)-VIb) and 2-Butylamino-2-methylpropiophenone (VIIIb) prepared from Thermal Rearrangement——A mixture of (+)-VIb and VIIIb ($[\alpha]_D^{28.5}$ +83.3° (c=0.938, EtOH)) (850 mg, 0.00388 mole) obtained by thermolysis of (*R*)(−)-Vb was treated similar to the racemate to give a viscous oil as a neutral fraction. This was distilled fractionally to afford a yellow viscous oil (960 mg), bp ~177° (0.03 mmHg). The oil obtained was submitted to column chromatography using silica gel (125 g, solv. IPE:*n*-hexane=2:1). Xb was obtained as pale brown crystals from the fraction between 600 ml to 700 ml (90 mg), mp 106—111°, and was recrystallized from EtOH–*n*-hexane to give pale brown needles, mp 111—113°. No depression was shown on the mixed melting point with an authentic sample. A fraction from 800 ml to 1075 ml gave a pink viscous oil, which was worked up the same as the racemate to afford (−)-IXb as yellow crystals (700 mg), bp ~182° (0.06 mmHg), mp 62—75°, mixed melting point with an authentic sample (cited later, mp 79—80.5°) was 70—79°, $[\alpha]_D^{14.5}$ −12.5° (c=2.28, EtOH). IR ν_{max}^{KBr} cm^{-1}: 1705, 1633, 732, 706. NMR (10% solution in $CDCl_3$) τ: 7.99 (3H, singlet, $-\overset{|}{\underset{|}{C}}-CH_3$), 7.39 (3H, singlet, $-COCH_3$), *ca.* 2.5 (10H, multiplet, benzene proton). Assignment of other peaks was difficult. These spectra were superimposable on those of an authentic sample. After treatment with charcoal, two recrystallizations from benzene–*n*-hexane gave a mixture, which was separated, of slightly yellow cotton–like crystals and pale yellow prisms. Cotton–like crystals, 140 mg, mp 89—91°. Prisms, 350 mg, mp 79.5—81°. The former was recrystallized from EtOH–benzene–*n*-hexane to give colorless cotton–like crystals, mp 89.5—91.5°. *Anal.* Calcd. for $C_{21}H_{25}O_2N$: N, 4.33. Found: N, 4.59. IR ν_{max}^{KBr} cm^{-1}: 1710, 1630. This spectrum was superimposable on that of an authentic sample of (±)-IXb. The latter was recrystallized from benzene–*n*-hexane to give colorless prisms, mp 80—81°, $[\alpha]_D^{14.5}$ −16.6° (c=1.45, EtOH). *Anal.* Calcd. for $C_{21}H_{25}O_2N$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.75; H, 7.69; N, 4.32. IR ν_{max}^{KBr} cm^{-1}: 1704, 1633. This spectrum was almost superimposable on that of (−)-IXb for column chromatographic purification.

(±)-3-Amino-3-phenyl-2-butanone ((±)-XIII)——Using a method reported previously,[10] (±)-XIII was prepared from (±)-VII by way of (±)-N-phthaloyl-α-methylphenylglycine-((±)-XVIII)(mp 183.5—186°, 45%), bp 98—100° (5 mmHg), 34% based on (±)-XVII (lit.[10] bp 123—124° (11.5 mmHg), 50%).

(*S*)(+)-3-Amino-3-phenyl-2-butanone ((*S*)(+)-XIII)——Similar to the racemate, (*S*)(+)-VII ($[\alpha]_D$ +85.8° (NHCl), optical purity 95%)[37] was converted to (*S*)(+)-XIII by way of (*S*)(+)-XVII (mp 148—151°, 34%, $[\alpha]_D^{31.5}$ +16.0° (c=0.998, EtOH)), bp 111.5—112.5° (8.5 mmHg), 59% based on (*S*)(+)-XVII, $[\alpha]_D^{27}$ +5.57° (l=0.1, neat), optical purity 99%.[17] IR ν_{max}^{cap} cm^{-1}: 3380, 3310, 1715, 762, 703 (lit.[10] bp 94—97° (4 mmHg), 26%, $[\alpha]_D^{10}$ +5.104° (l=0.1, neat)).

(±)-3-Butylamino-3-phenyl-2-butanone ((±)-VIb)——Freshly distilled *n*-butyraldehyde (2.99 g, 0.0414 mole) in anhydrous ether (20 ml) was added to a solution of (±)-XIII (2.26 g, 0.0138 mole) in anhydrous ether (20 ml) containing molecular sieves (3.0 g) under an N_2 atmosphere and cooling. The whole was left overnight at room temperature. Molecular sieves were filtered and washed with ether. Filtrate and washings were evaporated *in vacuo* below 20° under on N_2 atmosphere. A mixture of the residue and PtO_2 (330 mg) in EtOH (26 ml) was hydrogenated at room temperature and atmospheric pressure. After the theoretical

---

[37] The specific rotation cited here was calculated as an arithmetical mean from specific rotations of seven lots of the (*S*)(+)-VII used as starting material.

amount of H_2 gas was absorbed, the catalyst was filtered and washed with EtOH. The combined ethanolic filtrate and washings were evaporated to dryness under an N_2 atmosphere yielding a residual oil, which was dissolved in benzene (25 ml). The solution was extracted with 18% HCl (10 ml) and 10% HCl (10 ml). Combined acid extracts were warmed for a while, and washed with benzene. They were made alkaline with 40% NaOH under cooling and extracted with benzene (10 ml, 5 × 2). Combined organic layers were washed with sat. NaCl and dried over anhydrous K_2CO_3. Filtration and evaporation gave a pale yellow oil, which was chromatographed over alumina (solv. AcOEt:*n*-hexane = 1:10) and silica gel (solv. AcOEt:*n*-hexane = 1:3), successively. This was followed by fractional distillation under an N_2 atmosphere to give (±)-VIb as a colorless oil (1.08 g, 25%), bp 116—117.5° (3 mmHg). IR ν_{max}^{cap} cm^{-1}: 3332, 1716, 1602, 759, 701. NMR (10% solution in CCl_4) τ: 9.08 ($NH(CH_2)_3C\underline{H}_3$), 8.4—8.8 ($NHCH_2(CH_2)_2$–$C\underline{H}_2$), 8.46 (3H, singlet, $-\overset{|}{C}-CH_3$), 8.20 (1H, singlet, NH), 8.12 (3H, singlet, $-COCH_3$), 7.67 (2H, multiplet $NHCH_2-$), *ca.* 2.7 (5H, multiplet, benzene proton).

