43. Takehisa Kunieda, Kenji Koga, and Shun-ichi Yamada:
Studies on Optically Active Amino Acids. XI.*1
Synthesis, Resolution and Racemization
of Bicyclic α-Amino-ketones.

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The synthesis of optically active hexahydro-1H-pyrrolizin-1-one (I) from L-proline and
the resolution of hexahydro-1(5H)-indolizine (II), hexahydro-8(5H)-indolizine (III), and
hexahydro-2H-quinolizin-1(6H)-one (IV) by means of d-3-bromo-8-camphorsulfonic acid and
d-10-camphorsulfonic acid were described.

Their rate constants and half-times for racemization were determined under various
conditions, at 20°, and in aqueous ethanol I was found to be racemized very rapidly, while
in hydrochloric acid, no racemization was observed.

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Bicyclic systems containing a nitrogen atom at the bridge-head position such as
pyrrolizidine, indolizidine and quinolizidine are the structural units in the several
major classes of alkaloids such as lupin, senecio, indole alkaloids and so on, and many
organic chemists have paid an attention on their stereochemistry, in connection with
the behavior or the synthesis of many natural products.

Based on the above point of view, the present paper describes the results of the
investigation on the syntheses, resolution and racemization carried out in order to
examine the relationship between the structure and the behavior for racemization of
bicyclic α-amino-ketones such as hexahydro-1H-pyrrolizin-1-one (I), hexahydro-1(5H)-
indolizine (II), hexahydro-8(5H)-indolizine (III) and hexahydro-2H-quinolizin-1(6H)-one
(IV).

Although considerable difficulties appear to be encountered in the preparation of
such optically active ketones, Likhoshverstov and his co-workers*1 reported the synthesis
of optically active amino-ketone I, [α]D -22.4° (EtOH) by the application of the Dieckmann
cyclization reaction followed by decarboxylation with hydrochloric acid to ethyl 2-ethoxy-
carbonyl-1-pyrrolidinepropionate (V), prepared from L-proline. Reexamination of the
synthesis reported afforded the objective ketone I, [α]D -49.7° (EtOH), with higher
optical rotation and the calculation of the specific rotation of the ketone I indicates
that I is of over 75% optical purity, since I, [α]D -22.4° (EtOH), was led to [α]D -33°
(EtOH) of 1-methylene ppyrrolizidine, whose absolute value was reported to be [α]D
-100° (EtOH) by resolution.*2 This fact is of great significance in view of the synthetic
method of such a chemically and optically labile compound as I.

*1 Part XI. This Bulletin, 14, 1138 (1966).
*2 Hongo 7, Tokyo (戸野保, 西谷憲司, 佐野俊一).
An analogous synthetic sequences (Chart 2) applied to the optically active proline, 
pipecolic acid and phenylalanine with an intention to obtain optically active \( \alpha \)-amino-
ketones, II, III, IV, and XVI, were unsuccessful.

![Chemical structures and reaction arrows depicting the synthetic sequence.

Chart 2.

However, when examined in details, it was found that the intermediates, \( \beta \)-keto-
esters, X, XIII and XV could be isolated as optically active forms \([\alpha]_D -25.1^\circ (\text{EtOH})\), \([\alpha]_D +38.6^\circ (\text{EtOH})\) and \([\alpha]_D -13.3^\circ (\text{EtOH})\), respectively, except ethyl octahydro-1-oxo-2-
indolizinecarboxylate (XIII) which was completely racemic. Racemization was proved to
be occurred in the subsequent saponification-decarboxylation step using hydrochloric
acid.

The results could be explained as follows. The secondary carbanion A formed
prior to the tertiary could be cyclized to \( \beta \)-ketoesters, which were stabilized by the
tautomerism between B and C, thus retaining the optical activities.

![Chemical structures and reaction arrows depicting the tautomerism.

Chart 3.

The saponification-decarboxylation step, however, left the resulting ketones in the
equilibrium between D and E, thus racemizing the products. The comparative optical
stability of I is probably associated with the fact that such an enolization is seemed to be unfavorable energetically, owing to the lack of coplanarity of the pyrrolizidine ring system.

