Chem. Pharm. Bull.
15(3) 337~344 (1967)

UDC 547.745.02.07 : 541.65

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Studies on Optically Active Amino Acids. XII.[*1]
Synthesis, Resolution and Racemization of Bicyclic α-Amino-ketones.

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The synthesis of optically active hexahydro-1*H*-pyrrolizin-1-one (I) from L-proline and the resolution of hexahydro-1(5*H*)-indolizinone (II), hexahydro-8(5*H*)-indolizinone (III), and hexahydro-2*H*-quinolizin-1(6*H*)-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.

(Received July 4, 1966)

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-1*H*-pyrrolizin-1-one (I), hexahydro-1(5*H*)-indolizinone (II), hexahydro-8(5*H*)-indolizinone (III) and hexahydro-2*H*-quinolizin-1(6*H*)-one (IV).

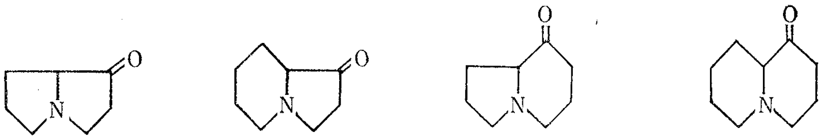
I II III IV

Chart 1.

Although considerable difficulties appear to be encountered in the preparation of such optically active ketones, Likhosherstov and his co-workers[1] reported the synthesis of optically active amino-ketone I, $[\alpha]_D$ −22.4° (EtOH) by the application of the Dieckmann cyclization reaction followed by decarboxylation with hydrochloric acid to ethyl 2-ethoxycarbonyl-1-pyrrolidinepropionate (V), prepared from L-proline. Reexamination of the synthesis reported afforded the objective ketone I, $[\alpha]_D$ −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, $[\alpha]_D$ −22.4° (EtOH), was led to $[\alpha]_D$ −33° (EtOH) of 1-methylenepyrrolizidine, whose absolute value was reported to be $[\alpha]_D$ −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).

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1) A.M. Likhosherstov, A.M. Krystin, N.K. Kochetkov : Doklady Akad. Nauk S.S.S.R., **141**, 361 (1961).

2) C.C.J. Culvenor, L.W. Smith : Aust. J. Chem., **15**, 328 (1962).

An analogous synthetic sequences (Chart 2) applied to the optically active proline, pipecolic acid and phenylalanine with an intention to obtain optically active α-aminoketones, II, III, IV, and XVI, were unsuccessful.