(*S*)(+)-3-Butylamino-3-phenyl-2-butanone ((*S*)(+)-VIb)——(*S*)(+)-XIII ($[\alpha]_D^{27}$ +5.57° (l=0.1, neat), optical purity 99%17)) (4.05 g, 0.0248 mole) was treated similar to (±)-XIII, except that an eluting solvent of silica gel column chromatography (*n*-hexane:acetone = 10:1) was used to give (*S*)(+)-VIb as a pale yellow oil (1.33 g, 24%), bp 115° (2.5 mmHg), $[\alpha]_D^{28.5}$ +114 (c=1.09, EtOH). IR ν_{max}^{cap} cm^{-1}: 3336, 1715, 1603, 762, 703.

(±)-N-Benzoyl-3-butylamino-3-phenyl-2-butanone ((±)-IXb)——(±)-VIb (530 mg, 0.00242 mole) was benzoylated and worked up the same as (±)-VIa to give a brown viscous oil as a neutral fraction. The oil was distilled fractionally to afford a pale yellow viscous oil, bp ~168.5° (0.04 mmHg). This was purified twice by column chromatography using silica gel (first solvent, IPE:*n*-hexane = 3:1; second solvent, CH_2Cl_2:IPE = 4:1) to give (±)-IXb as almost colorless crystals (420 mg), mp 88—91°, IR ν_{max}^{KBr} cm^{-1}: 1711, 1630. NMR (10% solution in $CDCl_3$) τ: 7.98 (3H, singlet, $-C-CH_3$), 7.88 (3H, singlet, $-COCH_3$), *ca.* 2.6 (10H, multiplet, benzene proton). Other peaks were too complicated for assignment of the origin of protons. Two recrystallizations from EtOH–*n*-hexane–pet. ether gave colorless cotton–like crystals, mp 90—91°. *Anal.* Calcd. for $C_{21}H_{25}O_2N$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.07; H, 7.82; N, 4.07. IR and NMR spectra were superimposable on those of (±)-IXb when purified by column-chromatography.

(*S*)(−)-N-Benzoyl-3-butylamino-3-phenyl-2-butanone ((*S*)(−)-IXb)——(*S*)(+)-VIb ($[\alpha]_D^{28.5}$ +114° (c=1.09, EtOH) (1.00 g, 0.00457 mole) was treated similar to (±)-VIb to give pale yellow crystals at the step of column chromatography (780 mg), mp 79—80.5°. $[\alpha]_D^{15}$ −15.7°. (c=2.18, EtOH). IR ν_{max}^{KBr} cm^{-1}: 1706, 1634, 732, 702. NMR spectrum was superimposable on that of an authentic sample of (±)-IXb. Optical purity of this sample was 99%, as it was obtained from (*S*)(+)-XIII with no effect on that compound's 99% optical purity. The percent of retention of optical activity with phenyl migration was 105%. An analytical sample was obtained after three recrystallizations from benzene–*n*-hexane as almost colorless prisms, mp 80—81°, $[\alpha]_D^{15}$ −15.9° (c=2.13, EtOH). *Anal.* Calcd. for $C_{21}H_{25}O_2N$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.79; H, 7.86; N, 4.61. IR and NMR spectra were superimposable on those of (*S*)(−)-IXb at the step of column chromatographic purification.

(±)-2-Hydroxy-2-phenyl-3-pentanone ((±)-XXI)——A solution of C_2H_5Li prepared from Li powder38) (3.32 g, 0.478 mole) and C_2H_5Br (17.4 g, 0.159 mole) in anhydrous ether (230 ml) was added to a suspension of the lithium salt of (±)-III, prepared from (±)-III·1/2 H_2O (11.2 g, 0.0639 mole) in anhydrous ether (80 ml). The mixture was refluxed with stirring for 30 hr, cooled, then decomposed with H_2O (100 ml). (±)-III·1/2 H_2O was recovered from the aqueous layer as yellow crystals (5.9 g, 53%). The ether layer was washed with sat. NaCl, 5% HCl and sat. NaCl, then dried over anhydrous Na_2SO_4, and evaporated to give a residual oil. This was distilled to afford a slightly yellow oil as a volatile fraction (4.23 g), bp 107—127° (7 mmHg). The oil was purified with column chromatography twice using silica gel (solv. CH_2Cl_2:IPE = 20:1, 10:1), followed by fractional distillation to give (±)-XXI as a colorless oil (3.14 g, 28% based on starting material used, 58% based on reacted acid), bp 100—105° (3 mmHg) (lit.39) bp 131—132° (10 mmHg). *Anal.* Calcd. for $C_{10}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.83; H, 8.18. IR ν_{max}^{cap} cm^{-1}: 3453, 1715, 756, 700. NMR (10% solution in CCl_4) τ: 9.09 (3H, triplet, J=7.2 cps, $-CH_2C\underline{H}_3$), 8.35 (3H, singlet, $-\overset{|}{C}-CH_3$), 7.65 (2H, quartet, J=7.2 cps, $-C\underline{H}_2-CH_3$), 5.66 (1H, singlet, –OH), *ca.* 2.7 (5H, multiplet, benzene proton).

(*S*)(+)-2-Hydroxy-2-phenyl-3-pentanone ((S)(+)-XXI)——(*S*)(+)-III ($[\alpha]_D^{22}$ +47.8° (c=1.49, H_2O), optical purity 85%11)) (10.7 g, 0.0648 mole) was treated as was (±)-III·1/2 H_2O to give (*S*)(+)-XXI as a colorless oil (3.29 g, 29% based on (*S*)(+)-III used, 75% based on reacted acid), bp 110—113° (5 mmHg), $[\alpha]_D^{26}$ +211° (c=0.940, C_6H_6). IR ν_{max}^{cap} cm^{-1}: 3443, 1710, 760, 702. Unreacted (*S*)(+)-III was recovered from the reaction mixture (6.6 g, 62%), mp 110—113°, $[\alpha]_D^{26}$ +47.6° (c=1.99, H_2O).

Thermal Rearrangement of (±)-3-Benzylimino-2-phenyl-2-pentanol ((±)-XXII)——i) Synthesis of (±)-XXII: (±)-XXI (6.02 g, 0.0338 mole) was condensed with benzylamine (10.86 g, 0.101 mole) similar to the synthesis of (±)-Va, except that anhydrous toluene was used as solvent and the refluxing period

---

38) T.D. Perrine and H. Rapoport, *Anal. Chem.*, **1948**, 635.