In order to study the racemization further in these bicyclic α-amino-ketones and to analyze them as a function of the ring conformations, the rate of racemization was measured. As it was impossible to assign the bridge-head proton\(^{1,6}\) of these α-amino-ketones in their NMR spectrogram\(^{8}\) clearly, the rate of racemization was planned to be measured polarimetrically.

Resolutions of racemic bicyclic α-amino-ketones II, III and IV, were achieved using \(d\)-3-bromo-8-camphorsulfonic acid\(^{8}\) (abbreviated as B.C.S.) and \(d\)-10-camphorsulfonic acid (abbreviated as C.S.) as resolving agents.

\((-\)II, \([\alpha]_D -105^\circ (\text{EtOH})\) and \((-\)IV, \([\alpha]_D -37^\circ (\text{EtOH})\), were recovered from the corresponding B.C.S. salt, m.p. 161.5\(^\circ\), \([\alpha]_D +38.7^\circ (\text{H}_2\text{O})\)\(^{8}\) and m.p. 196\(^\circ\), \([\alpha]_D +61.2^\circ (\text{H}_2\text{O})\), respectively. The resolution of III by means of B.C.S. could not be achieved but \((+\)III, \([\alpha]_D +0.93^\circ (\text{EtOH})\) was obtained from the corresponding C.S. salt, m.p. 97–101\(^\circ\), \([\alpha]_D +16.0^\circ (\text{H}_2\text{O})\), though this sample seems to be only partially resolved.

On heating with an equimolecular amount of hydroxylamine hydrochloride in ethanol,\(^7\) optically active ketones II, III and IV gave the corresponding active oxime.

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**Fig. 1. Racemization of Hexahydro-1H-pyrrolizin-1-one (I), Hexahydro-1(5H)-indolizine (II), Hexahydro-8(5H)-indolizine (III) and Hexahydro-2H-quinolizin-1(6H)-one (IV) in 80% EtOH at 20,0^\circ\) ± 0.1. \(a_0\) and \(a\) are the initial rotation and the rotation after definite time, respectively.**

**Fig. 2. Racemization of Hexahydro-1H-pyrrolizin-1-one (I), Hexahydro-1(5H)-indolizine (II), Hexahydro-8(5H)-indolizine (III) and Hexahydro-2H-quinolizin-1(6H)-one (IV) in Dioxane-Acetic Acid (20:1 (W/W)) at 20.0^\circ ± 0.1. \(a_0\) and \(a\) are the initial rotation and the rotation after definite time, respectively.**

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\(^8\) The spectra were measured in CDCl\(_3\) at 100 Mc.p.s. with a Varian HR-100 spectrometer.

\(^{4}\) The ammonium salt of B.C.S. was prepared from \(d\)-camphor according to the method reported\(^{6,9}\) and recrystallized from H\(_2\)O as colorless prisms. The free acid (B.C.S.) was obtained from the above salt by passing the solution over Amberlite IR-120 (H\(^+\)) and eluting with H\(_2\)O. This method seems to be superior to the reported methods\(^{6,9}\) in its yield, purity, and easy operation.

\(^{5}\) This was was mutarotated to \([\alpha]_D +52.6^\circ\) on standing at room temperature overnight.


derivatives, while I afforded an inactive one and this seems to be of no coincidence with that described above.

Now it is necessary to compare the rate constants of the racemization of these ketones under the same condition and so (a) 80% aqueous ethanol and (b) dioxane-acetic acid were chosen as solvent systems, being enough to compare the relative facilities for racemization.

A decrease of the optical rotations of I, II and IV was measured at 589 mμ, while III was done at 460 mμ owing to the small specific rotation, at 20.0° ±0.1. In each case the logarithms of the term \( \alpha/\alpha_0 \), where \( \alpha_0 \) and \( \alpha \) were the initial rotation and the rotation after time \( t \), at appropriate intervals of time were plotted against time \( t \) to draw a good straight line as shown in Figs. 1 and 2, which indicated that this reaction was the first order reaction for substrate. The pseudo first order rate constant \( k \) and half-time \( (t_{1/2}) \) for racemization were calculated from the graph and the results were given in Table I.