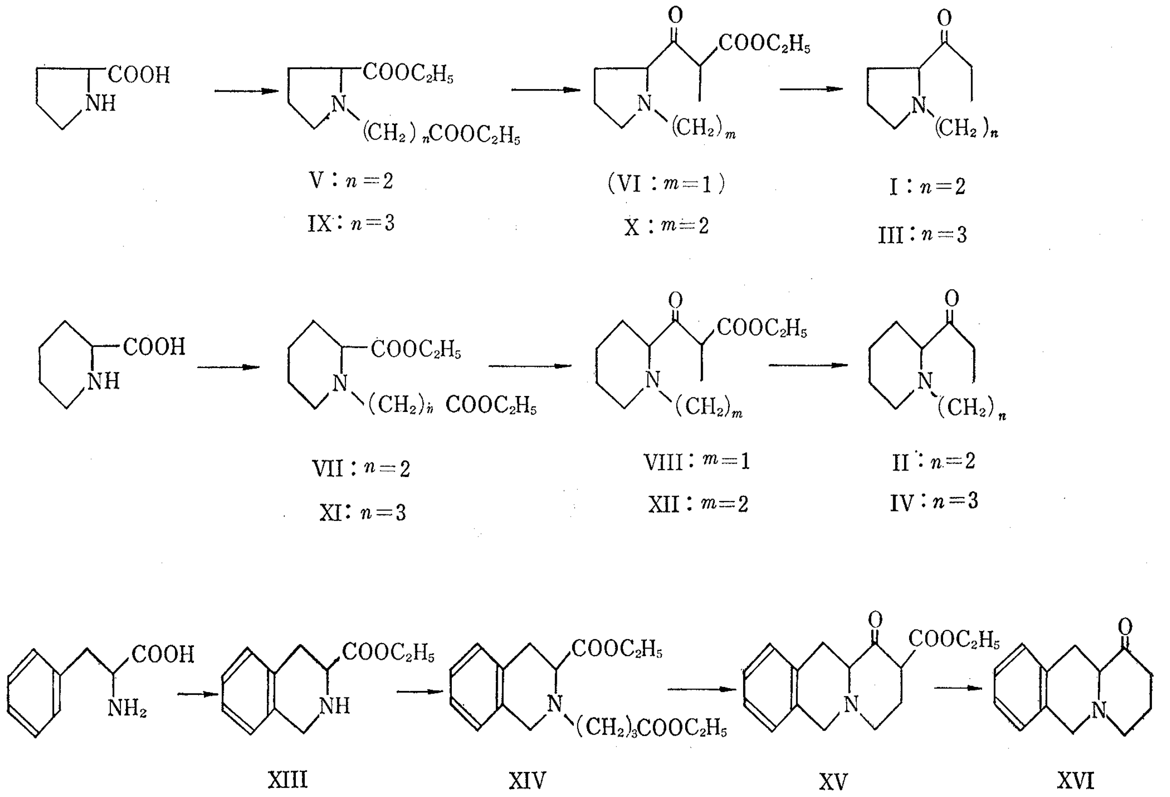

Chart 2.

However, when examined in details, it was found that the intermediates, β-ketoesters, X, XII and XV could be isolated as optically active forms $[\alpha]_D$ −25.1°(EtOH), $[\alpha]_D$ +38.6°(EtOH) and $[\alpha]_D$ −13.3°(EtOH), respectively, except ethyl octahydro-1-oxo-2-indolizinecarboxylate (VIII) 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 β-ketoesters, which were stabilized by the tautomerism between B and C, thus retaining the optical activities.

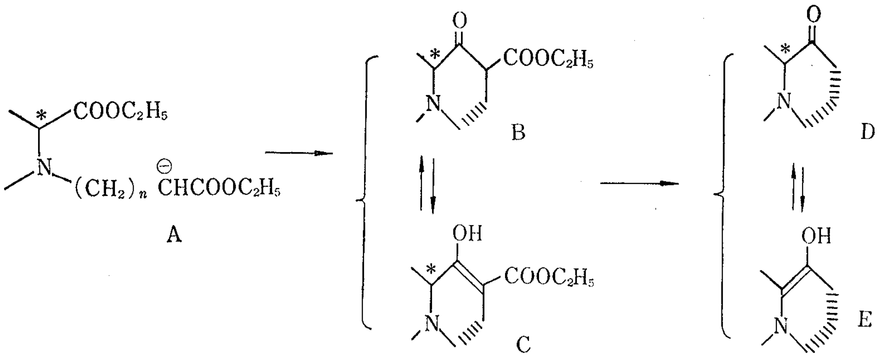

Chart 3.

The saponification-decarboxylation step, however, left the resulting ketones in the equilibrium between D and E, thus racomizing 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[3,4] of these α-amino-ketones in their NMR spectrogram[*3] 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[*4] (abbreviated as B.C.S.) and *d*-10-camphorsulfonic acid (abbreviated as C.S.) as resolving agents.