39) A.M. Yanovitskaya, *J. Gen. Chem., USSR*, **22**, 1213 (1952).

continued for 27 hr to give (±)-XXII as a pale yellow viscous oil (8.41 g, 93%), bp 161—175° (0.07 mmHg). IR $\nu_{\max}^{\text{cap}}$ cm^{-1}: 3275, 1711 (weak), 1653.

ii) Thermal Rearrangement of (±)-XXII: The solution of (±)-XXII (8.41 g, 0.0315 mole) in freshly distilled decalin (84 ml) was refluxed for 10 hr and worked up as the same as the thermal rearrangement of (±)-Va to give a brown oil as the basic fraction. The oil was distilled fractionally under an N_2 atmosphere to give a yellow oil (4.50 g), bp 40—154° (0.035 mmHg). This was submitted to column chromatography using silica gel (solv. CH_2Cl_2:IPE=10:1) to afford a mixture of (±)-XXIII and a small amount of (±)-XXIV (4.05 g, 48%). IR $\nu_{\max}^{\text{cap}}$ cm^{-1}: 3342, 1713, 1678. NMR (10% solution in CCl_4) τ: 9.23 (*ca.* 3H, triplet $J=7.2$ cps, $-CH_2-\underline{CH_3}$), 8.58 (0.4H, singlet, $-\overset{|}{C}-CH_3$), 8.13 (3H, singlet, $-COCH_3$), *ca.* 7.8 (*ca.* 3H, multiplet, $-\underline{CH_2}-CH_3$ and NH), 6.65 (2H, singlet, $-CH_2C_6H_5$), *ca.* 2.8 (*ca.* 10H, multiplet, benzene proton). The separation of (±)-XXIII and (±)-XXIV was successful by two column chromatographies using silica gel (first solvent, *n*-hexane:CH_2Cl_2:IPE=20:10:1; second solvent, 10:10:1), but the mixture of (±)-XXIII and (±)-XXIV was used for the following reaction without further purification.

Semicarbazone of acetophenone was obtained from the neutral fraction (1.43 g), mp 194—196°. The yield of acetophenone was calculated as 1.06 g (23%) based on the yield of acetophenone semicarbazone.

Thermal Rearrangement of (*S*)(+)-3-Benzylimino-2-phenyl-2-pentanol ((*S*)(+)-XXII)——i) Synthesis of (*S*)(+)-XXII: (*S*)(+)-XXI ($[\alpha]_D^{26}$ +211° ($c=0.940$, C_6H_6) 3.06 g, and $[\alpha]_D^{26.5}$ +218° ($c=0.986$, C_6H_6) 3.16 g. Both were prepared from (*S*)(+)-III ($[\alpha]_D^{26}$ +47.6° ($c=1.99$, H_2O)) which was 92% optically pure)(6.22 g, 0.0349 mole). Treatment was similar to (±)-XXI, except that the reaction mixture was refluxed for 25 hr to give (*S*)(+)-XXII as a pale yellow viscous oil (8.84 g, 95%), bp 155—163.5° (0.04 mmHg), $[\alpha]_D^{27}$ +218° ($c=0.876$, C_6H_6). IR $\nu_{\max}^{\text{cap}}$ cm^{-1}: 3264, 1713 (weak), 1663, 766, 746, 700.

ii) Thermal Rearrangement of (*S*)(+)-XXII: Thermolysis of (*S*)(+)-XXII (8.76 g, 0.0328 mole) was performed as for (±)-XXII to afford a mixture of (−)-XXIII and a some (−)-XXIV from the basic fraction (4.64 g, 53%), $[\alpha]_D^{26.5}$ −24.2° ($c=1.10$, C_6H_6). IR $\nu_{\max}^{\text{cap}}$ cm^{-1}: 3343, 1712, 1680. The neutral fraction contained acetophenone (980 mg, 25%).

Benzoylation of a Mixture of (±)-3-Benzylamino-3-phenyl-2-pentanone ((±)-XXIII) and (±)-2-Benzylamino-2-methylbutyrophenone ((±)-XXIV) prepared by the Thermal Rearrangement——Benzoyl chloride (3.08 g, 0.0209 mole) was added to a solution of a mixture of (±)-XXIII and (±)-XXIV (3.91 g, 0.0146 mole) obtained from thermolysis of (±)-XXII in anhydrous pyridine (40 ml). The whole was refluxed for 6 hr, then poured onto ice and water (160 ml) and kept overnight at room temperature. The mixture was acidified with conc. HCl under cooling, and extracted with AcOEt containing 10% MeOH (50 ml×2) and CH_2Cl_2 (50 ml×2, 30 ml). Combined extracts were washed with sat. NaCl, 5% Na_2CO_3, sat. NaCl, then dried over anhydrous Na_2SO_4, and evaporated to dryness to give a mixture of a brown oil and crystals (A) (2.80 g). A mixture of (±)-XXIII and (±)-XXIV was recovered from the aq. HCl layer as a brown oil (1.96 g). A mixture of a portion (490 mg, 0.00202 mole) of this oil, benzoylchloride (520 mg, 0.00404 mole) and anhydrous pyridine (5 ml) was refluxed for 30 hr and worked up in the usual way to give a dark brown viscous oil from the neutral fraction (B) (470 mg). Fraction A, obtained earlier, was chromatographed twice over silica gel (first solvent, *n*-hexane:CH_2Cl_2:IPE=10:10:1; second solvent, CH_2Cl_2:IPE=10:1) to afford soft brown crystals as the fraction containing all the (±)-XXVI (890 mg). These were separated with column chromatography using silica gel (solv. *n*-hexane:CH_2Cl_2:IPE=3:2:1) to two fractions. One of these fractions contained pale yellow crystals (C) (400 mg), the other contained a pale brown viscous oil (D). Chromatography of fraction C over silica gel (solv. CH_2Cl_2:IPE=10:1) gave (±)-XXVI as a colorless solid (240 mg), mp 189—191°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1684, 1621. This spectrum was almost superimposable on that of an authentic sample prepared from (±)-isovaline ((±)-XXVII). NMR (6% solution in $CDCl_3$) τ: 9.16 (3H, triplet $J=7.2$ cps, $-CH_2-\underline{CH_3}$), 8.42 and 8.32 (3H, two peaks of singlet, $-\overset{|}{C}-CH_3$), 7.8—8.2 (2H, multiplet, $-\underline{CH_2}-CH_3$), 5.15 (2H, AB type quartet, but not clear, $-CH_2\ C_6H_5$), 2.1, 2.7 (15H, multiplet, benzene proton). This NMR spectrum was same as that of an authentic sample. Two recrystallizations from benzene gave colorless needles, mp 191.5—192.5°. *Anal.* Calcd. for $C_{25}H_{25}O_2N$: C, 80.83; H, 6.78; N, 3.77. Found: C, 81.11; H, 6.70; N, 4.00. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1685, 1622. This IR spectrum was superimposable on that of (±)-XXVI at the step of column chromatographic purification.