Such a remarkable fact that I was racemized very easily under these conditions compared with that under the strong acidic condition in decarboxylation reaction described above, suggests that the different mechanism from that under acidic condition is operative.

Further, the rate of racemization of I depends upon the content of water in ethanol solvent, thus \( t_{1/2} \) being 230, 120 and 80 minutes in abs. EtOH, 95% EtOH and 80% EtOH, respectively, indicating the pallidism between the rate and the polarity of the solvent.

The following facts were also observed that in the presence of an excess hydrochloric acid, no racemization of I was observed in agreement with the case in decarboxylation reaction mentioned above, while in less than equimolarity the racemization was occurred very rapidly. The addition of triethylamine into EtOH did not give any effect on the rate in both cases of I and IV.

In such a strongly acidic condition as hydrochloric acid, the protonation to nitrogen and carbonyl group would facilitate the formation of coplanar intermediates by the enolization resulting in racemization in the cases of II, III and IV, while in I such a coplanarity would be inhibited due to the large strain.

On the other hand, with regard to the points of little effect of the stronger base, triethylamine, on the rate of racemization and the bridge-head proton being very close to the lone pair of nitrogen atom in the case of I as compared with the cases of II, III

![Chart 4.](chart-4.png)
and N, the easy racemization of I in aqueous ethanol might be explained as follows; the strong basicity of nitrogen atom in I which is highly strained, will facilitate the abstraction of hydrogen atom at bridge-head because of neighboring effect and the more the solvent is polar, the easier the abstraction may occur and the ring flapping will take place without enolization, resulting in the racemization. The role of acetic acid in solvent system (b) might be considered to drive the solvent polarity stronger to release the hydrogen atom at bridge-head.

Further elucidation of the mechanism of racemization process must await more information and will be the subject of a future publication.

Experimental

(−)-Ethy 2-Ethoxycarbonyl-1-pyrrolidinone (V) — A mixture of 32 g. of α-proline ethyl ester,13) [α]D = −43.5° (c = 3.8), and 50 ml. of freshly distilled ethyl acrylate was heated in 40 ml. of EtOH under reflux for 6.3 hr. Low boiling materials were removed in vacuo and the distillation of the residue afforded 47.2 g. (97% yield) of (−)-V as a colorless liquid, b.p. 113~120°, [α]D = −66.4° (c = 1.7). Anal. Calcd. for C₉H₁₄O₃N: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.01; H, 8.60; N, 5.74.

(−)-Hexahydro-1H-pyrrolizin-1-one (I) — To a suspension of alcohol-free NaOEt (prepared from 4.7 g. (0.2 atom) of metallic sodium) in 100 ml. of abs. toluene was added a solution of 47.2 g. (0.195 mole) of the above diester V in 150 ml. of abs. toluene. The reaction mixture was refluxed with stirring for 1.5 hr. under N₂ atmosphere. After cooling, the reaction product was extracted with ca. 200 ml. of H₂O. To the extract was added 230 ml. of conc. HCl and the mixture was heated on a water-bath for 1.7 hr. until the ferric chloride test became negative. The mixture was evaporated in vacuo and the residue was made strongly basic with K₂CO₃ under cooling and then it was extracted with ether. After drying and removal of the ether, the residue was distilled under N₂ stream. Hexahydro-1H-pyrrolizin-1-one (I), weighing 9.5 g. (39%), was obtained as a colorless liquid, which was very unstable in air, b.p. 65°, [α]D = −49.7° (c = 2.5) (lit. 11) [α]D = −22.4° (c = 1.25), [α]D = −59.2° (c = 2.3, dioxane). The IR spectrum (CHCl₃) showed no Bohmann band.8)

The picrate was formed in ether and recrystallized from EtOH as yellow needles, m.p. 165~167°. Anal. Calcd. for C₁₅H₂₀O₅N₂: C, 44.07; H, 3.98; N, 15.82. Found: C, 44.06; H, 3.90; N, 15.92.