(−)-II, $[\alpha]_D$ −105°(EtOH) and (−)-IV, $[\alpha]_D$ −37°(EtOH), were recovered from the corresponding B.C.S. salt, m.p. 161.5°, $[\alpha]_D$ +38.7°(H_2O)[*5] and m.p. 196°, $[\alpha]_D$ +61.2° (H_2O), respectively. The resolution of III by means of B.C.S. could not be achieved but (+)-III, $[\alpha]_D$ +0.93°(EtOH) was obtained from the corresponding C.S. salt, m.p. 97~101°, $[\alpha]_D$ +16.0°(H_2O), 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

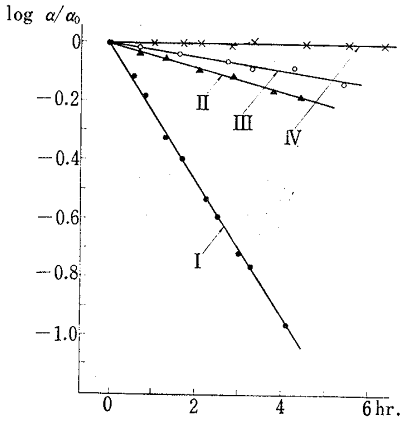

Fig. 1. Racemization of Hexahydro-1*H*-pyrrolizin-1-one (I), Hexahydro-1(5*H*)-indolizinone (II), Hexahydro-8(5*H*)-indolizinone (III) and Hexahydro-2*H*-quinolizin-1(6*H*)-one (IV) in 80% EtOH at 20.0° ±0.1. α_0 and α are the initial rotation and the rotation after definite time, respectively

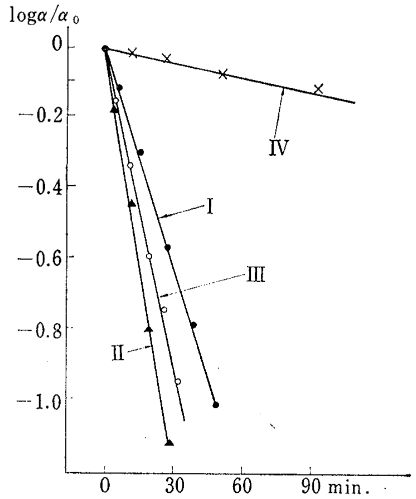

Fig. 2. Racemization of Hexahydro-1*H*-pyrrolizin-1-one (I), Hexahydro-1(5*H*)-indolizinone (II), Hexahydro-8(5*H*)-indolizinone (III) and Hexahydro-2*H*-quinolizin-1(6*H*)-one (IV) in Dioxane-Acetic Acid (20:1 (W/W)) at 20.0°±0.1. α_0 and α are the initial rotation and the rotation after definite time, respectively

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[*3] 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[5,6] and recrystallized from H_2O 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_2O. This method seems to be superior to the reported methods[5,6] in its yield, purity, and easy operation.

[*5] This was mutarotated to $[\alpha]_D$ +52.6° on standing at room temperature overnight.

3) cf. H.P. Hamlow, S. Okuda, N. Nakagawa: Tetrahedron Letters, **1964**, 2553.

4) cf. F. Bohlmann, D. Schumann, H. Schulz: *Ibid.*, **1965**, 173.

5) F.S. Kipping, W.J. Pope: J. Chem. Soc., **63**, 577 (1893).

6) H. Regler, F. Hein: J. prakt. Chem., **148**, 1 (1937).

7) C.A. Grob, H.P. Fischer, H. Lind, E. Renk: Helv. Chim. Acta, **46**, 1190 (1963).

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 α/α_0, where α_0 and α 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 pallarelism 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.

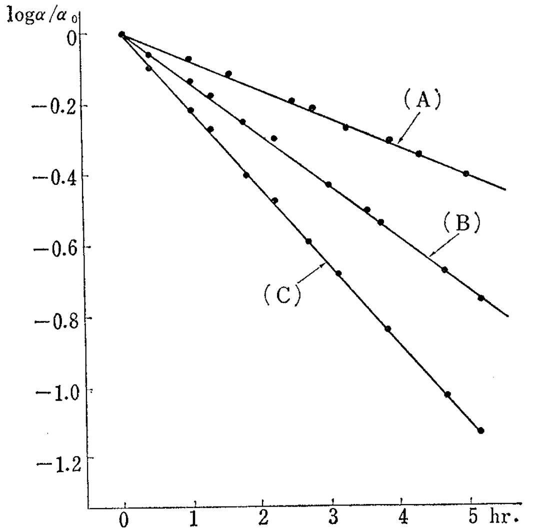

Fig. 3. Racemization of Hexahydro-1*H*-pyrrolizin-1-one (I) in abs. EtOH (A), 95% EtOH (B) and 80% EtOH (C) at 20.0°+0.1. α_0 and α are the initial rotation and the rotation after definite time, respectively