Fraction B was submitted to column chromatography using silica gel (solv. *n*-hexane:CH_2Cl_2:IPE=3:2:1) to give a yellow viscous oil as the fraction containing (±)-XXV (280 mg). A mixture of this oil and a portion of fraction D (total 450 mg) was chromatographed four times over silica gel (first solvent, CH_2Cl_2:IPE=4:1; second solvent, CH_2Cl_2:IPE=10:1; third solvent, IPE:*n*-hexane=3:1; fourth solvent, CH_2Cl_2:IPE=10:1) to afford (±)-XXV as slightly yellow crystals (360 mg), mp 103—106°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1714, 1631. This IR spectrum was superimposable on that of an authentic sample prepared from (±)-α-ethylphenylglycine. NMR (10% solution in $CDCl_3$) τ: 9.10 (3H, triplet, $J=7.2$ cps, $-CH_2\underline{CH_3}$) 7.71 (3H, singlet, $-COCH_3$), 7.2—8.3 (2H, multiplet, $-CH_2-\underline{CH_3}$). 5.53 (2H, singlet, $-CH_2\ C_6H_5$), *ca.* 2.7 (15H, multiplet, benzene proton). This NMR spectrum was identical with that of an authentic sample. Three recrystallizations from EtOH–IPE–*n*-hexane gave almost colorless prisms, mp 106—107°. IR and NMR spectra were superimposable on those of (±)-XXV at the point just after last column chromatography. *Anal.* Calcd. for $C_{25}H_{25}O_2N$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.69; H, 6.73; N, 3.65.

Benzoylation of a Mixture of (−)-3-Benzylamino-3-phenyl-2-pentanone ((−)-XXIII) and (−)-2-Benzylamino-2-methylbutyrophenone ((−)-XXIV)——Benzyl chloride (3.46 g, 0.0219 mole) was added to a solution of a mixture of (*R*)(−)-XXIII and (−)-XXIV ($[\alpha]_D^{26.5}$ −24.2° (c=1.10, C_6H_6)) (4.38 g, 0.0164 mole) prepared from thermolysis of (*S*)(+)-XXII in anhydrous pyridine (44 ml). The whole was refluxed for 6 hr, poured onto cold water (176 ml) and left overnight at room temperature. The mixture was adjusted to pH 1 with conc. HCl (50 ml) and extracted with CH_2Cl_2 (50 ml × 4). Combined extracts were washed with sat. NaCl, 5% Na_2CO_3 and sat. NaCl, dried over anhydrous Na_2SO_4, then evaporated *in vacuo* to give a dark brown oil (4.55 g). Because of contamination of a starting materials, this oil was triturated with benzene (10 ml). Undissolved crystals (A) were filtered and washed with benzene. Filtrate and washings were combined and extracted with 10% HCl (10 ml × 2, 5 ml). The organic layer was washed with sat. NaCl, dried over anhydrous Na_2SO_4 and evaporated to dryness to give a residual oil, which was combined with fraction A. The entire neutral fraction (B) weighed 2.91 g. A mixture of (—)-XXIII and (−)-XXIV (2.41 g, 0.00902 mole) recovered from both aq. HCl layers was dissolved in anhydrous pyridine (24 ml). Benzoyl chloride (2.53 g, 0.0271 mole) was added to this solution. The whole was refluxed for 37 hr and worked up as usual to give a dark brown viscous oil (C) in the neutral fraction (2.57 g). Column chromatography of fractionB over silica gel (solv. *n*-hexane:CH_2Cl_2:IPE=10:5:1, a ratio of *n*-hexane was decreased stepwise) gave two fractions. One contained a mixture of yellow crystals and oil (D) (1.55 g), which was a mixture of all of the (+)-XXVI and a portion of the (+)-XXV. The other was an oil (E) containing (+)-XXV. Fraction D was further chromatographed over silica gel (155 g, solv. *n*-hexane:CH_2Cl_2:IPE=10:5:1 was used till 1900 ml, followed by *n*-hexane:CH_2Cl_2:IPE=3:2:1). Fractions from 2050 ml to 2200 ml gave (+)-XXVI as colorless crystals partially coloreed (400 mg), mp 202—212°. ORD (c=0.604, $CHCl_3$): peak $[\alpha]_{342}^{25.5}$ +63.1°. IR ν_{max}^{KBr} cm^{-1}: 1683, 1616. This IR spectrum was superimposable on that of an authentic sample prepared from (*R*)(−)-isovaline ((*R*)(−)-XXVII). NMR spectrum was identical with those of (±)-XXVI and an authentic sample. Two recrystallizations from EtOH–benzene–*n*-hexane gave colorless pillars, mp 215—216°. *Anal.* Calcd. for $C_{25}H_{25}O_2N$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.80; H, 6.69; N, 4.04. ORD (c=0.994, $CHCl_3$): peak $[\alpha]_{26}^{342}$ +69.9°. IR and NMR spectra were identical with those of (+)-XXVI from column chromatographic purifications.

Fractions from 2250 ml to 2475 ml from the column chromatography of fraction D gave a yellow viscous oil (F). Fraction C was chromatographed twice (first solvent, *n*-hexane:CH_2Cl_2:IPE=10:5:1; second solvent, *n*-hexane:CH_2Cl_2:IPE=3:2:1) to afford a viscous oil, to which fraction E and F was added to give a pale brown viscous oil containing all the (+)-XXV (2.64 g). A portion (1.66 g) of this oil was submitted to a column chromatography using silica gel (166 g, solv. *n*-hexane:CH_2Cl_2:IPE=3:2:1). A pale brown viscous oil obtained from the fractions from 750 ml to 1175 ml was purified with column chromatography again using silica gel (solv. CH_2Cl_2:IPE=10:1) to give (+)-XXV as pale yellow crystals (1.42 g), mp 98—103°, $[\alpha]_D^{19}$ +92.4 (c=1.11, EtOH). IR ν_{max}^{KBr} cm^{-1}: 1716, 1622. This spectrum was superimposable on that of an authentic sample of an enantiomer prepared from (*S*)(+)-XXX. NMR (10% solution in $CDCl_3$) τ: 9.10 (3H, triplet, J=7.2 cps, $-CH_2-C\underline{H}_3$), 7.70 (3H, singlet, $-COCH_3$), 7.1—8.3 (2H, multiplet, $-C\underline{H}_2-CH_3$), 5.50 (2H, singlet, $C_6H_5CH_2-$), 2.3—3.1 (15H, multiplet, benzene proton). This NMR spectrum was identical with that of an authentic sample of the enantiomer. An analytical sample was prepared by four recrystallizations from EtOH–IPE–*n*-hexane to give almost colorless pillars, mp 104—105.5°, $[\alpha]_D^{17}$ +102° (c=1.02, EtOH). *Anal.* Calcd. for $C_{25}H_{25}O_2N$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.64; H, 6.86; N, 4.07. IR ν_{max}^{KBr} cm^{-1}: 1716, 1622. This IR spectrum was superimposable on that of (+)-XXV at the step of column chromatographic purification.