The oxime hydrochloride was prepared on heating with an equimolar amount NH₄OH-HCl in EtOH and recrystallized from EtOH as colorless prisms, m.p. 172~173°, [α]D = 0° (c = 1). Anal. Calcd. for C₁₅H₁₃ONCl: C, 47.60; H, 7.37; N, 15.70. Found: C, 47.81; H, 7.33; N, 15.71.


D- and L-Piperolic Acid — According to the method reported,2~4) α-picoline was converted to dl-piperic acid, which was resolved by means of d-tartaric acid. d-Piperic acid bi-d-tartarate was obtained from EtOH as colorless prisms, m.p. 191~193° (decomp.), [α]D = 20.0° (c = 6.5, H₂O) (lit.9,10) m.p. 182°, [α]D = 20.3° (c = 6.4, H₂O); m.p. 192~193°, [α]D = 22.3° (c = 6.4, H₂O). L-Piperic acid was recovered from the salt in the usual manner, m.p. 267~269°, [α]D = 25.3° (c = 1.65, H₂O) (lit.9,10) m.p. 264~267°, [α]D = 25.4°, [α]D = 26.3° (H₂O).

The IR spectrum (KBr) was identical with that of an authentic sample.13) From the mother liquor was also obtained l-isomer with less optical purity, [α]D = −21.5° (c = 2, H₂O).

(−)-Ethyl 2-Ethoxycarbonyl-1-piperidinepropionate (VII) — A solution of 3.5 g. (0.002 mole) of l-piperic acid ethyl ester,17) b.p. 90~100°, [α]D = −12.4° (c = 1), and 20 ml. of freshly distilled ethyl acrylate in 20 ml. of EtOH was refluxed for 5.5 hr. Low boiling materials were distilled off and the distillation of the residue gave 3.4 g. (90%) of diester VII as a colorless liquid, b.p. 127~132°, [α]D = −26.7° (c = 2.1). Anal. Calcd. for C₁₇H₂₀O₅N: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.87; H, 8.96; N, 5.51.

Hexahydro-1(5H)-indolizinozine (II)—This was obtained from 3.4 g. of the above diester VII in 42% yield, being analogous to the procedure described for I. A very unstable colorless liquid, b.p. 65–70°, ($\alpha_\text{D}$) $^\circ$ +0° (c=5.8) (lit.,$^{13}$) b.p. 85° was afforded.

The oxime was recrystallized from isopropyl alcohol–isopropyl ether as colorless prisms, m.p. 115–116°. Anal. Calcd. for C$_5$H$_5$NO$_2$: C, 62.30; H, 9.15; N, 18.17. Found: C, 62.45; H, 8.97; N, 17.90.

The picate was recrystallized from acetone as yellow needles, m.p. 170–171° (lit.$^{13}$) m.p. 175–176°. Anal. Calcd. for C$_5$H$_5$NO$_2$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.74; H, 4.55; N, 15.47.

The picrolene was prepared from EtOH as yellow prisms, m.p. 174–175°. Anal. Calcd. for C$_5$H$_5$O$_2$N$_2$: C, 53.59; H, 5.25; N, 17.36. Found: C, 53.64; H, 5.39; N, 17.57.

(->)Hexahydro-1(5H)-indolizinone (II)$^{*8}$—A solution of 5.0 g. (0.065 mole) of dl-ketone II and 11.5 g. (0.07 mole) of B.C.S. dissolved in 20 ml. of acetone was kept in the refrigerator overnight. The colorless crystals were collected by filtration, weighing 10 g., m.p. 90–110°. Several recrystallizations from acetone afforded 3.2 g. of (->)-hexahydro-1(5H)-indolizinone 3-bromo-8-camporphosulfonate as colorless prisms, m.p. 160–161.5°, ($\alpha_\text{D}$) $^\circ$ +38.7° (c=1.25, H$_2$O). Anal. Calcd. for C$_5$H$_5$O$_2$N$_2$Br$_2$: S, 48.00; H, 6.22; N, 3.11. Found: C, 53.17; H, 6.10; N, 3.12.