Resolution of Isovaline (XXVII)——A reflux of a mixture (±)-2-phenyl-4-ethyl-4-methyl-2-oxazolin-5-one prepared from (±)-XXVII,40) using the method reported previously20) and an equivalent amount of *l*-menthol in anhydrous toluene with a trace of *p*-toluenesulfonic acid, gave a mixture of diastereomeric menthylesters, which was separated20) and hydrolyzed with aqueous alcoholic KOH and 47% HBr, successively, to afford (*R*)(−)-XXVII·H_2O (88% based on menthylester), $[\alpha]_D^{27}$ −12.7° (c=1.85, H_2O) (lit.20) $[\alpha]_D^{21}$ −11.9° (c=0.786, H_2O).

(±)-N-Phthaloyl-isovaline ((±)-XXVIII)——(±)-XXVII·H_2O (20.4 g, 0.150 mole) was phthaloylated similar to the phthaloylation of XIV to give (±)-XXVIII as colorless prisms (24.3 g, 60%), mp 138—141° (lit.35) mp 137—138°, 54%). IR ν_{max}^{KBr} cm^{-1}: 1770, 1725, 1713, 720.

(*R*)(+)-N-Phthaloyl-isovaline ((*R*)(+)-XXVIII)——(*R*)(−)-XXVII·H_2O ($[\alpha]_D^{27}$ −11.8° (c=1.87, H_2O) 1.11 g, $[\alpha]_D^{27}$ −12.7° (c=1.85, H_2O) 8.89 g, optically pure21)) (10.0 g, 0.0740 mole) was treated as same as the racemate, except that aqueous 30% EtOH was used as solvent for recrystallization41) to give (*R*)(+)-XXVIII as colorless crystals (12.95 g, 71%), mp 150—153°, $[\alpha]_D^{28}$ +2.25° (c=1.07, EtOH). Two recrystallizations from aqueous EtOH gave colorless needles, mp 153—154°, $[\alpha]_D^{30}$ +2.91° (c=3.02, EtOH). *Anal.* Calcd. for

---

40) P.A. Levene and R.E. Steiger, *J. Bio. Chem.*, **76**, 299 (1928).

41) Since the starting material, (*R*)(−)-XXVII·H_2O, was optically pure, purification by recrystallization had no effect on the optical purity of compounds during correlation.

$C_{13}H_{13}O_4N$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.36; H, 5.23; N, 5.83. IR ν_{max}^{KBr} cm^{-1}: 1769, 1724, 1708, 720.

(±)-2-Amino-2-methylbutyrophenone ((±)-XXIX)——A mixture of (±)-XXVIII (5.00 g, 0.0202 mole) and $SOCl_2$ (5 ml) was refluxed for 1 hr. Excess $SOCl_2$ was evaporated under reduced pressure in an N_2 atmosphere. Addition of anhydrous benzene, followed by evaporation, was repeated three times to completely remove $SOCl_2$. The acid chloride of (±)-XXVIII obtained was used for further experiments. A solution of acid chloride in anhydrous benzene (25 ml) was added to the suspension of $AlCl_3$ (4.8 g, 0.0359 mole) in anhydrous benzene (20 ml) under stirring. The reaction mixture was stirred for 17.5 hr at 37° and treated with 2% HCl (25 ml). Undissolved material was filtered. The organic layer which separated was washed with sat. NaCl, 5% Na_2CO_3 and sat. NaCl, then dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give a brown viscous oil, which was dissolved in a mixture of AcOH (20 ml) and 48% HBr (20 ml). The whole was refluxed for 6 hr and evaporated to dryness *in vacuo*. Addition of H_2O followed by evaporation was repeated twice giving a residue, to which was added H_2O (30 ml). Undissolved material was filtered and washed with water. Combined filtrate and washings were washed with AcOEt (25 ml), made alkaline with 40% NaOH (6 ml) and extracted with benzene (20 ml × 2, 10 ml). Combined benzene layers were washed with sat. NaCl, dried over anhydrous K_2CO_3 and evaporated *in vacuo* under an N_2 atmosphere to give a residual oil, which was distilled fractionally under an N_2 atmosphere to afford (±)-XXIX as a colorless oil (1.03 g, 29%), bp 103—105° (3 mmHg). IR ν_{max}^{KBr} cm^{-1}: 3376, 3305, 1678, 1601, 768, 708.

(±)-N-Benzoyl-2-amino-2-methylbutyrophenone: colorless cotton–like crystals (from EtOH–benzene), mp 153—154.5°. *Anal.* Calcd. for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.81; H, 6.69; N, 5.14. IR ν_{max}^{KBr} cm^{-1}: 3276, 1678, 1633, 1530.

(*R*)(−)-2-Amino-2-methylbutyrophenone ((*R*)(−)-XXIX)——(*R*)(+)-XXVIII ($[\alpha]_D^{28}$ +2.25° (c=1.07, EtOH)) (10.0 g, 0.0405 mole) was treated the same as (±)-XXVIII to give (*R*)(−)-XXIX as a colorless oil (1.71 g, 24%), bp 108—111° (5.5 mmHg), $[\alpha]_D^{27.5}$ −18.7° (c=1.14, C_6H_6). IR ν_{max}^{cap} cm^{-1}: 3359, 3305, 1673, 1599.

(*R*)(+)-N-Benzoyl-2-amino-2-methylbutyrophenone: colorless needles (from benzene), mp 147—148°, $[\alpha]_D^{19}$ +11.2° (c=1.04, EtOH). *Anal.* Calcd. for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.18; H, 6.55; N, 4.80. IR ν_{max}^{KBr} cm^{-1}: 3264, 1674, 1628, 1521.

(±)-2-Benzylamino-2-methylbutyrophenone ((±)-XXIV)——(±)-XXIX (1.23 g, 0.00694 mole) was treated the same as in the synthesis of VIIIa from XVI, to give (±)-XXIV as a pale yellow oil by way of (±)-2-benzylimino-2-methylbutyrophenone (bp 152.5—156° (0.075 mmHg)) (1.19 g, 65%), bp 161—166° (0.06 mmHg). IR ν_{max}^{cap} cm^{-1}: 3327, 1675, 1598, 698. NMR (10% solution in CCl_4) τ: 9.16 (3H, triplet, J=7.2 cps, $-CH_2-C\underline{H}_3$), 8.60 (3H, singlet, $-\overset{|}{\underset{|}{C}}-CH_3$), 8.53 (1H, singlet, –NH), 8.12 (2H, quartet J=7.2 cps, $-C\underline{H}_2-CH_3$), 6.45 (2H, quartet J_{AB}=12 cps, $C_6H_5CH_2-$), *ca.* 1.75 and 2.6—2.85 (10H, multiplet, benzene proton).

(*R*)(−)-2-Benzylamino-2-methylbutyrophenone ((*R*)(−)-XXIV)——(*R*)(−)-XXIX ($[\alpha]_D^{27.5}$ −18.7° (c=1.14, benzene)) (1.20 g, 0.00678 mole) was treated similar to (±)-XXIX, except that column chromatography was carried out over silica gel (solv. *n*-hexane:CH_2Cl_2:IPE=10:10:1) instead of alumina to give (*R*)(−)-XXIV as a slightly yellow oil by way of (*R*)(−)-2-benzylimino-2-methylbutyrophenone (bp 161—162° (0.07 mmHg), $[\alpha]_D^{33}$ −76.1° (c=1.15, EtOH)) (1.24 g, 68%), bp 157—160° (0.03 mmHg), $[\alpha]_D^{29}$ −32.8° (c=1.09, C_6H_6). IR ν_{max}^{cap} cm^{-1}: 3316, 1674, 702.

(±)-N-Benzoyl-2-benzylamino-2-methylbutyrophenone ((±)-XXVI)——A mixture of (±)-XXIV (530 mg, 0.00198 mole), benzoyl chloride (420 mg, 0.00297 mole) and anhydrous pyridine (5.3 ml) was refluxed for 6 hr and worked up as usual to give a yellow solid as a neutral fraction, which was recrystallized from benzene to afford (±)-XXVI as almost colorless cotton–like crystals (550 mg, 75%), mp 191—192°. Two recrystallizations from benzene gave colorless cotton–like crystals, mp 190.5—191.5°. *Anal.* Calcd. for $C_{25}H_{25}O_2N$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.72; H, 6.84; N, 3.66. IR ν_{max}^{KBr} cm^{-1}: 1687, 1621. NMR (*ca.* 7% solution in $CDCl_3$) τ: 9.17 (3H, triplet, J=7.2 cps, $-CH_2-C\underline{H}_3$), 8.44 (3H, singlet, $-\overset{|}{\underset{|}{C}}-CH_3$), 7.85 (2H, quartet, J=7.2 cps, $-C\underline{H}_2-CH_3$), 5.13 (2H, quartet, J=15.6 cps, $C_6H_5CH_2-$), 1.95—2.8 (15H, multiplet, benzene proton).

(*R*)(+)-N-Benzoyl-2-benzylamino-2-methylbutyrophenone ((*R*)(+)-XXVI)——The same treatment of (*R*)(−)-XXIV ($[\alpha]_D^{29}$ −32.8° (c=1.09, C_6H_6)) (700 mg, 0.00262 mole) as for (±)-XXIV gave a pale yellow solid as a neutral fraction. This was purified with column chromatography using silica gel (solv. *n*-hexane:CH_2Cl_2:IPE=5:2:1, finally CH_2Cl_2) followed by two recrystallizations[41] from EtOH–benzene to give (*R*)(+)-XXVI as colorless needles (290 mg), mp 215—216°, ORD (c=0.604, $CHCl_3$): peak $[\alpha]_{342}^{26.5}$ +68.9°. The optical purity of this sample was 100%. Optical rotation of (+)-XXVI obtained from thermolysis followed by benzoylation of (*S*)(+)-XXII (optical purity 92%) was $[\alpha]_{342}^{25.5}$ +63.1° (c=0.604, $CHCl_3$). Thus, the percent of retention of optical purity with methyl migration was calculated as 100%. *Anal.* Calcd. for $C_{25}H_{25}O_2N$: C, 80.83; H, 6.78; N, 3.77. Found: C, 81.13; H, 6.79; N, 3.74. IR ν_{max}^{KBr} cm^{-1}: 1681, 1615.

(±)-α-Ethylphenylglycine——(±)-5-Ethyl-5-phenylhydantoin[42] prepared from propiophenone was hydrolyzed with aqueous $Ba(OH)_2$ solution according to Herbst's method.[43] At the working up, filtrate and washings of $BaCO_3$ were acidified with conc. HCl and evaporated to dryness to give amino acid hydrochloride, which was extracted with EtOH and submitted to column chromatography using Amberlite IR 120 (H^+ form) to afford (±)-α-ethylphenylglycine (71%) (lit.[43] 90%).

(±)-N-Formyl-α-ethylphenylglycine ((±)-XXX)——A mixture of acetic anhydride (25.6 g, 0.250 mole) and 98% formic acid (11.8 g, 0.250 mole) was warmed at 50—60° with stirring for 2.5 hr. (±)-α-ethylphenylglycine (8.97 g, 0.0500 mole) was added to this solution and the whole was warmed at 50—60° for 2 hr with stirring, then treated with H_2O (30 ml) under cooling, and kept overnight at room temperature. The reaction mixture was evaporated to dryness to give a residue, which was recrystallized from aqueous EtOH to afford (±)-XXX as colorless crystals (8.77 g, 85%), mp 188—189° (decomp.) (lit.[24] mp 193°).

Resolution of N-Formyl-α-ethylphenylglycine(XXX)——The quinine salt of (±)-XXX, prepared by Sobotka's method,[24] was recrystallized from 20% aqueous EtOH five times to give a diastereomeric salt (42.5 g), mp 187—190°, $[\alpha]_D^{25}$ −68.9° (c=1.04, EtOH). Recrystallization of the (*S*)(+)-XXX obtained from this salt from aqueous EtOH, gave (*S*)(+)-XXX as colorless prisms (12.96 g), mp 204—205.5° (decomp.), $[\alpha]_D^{26}$ +126° (c=1.05, 1N NaOH) (lit.[24] mp 212°, $[\alpha]_D$ +126° (c=1.00, aq. alkali)). The (*R*)(−)-XXX recovered from all the mother liquors of recrystallizations of the quinine salt was recrystallized from aqueous EtOH eight times to give (*R*)(−)-XXX as colorless pillars, mp 203—205° (decomp.), $[\alpha]_D^{27}$ −124° (c=1.03, 1N NaOH).