Two grams of the salt was dissolved in 5 ml. of H$_2$O, the solution was made strongly basic with K$_2$CO$_3$ and later extracted with benzene. The extract was dried and evaporated in vacuo under N$_2$ atmosphere. Distillation of the residue under N$_2$ atmosphere afforded 0.46 g. of (->)II as a colorless liquid, b.p. 68–70°, ($\alpha_\text{D}$) $^\circ$ -105° (c=4.6), ($\alpha_\text{D}$) $^\circ$ -107.3° (c=0.8, dioxane).

The oxime hydrochloride was obtained from EtOH–isopropyl ether as colorless prisms, m.p. 193–194°, ($\alpha_\text{D}$) $^\circ$ -22.0° (c=1, H$_2$O). Anal. Calcd. for C$_5$H$_5$NO$_2$Cl: C, 50.39; H, 7.87; N, 14.70. Found: C, 50.62; H, 7.90; N, 14.81.

The enantiomeric base II, b.p. 80°, ($\alpha_\text{D}$) $^\circ$ +30° (c=1.28), was also obtained on the same treatment of mother liquor.

Ethyl Octahydropyra-1-oxo-2-indolizinocarboxylic acid (VIII)—To a suspension of NaOH prepared from 0.7 g. (0.03 atom) of metallic sodium in 80 ml. of absolute toluene was added 7.5 g. (0.03 mole) of diester VII and the mixture was refluxed for 2 hr. under N$_2$ stream. After cooling, the product was extracted with 40 ml. of H$_2$O, the aqueous solution was adjusted to neutral by adding either dry ice or AcOH and it was extracted with ether and CH$_2$Cl$_2$. The combined extract was dried and evaporated in vacuo. The residue was distilled in the atmosphere of N$_2$ to yield 1.5 g. (25%) of $\beta$-ketoester VII as a viscous colorless liquid. b.p. 64–105°, ($\alpha_\text{D}$) $^\circ$ +90° (c=3.8). Anal. Calcd. for C$_5$H$_5$O$_2$N$_2$: C, 62.54; H, 6.81; N, 6.63. Found: C, 62.56; H, 8.20; N, 6.88. IR $\nu$$_{\text{NH}}$ cm$^{-1}$: 2790, 2720, 2680, 1770 (s), 1730 (s), 1680 (w), 1630 (w).

(->)-Ethyl 2-Ethoxyacrylamide-1-pyrrolidinebutyrate (IX)—A solution of 19 g. (0.133 mole) of l-proline ethyl ester and 30 g. (0.154 mole) of ethyl 4-bromobutyrate$^{(4,10)}$ prepared from 7-butyro lactone in 60 ml. of acetone was stirred under reflux for 3.5 hr. in the presence of 20 g. of anhydrous K$_2$CO$_3$. After the filtration, the filtrate was evaporated in vacuo and the residue was taken up in ether. The ether solution was washed with aqueous K$_2$CO$_3$ and dried. After the removal of the ether the residue was distilled to yield 28.5 g. (83.5%) of diester IX as a slightly yellow liquid, b.p. 65–102°, ($\alpha_\text{D}$) $^\circ$ -25.1° (c=2.7). Anal. Calcd. for C$_5$H$_5$O$_2$N$_2$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.64; H, 7.80; N, 6.51. IR $\nu$$_{\text{NH}}$ cm$^{-1}$: 2790, 1742 (s), 1728 (s), 1652 (s), 1618 (s).

From toluene layer was recovered 4.2 g. (28%) of starting material, b.p. 130–138°, ($\alpha_\text{D}$) $^\circ$ -46° (c=3.88). This indicated that racemization was somewhat occurred.

Hexahydro-8(5H)-indolizinone (III)—Three grams of the above $\beta$-ketoester X was heated in 20 ml. of 10% HCl for 2 hr. on a water–bath to decarboxylate. The solvent was evaporated to dryness in vacuo. The residue was treated with K$_2$CO$_3$ in a usual manner and the product was distilled under N$_2$ atmosphere to yield 1.3 g. (65%) of a colorless liquid which darkened rapidly in air, b.p. 65–67°, $\alpha_\text{D}$ $^\circ$ +0° (1=1 cm, neat).

The oxime was recrystallized from isopropyl ether as colorless prisms, m.p. 117–118°. Anal. Calcd. for C$_5$H$_5$NO$_2$: C, 62.30; H, 9.15; N, 18.17. Found: C, 62.44; H, 9.04; N, 17.81.

The picate was formed in ether and recrystallized from EtOH as yellow needles, m.p. 147–148° (lit.$^{13}$) 144–145°. Anal. Calcd. for C$_5$H$_5$O$_2$N$_2$: C, 45.65; H, 4.35; N, 15.21. Found: C, 45.70; H, 4.40; N, 15.48.

88 We thank Mr. H. Horiguchi for his assistance in this experimental procedure.
(+)-Hexahydo-8(5H)-indolizine (III) — a) A solution of 3.6 g. (0.026 mole) of dl- ketone III and 8.5 g. (0.027 mole) of B. C. S. dissolved in 40 ml. of acetone was allowed to stand at room temperature for 2 days. Crystals were separated by filtration and recrystallized several times from acetone. 8.3 g. of the corresponding B. C. S. salt monohydrate was obtained as colorless prisms, m. p. 130°—131°, [α]_D^20 +56.8° (c=2.07, H_2O). *Anal.* Calcd. for C_kH_mO_nN_rBr_sH_2O : C : 45.94; H : 6.41; N : 3.00. Found : C : 45.96; H : 6.50; N : 3.18.

The amino-ketone recovered from the above salt was optically inactive, b. p. 90°—93°, [α]_D^20 +6° (c=5.3).

b) In 60 ml. of acetone were dissolved 5.6 g. (0.04 mole) of dl-ketone III and 9.5 g. (0.041 mole) of C. S. 20 ml. of abs. ether was added. The mixture was kept in the refrigerator overnight. Colorless crystals were separated weighing 5 g. Several recrystallizations from acetone afforded (+)-hexahydo-8(5H)-indolizine 10-camphorsulfonate monohydrate as colorless prisms, m. p. 97°—101°, [α]_D^20 +16.0° (c=2, H_2O). *Anal.* Calcd. for C_kH_mO_nNS_2H_2O : C : 55.50; H : 8.02; N : 3.60. Found : C : 55.75; H : 7.89; N : 3.77.

The amino-ketone III recovered from this salt had the rotation of [α]_D^20 +0.93° (c=4.3). The oxime hydrochloride was obtained from EtOH as colorless prisms, m. p. 176°, [α]_D^20 +7.9° (c=1.7, H_2O). *Anal.* Calcd. for C_kH_mO_nN_Cl : C : 50.39; H : 7.93; N : 14.69. Found : C : 50.50; H : 8.08; N : 14.87.

(+)-Ethyl 2-Ethoxy carbonyl-1-piperidinebutyrate (XI) — Starting with 10.2 g. of n-pipocatic acid ethyl ester, b. p. 100°, [α]_D^20 +13.3° (c=3.12), this was obtained in the same way as I. The product was distilled under the reduced pressure to afford 13 g. (74%) of XI as a colorless liquid, b. p. 80° 120°—130°, [α]_D^20 +46.0° (c=2.34). *Anal.* Calcd. for C_kH_mO_nN : C : 61.96; H : 9.29; N : 5.16. Found : C : 62.19; H : 8.82; N : 5.11.

Hexahydo-2H-quinolizin-1(6H)-one (IV) — This was prepared in 50% yield starting with 4.0 g. of the above diester XI in the same procedure described for I. A colorless unstable liquid, b. p. 80°—90°, [α]_D^20 +6° (c=10), was afforded (lit.,[15] b. p. 94°).