(±)-Ethyl N-Ethoxycarbonylacetyl-α-ethylphenylglycinate ((±)-XXXI)——$SOCl_2$ (8.9 g, 0.0744 mole) was added to a suspension of (±)-α-ethylphenylglycine hydrochloride (8.0 g, 0.0372 mole) in abs. EtOH (80 ml) under cooling. The whole was refluxed for 6 hr and evaporated to dryness. Addition of $CHCl_3$ followed by evaporation was repeated three times to give a residue, which was triturated with $CHCl_3$. Undissolved α-ethylphenylglycine hydrochloride was filtered off (4.00 g) and washed with $CHCl_3$. Combined filtrate and washings were evaporated *in vacuo* to give (±)-ethyl α-ethylphenylglycinate hydrochloride as a yellow viscous oil (4.9 g, 0.0201 mole). Ethoxycarbonylacetylchloride (3.03 g, 0.0201 mole) in $CHCl_3$ (20 ml) under stirring and cooling was added to a mixture of this hydrochloride, triethylamine (4.48 g, 0.0442 mole) and $CHCl_3$ (25 ml). After the mixture was stirred for 30 min. at room temperature thin layer chromatography (silica gel, solv. *n*-hexane:CH_2Cl_2:IPE=1:1:1) showed it to be an unreacted aminoester hydrochloride. Addition of triethylamine (1.12 g) and ethoxycarbonylacetylchloride (1.52 g) followed by stirring at room temperature was repeated twice to confirm the disappearance of the starting material. Working up of the reaction mixture was performed similar to the synthesis of (*R*)(−)-XI, except for the solvent (*n*-hexane:CH_2Cl_2:IPE=3:2:2) in column chromatography using silica gel, to give (±)-XXXI as a yellow viscous oil (5.38 g, 90% based on reacted amino acid hydrochloride). (±)-XXXI obtained above was used for next experiments without purification.

(*S*)(+)-Ethyl N-Ethoxycarbonylacetyl-α-ethylphenylglycinate ((*S*)(+)-XXXI)——A mixture of (*S*)(+)-XXX ($[\alpha]_D^{25}$ +126° (c=1.05, 1N NaOH), optically pure) (7.00 g, 0.00338 mole) and 10% HCl (70 ml) was refluxed for 3 hr and evaporated to dryness. Addition of H_2O followed by evaporation was repeated three times. Drying in a desiccator gave crude amino acid hydrochloride as a slightly yellow solid. Esterification of this amino acid hydrochloride was performed as for the racemate (esterification of recovered amino acid hydrochloride was repeated twice) to give crude ethyl α-ethylphenylglycinate hydrochloride as a pale yellow viscous oil, which was acylated similar to the racemate to afford (*S*)(+)-XXXI as a yellow viscous oil (8.67 g, 80%), $[\alpha]_D^{25}$ +42.2° (c=1.81, C_6H_6). This sample underwent the following step without further purification.

(±)-5-Ethyl-5-phenylpyrrolidine-2,4-dione ((±)-XXXII)——(±)-XXXI (3.41 g, 0.00106 mole) was treated the same as (*R*)(−)-XI to give (±)-XXXII as yellow crystals (1.80 g, 84%), mp 147—149° with sintering from 143°. Three recrystallizations from EtOH:IPE:*n*-hexane gave colorless prisms, mp 148.5—149.5°. *Anal.* Calcd. for $C_{12}H_{13}O_2N$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.94; H, 6.56; N, 6.66. IR ν_{max}^{KBr} cm⁻¹: 3160, 3068, 1766, 1691. IR $\nu_{max}^{CHCl_3}$ cm⁻¹: 3405, 3187, 3083, 1768, 1695. NMR (6% solution in $CDCl_3$) τ: 9.09 (3H, triplet, J=7.2 cps, $-CH_2-C\underline{H}_3$), 7.84 (2H, quartet, J=7.2 cps, $-C\underline{H}_2-CH_3$), 6.97 (2H, singlet, $-CO-CH_2-CO-$), 2.5—2.7 (5H, multiplet, benzene proton), 1.32 (1H, singlet, NH).

(*S*)(+)-5-Ethyl-5-phenylpyrrilidin-2,4-dione ((*S*)(+)-XXXII)——Same treatment of (*S*)(+)-XXXI ($[\alpha]_D^{25}$ +42.2° (c=1.81, C_6H_6)) (8.67 g, 0.0270 mole) as for (±)-XXXI gave (*S*)(+)-XXXII as pale brown crystals (4.86 g, 89%), mp 122—127°, $[\alpha]_D^{23.5}$ +85.3° (c=1.04, EtOH). An analytical sample was obtained as colorless leaflets after column chromatography using silica gel (solv. AcOEt:CH_2Cl_2=1:1) followed by four recrystallizations from EtOH–IPE–*n*-hexane, mp 127—128°, $[\alpha]_D^{19}$ +87.1° (c=1.02, EtOH). *Anal.* Calcd. for $C_{12}H_{13}O_2N$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.30; H, 6.71; N, 6.96. IR ν_{max}^{KBr} cm⁻¹: 3160, 3083, 1765, 1689.

(±)-3-Amino-3-phenyl-2-pentanone ((±)-XXXIII)——A suspension of (±)-XXXII (1.80 g, 0.00887 mole) in conc. HCl (18 ml) was refluxed for 4 hr and worked up similar to the synthesis of (±)-XIII, to give (±)-XXXIII as a colorless oil (1.36 g, 87%), bp 108—110° (5 mmHg). IR ν_{max}^{cap} cm⁻¹: 3384, 3317, 1711, 1602,

---

42) H.T. Bucherer and V.A. Lieb, *J. Prakt. Chem.*, **141**, 5 (1934).

43) R.M. Herbst and T.B. Johnson, *J. Am. Chem. Soc.*, **54**, 2463 (1932).

757, 701. NMR (10% solution in CCl_4) τ: 9.21 (3H, triplet, $J=7.2$ cps, $-CH_2-C\underline{H}_3$), 8.35 (2H, singlet, NH_2), 8.11 (3H, singlet, $-COCH_3$), 7.99 (2H, quartet, $J=7.2$ cps, $-C\underline{H}_2-CH_3$), 2.72 (5H, singlet, benzene proton).

Hydrochloride: colorless powderish crystals (from H_2O–EtOH–ether), mp 227—228.5° (melted with decomposition). *Anal.* Calcd. for $C_{10}H_{16}ONCl$: C, 61.82; H, 7.55; N, 6.56. Found: C, 62.03; H, 7.41; N, 6.94. IR ν_{max}^{KBr} cm^{-1}: 3000—2800 (broad), 1724, 761, 704.