(+)-Ethyl Octahydo-1-oxo-2-quinolizincarboxylate (XII) — Four grams (0.015 mole) of the above diester XI was subjected to the Dieckmann cyclization using NaOEt (prepared from 0.35 g. (0.015 atom) of metallic sodium) in the same way as VII. Distillation of the product afforded 0.85 g. (26%) of XII as a viscous pale yellow liquid, b. p. 109°—115°, [α]_D^20 +38.6° (c=5.0). *Anal.* Calcd. for C_kH_mO_nN : C : 63.97; H : 8.50; N : 6.22. Found : C : 63.97; H : 8.38; N : 6.49. IR ν_cmb^-1 cm^-1 : 2790, 2640, 1740 (m), 1723 (m), 1658 (s), 1620 (s).

(−)-Hexahydo-2H-quinolizin-1(6H)-one (IV) — A solution of 5.8 g. (0.038 mole) of dl-ketone IV and 12 g. (0.039 mole) of B. C. S. in 30 ml. of acetone was allowed to stand at room temperature overnight. The crystals separated were collected by filtration and recrystallized from acetone yielding 4.0 g. of (−)-hexahydo-2H-quinolizin-1(6H)-one 3-bromo-8-camphorsulfonate as colorless prisms, m. p. 155°—159°, [α]_D^20 +61.2° (c=2, H_2O). *Anal.* Calcd. for C_kH_mO_nNBr_s : C : 49.13; H : 6.46; N : 3.01. Found : C : 49.18; H : 6.63; N : 3.17. a-amino-ketone IV recovered from the salt in the same way as (−)-II had b. p. 90°—95°, the rotation [α]_D^20 −37° (c=5.5), [α]_D^20 −31.7° (c=3.3, isooctane) (lit.,[14] [α]_D^20 −32.9° (c=1.5, isooctane)).

The oxime hydrochloride was obtained from EtOH—isopropyl ether as colorless needles, m. p. 218°—219°, [α]_D^20 −62.1° (c=1.2, H_2O). *Anal.* Calcd. for C_kH_mO_nN_Cl : C : 52.81; H : 8.31; N : 13.69. Found : C : 52.96; H : 8.36; N : 13.71.

The oxime was recrystallized from isopropanol as colorless prisms, m. p. 139°—140°, [α]_D^20 −62.4° (c=0.8).


The analogous treatment of the mother liquor afforded the enantiomeric (+)-amino-ketone IV, [α]_D^20 +22.7° (c=1.88), which gave oxime hydrochloride, [α]_D^20 +38.6° (c=1, H_2O).

Ethyl 1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (XIII) — According to the reported method,[17] 1-phenylalanine in place of dl-phenylalanine was subjected to the Pictet—Spengler reaction to give 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid hydrochloride, which was esterified by SOCl_2—EtOH. Distillation of the product afforded (−)-ethyl 1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (XII) in 60% yield as a pale yellow liquid, b. p. 115°—121°, [α]_D^20 −76.8° (c=0.7).

The hydrochloride was recrystallized from EtOH as colorless pillars, m. p. 203°—205° (decomp.), [α]_D^20 −85.7° (c=1.2, H_2O). *Anal.* Calcd. for C_kH_mO_nN_Cl : C : 59.63; H : 6.63; N : 5.80. Found : C : 59.76; H : 6.75; N : 5.71.

The picrate was formed in ether and recrystallized from EtOH as yellow needles, m. p. 198°—199°. *Anal.* Calcd. for C_kH_mO_nN_2 : C : 49.77; H : 4.15; N : 12.90. Found : C : 49.82; H : 4.40; N : 12.97.


(−)-Ethyl 3-Ethoxycarbonyl-1,2,3,4-tetrahydro-2-isquinolinolinebutrate (XIV)——This was prepared from the above ester XIV in 35% yield, according to the modified procedure described for X. Distillation of the product gave a pale yellow viscous liquid, b.d. of 180~190°C, [α]D^2 = −7.4°(c=5). Anal. Calcd. for C_{18}H_{20}O_3 N: C, 67.69; H, 7.89; N, 4.39. Found : C, 67.53; H, 7.48; N, 4.35.

(−)-Ethyl 1,3,4,6,11a-Hexahydro-1-oxo-2H-benzo[6]quinolizine-2-carboxylate (XV)——A mixture of 12.1 g. (0.04 mole) of the above diester XIV and 0.91 g. (0.04 mole) of NaH in 120 ml. of abs. dioxane was gently refluxed for 1 hr., under N_2 stream. The solvent was removed in vacuo, the resulting solid was dissolved in a little volume of H_2O and washed with benzene, repeatedly. The aqueous layer was neutralized with AcOH and it was extracted with benzene. The extract was dried and evaporated to dryness in vacuo under N_2 atmosphere. The resulting yellow solid was recrystallized from aqueous EtOH to afford 5.5 g. (53%) of β-ketoster XV as yellow needles, m.p. 79~79.5°C, [α]D^2 = −13.3°(c=1.5). Anal. Calcd. for C_{18}H_{20}O_3 N: C, 70.33; H, 6.96; N, 5.10. Found : C, 69.98; H, 6.83; N, 5.26. UV λ_{max}^ε (log ε) : 235 (4.04), 383 (3.38). IR ν_{max} cm⁻¹ : 2800, 2775, 1650 (s), 1621 (m).

3,4,11a-Tetrahydro-2H-benz[6]quinolizine-1(6H)-one (XVI)——1.5 g. of the above β-ketoster XV was decarboxylated on heating for 5 hr. in 15 ml. of 10% HCl. After the usual treatment, 0.65 g. (59%) of the product was obtained from EtOH as yellow plates, m.p. 96~98°C, [α]D^2 = 0°(c=1.5) (lit. 17~18 m.p. 98~100°C). The IR spectrum (KBr) was identical with that of an authentic specimen prepared by the Clemo’s method.17 Anal. Calcd. for C_{18}H_{16}O_3 N: C, 77.60; H, 7.45; N, 6.96. Found : C, 77.55; H, 7.66; N, 6.80.

### Table I. Data for Racemization of Bicyclic α-Amino-ketones (20°±0.1)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Solvents</th>
<th>Pseudo first order rate constants (k) min⁻¹</th>
<th>Half-times for racemization (t½) min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>a</td>
<td>8.6×10⁻⁸</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>4.9×10⁻⁸</td>
<td>10</td>
</tr>
<tr>
<td>II</td>
<td>a</td>
<td>1.5×10⁻⁸</td>
<td>530</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>9.2×10⁻⁸</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>a</td>
<td>7.7×10⁻⁴</td>
<td>900</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>6.6×10⁻⁴</td>
<td>10</td>
</tr>
<tr>
<td>N</td>
<td>a</td>
<td>~0</td>
<td>+∞</td>
</tr>
<tr>
<td></td>
<td>b</td>
<td>2.8×10⁻³</td>
<td>250</td>
</tr>
</tbody>
</table>

Solvent a: 80% EtOH  Solvent b: Dioxane-Acetic Acid (20:1)

**Measurement of the Rate for Racemization**——All α-amino-ketones were purified by distillation in the atmosphere of nitrogen just before the use. In 10 ml. of (a) 80% EtOH (w/w) or (b) dioxane-acetic acid (20:1, w/w), about 0.0035 mole each of the sample was dissolved and the solution was tightly closed into the measuring cell (l=5 cm), which was placed in a 20.0°C±0.1 constant temperature bath. The decrease of the optical rotation (α) at appropriate intervals of time was measured at 589 mp for I, II and N and 460 mp for III. The degree of decomposition was checked by ultraviolet spectroscopic analysis.

In each case the logarithms of α/α₀ were plotted against time t to draw a good straight line (Figs. 1 and 2). The pseudo first order rate constants (k) and half-time (t½) for racemization were determined graphically, using the expression

\[ \text{k} t = \ln \frac{\alpha_0}{\alpha} \]

where α₀ is the initial rotation and α is the rotation after time t. The results were summarized in Table I.

In Fig. 3, the results of racemization of I were given in abs. EtOH, 95% EtOH and 80% EtOH at 20.0°C±0.1.

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