(*S*)(+)-3-Amino-3-phenyl-2-pentanone ((*S*)(+)-XXXIII)——(*S*)(+)-XXXII ($[\alpha]_D^{23.5}$ +85.3° ($c=1.04$, EtOH)) (3.96 g, 0.0195 mole) was hydrolyzed by the same procedure as above to give (*S*)(+)-XXXIII as a colorless oil (3.05 g, 88%), bp 118—119° (8.5 mmHg), $[\alpha]_D^{26}$ +32.6° ($c=1.20$, C_6H_6). IR ν_{max}^{cap} cm^{-1}: 3373, 3312, 1710, 1602, 758, 703.

Hydrochloride: colorless powderish crystals (from H_2O–EtOH–ether), mp 234—235.5° (melted under decomposition), $[\alpha]_D^{19}$ +200° ($c=0.658$, EtOH). *Anal.* Calcd. for $C_{16}H_{16}ONCl$: C, 61.82; H, 7.55; N, 6.56. Found: C, 61.80; H, 7.66; N, 6.26. IR ν_{max}^{KBr} cm^{-1}: *ca.* 2850 (broad), 1725, 1606.

(±)-3-Benzylamino-3-phenyl-2-pentanone ((±)-XXIII)——After azeotropic removal of water from a mixture of freshly distilled benzaldehyde (3.80 g, 0.0357 mole), a trace of *p*-toluenesulfonic acid·H_2O and anhyd. toluene (30 ml) using Dean–Stark apparatus, (±)-XXXIII (2.11 g, 0.0119 mole) and anhyd. toluene (10 ml) were added. The whole was refluxed for 3 hr and worked up as for the synthesis of (*R*)(−)-VIa except that *n*-hexane–IPE–CH_2Cl_2 (3:2:1) was used as solvent in column chromatography, to give (±)-XXIII as a colorless oil (2.19 g, 69%) by way of (±)-3-benzylimino-3-phenyl-2-pentanone (bp 152—153° (0.04 mmHg)), bp 150—152° (0.07 mmHg). IR ν_{max}^{cap} cm^{-1}: 3343, 1713, 1602, 1585. NMR (10% solution in CCl_4) τ: 9.23 (3H, triplet, $J=7.2$ cps, $-CH_2-C\underline{H}_3$), 8.13 (3H, singlet, $-COCH_3$), *ca.* 7.8 (3H, multiplet, $-C\underline{H}_2-CH_3$, and NH), 6.65 (2H, singlet, $-CH_2-C_6H_5$), 2.7—2.9 (10H, multiplet, benzene proton).

(*S*)(+)-3-Benzylamino-3-phenyl-2-pentanone ((*S*)(+)-XXIII)——(*S*)(+)-XXXIII ($[\alpha]_D^{26}$ +32.6° ($c=1.20$, C_6H_6)) (1.50 g, 0.0847 mole) was treated the same as (±)-XXXIII to give (*S*)(+)-XXIII as a colorless oil (1.56 g, 69%) by way of (*S*)(−)-3-benzylimino-3-phenyl-2-pentanone (bp 168° (0.09 mmHg), $[\alpha]_D^{26}$ −4.84° ($l=0.1$, neat)), bp 159—172° (0.07 mmHg), $[\alpha]_D^{23}$ +37.0° ($c=1.16$, C_6H_6). IR ν_{max}^{cap} cm^{-1}: 3336, 1708, 1602.

(±)-N-Benzoyl-3-benzylamino-3-phenyl-2-pentanone ((±)-XXV)——Benzoyl chloride (1.05 g, 0.00748 mole) was added to a solution of (±)-XXIII (1.00 g, 0.00374 mole) in anhyd. pyridine (10 ml). The whole was refluxed for 34 hr, poured onto H_2O (40 ml) and kept overnight at room temperature. The mixture was acidified with conc. HCl (10 ml) under cooling and extracted with benzene (20 ml × 2, 10 ml). Combined benzene extracts were washed with sat. NaCl, 5% Na_2CO_2 and sat. NaCl, dried over anhyd. Na_2SO_4 and evaporated to dryness to give a brown viscous oil (1.7 g), which was submitted to column chromatography using silica gel (silica gel 160 g, solv. *n*-hexane:CH_2Cl_2:IPE=3:2:1). Fractions from 875 ml to 1175 ml gave a yellow viscous oil (760 mg), which was again purified with column chromatography using silica gel (solv. CH_2Cl_2:IPE=10:1), to afford (±)-XXV as pale yellow crystals (610 mg), mp 103—106°. IR ν_{max}^{KBr} cm^{-1}: 1713, 1631. NMR (10% solution in $CDCl_3$) τ: 9.09 (3H, triplet, $J=7.2$ cps, $-CH_2-C\underline{H}_3$), 7.72 (3H, singlet, $-COCH_3$), 7.1—8.3 (2H, multiplet, $-C\underline{H}_2-CH_3$), 5.51 (2H, singlet, $-CH_2-C_6H_5$), 2.4—2.9 (15H, multiplet, benzene proton). Three recrystallizations from EtOH–IPE–*n*-hexane gave slightly yellow prisms, mp 106—107°. *Anal.* Calcd. for $C_{25}H_{25}O_2N$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.55; H, 6.89; N, 3.66. IR and NMR spectra were identical with those of (±)-XXV just after column chromatography.

(*S*)(−)-N-Benzoyl-3-benzylamino-3-phenyl-2-pentanone ((*S*)(−)-XXV)——(*S*)(+)-XXIII ($[\alpha]_D^{23}$ +37.0° ($c=1.16$, C_6H_6)) (1.40 g, 0.00524 mole) was treated similarly to give (*S*)(−)-XXV as pale yellow crystals after purfiication with column chromatography (980 mg), mp 100—104°, $[\alpha]_D^{18.5}$ −101° ($c=1.09$, EtOH). IR ν_{max}^{KBr} cm^{-1}: 1715, 1621. This sample was optically pure. Optical rotation of (+)-XXV obtained by thermal rearrangement followed by benzoylation from (*S*)(+)-XXII (92% optically pure) was $[\alpha]_D^{19}$ +92.4° ($c=1.11$, EtOH). The percent of retention of optical activity accompanying phenyl migration was estimated as 108 %. Four recrystallizations from EtOH–IPE–*n*-hexane gave yellow pillars, mp 104.5—105.5°, $[\alpha]_D^{16}$ −104° ($c=0.964$, EtOH). *Anal.* Calcd. for $C_{25}H_{25}O_2N$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.79; H, 6.81; N, 4.12. IRν_{max}^{KBr} cm^{-1}: 1716, 1622. This spectrum was superimposable on that of (−)-XXV at the purification step of column chromatography.

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