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

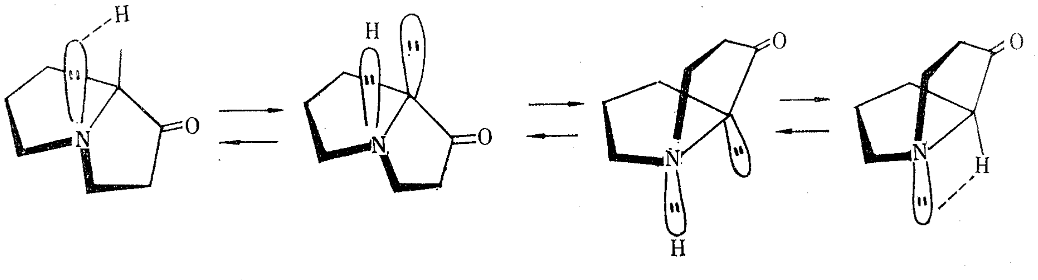

Chart 4.

and Ⅳ, 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[*6]

(−)-Ethyl 2-Ethoxycarbonyl-1-pyrrolidinepropionate (V)——A mixture of 32 g. of L-proline ethyl ester,1) $[\alpha]^{8}_{\mathrm{D}}$ −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. (87%) of (−)-V as a colorless liquid, b.p$_2$ 113～120°, $[\alpha]^{15}_{\mathrm{D}}$ −66.4°(c=1.7). *Anal.* Calcd. for $C_{12}H_{21}O_4N$: C, 59.24; H, 8.70; N, 5.76. Found : C, 59.01; H, 8.60; N, 5.74.

(−)-Hexahydro-1*H*-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 N_2 atmosphere. After cooling, the reaction product was extracted with ca. 200 ml. of H_2O. 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 K_2CO_3 under cooling and then it was extracted with ether. After drying and removal of the ether, the residue was distilled under N_2 stream. Hexahydro-1*H*-pyrrolizin-1-one (I), weighing 9.5 g. (39%), was obtained as a colorless liquid, which was very unstable in air, b.p$_4$ 65°, $[\alpha]^{9}_{\mathrm{D}}$ −49.7° (c=2.5) (lit.,1) $[\alpha]^{21}_{\mathrm{D}}$ −22.4°(c=1.25)), $[\alpha]^{9}_{\mathrm{D}}$ −59.2°(c=2.3, dioxane). The IR spectrum ($CHCl_3$) showed no Bohlmann band.8)

The picrate was formed in ether and recrystallized from EtOH as yellow needles, m.p. 165～167°. *Anal.* Calcd. for $C_{13}H_{14}O_8N_4$: 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 $NH_2OH \cdot HCl$ in EtOH and recrystallized from EtOH as colorless prisms, m.p. 172～173°, $[\alpha]^{25}_{\mathrm{D}}$ ±0 (c=1). *Anal.* Calcd. for $C_7H_{13}ON_2Cl$: C, 47.60; H, 7.37; N, 15.70. Found : C, 47.81; H, 7.33; N, 15.71.

The oxime was obtained from the above oxime hydrochloride as colorless prisms, m.p. 158～160°. *Anal.* Calcd. for $C_7H_{12}ON_2$: C, 59.97; H, 8.63; N, 19.99. Found : C, 60.19; H, 8.58; N, 20.09.

D- and L-Pipecolic Acid——According to the method reported,9～11) α-picoline was converted to *dl*-pipecolic acid, which was resolved by means of *d*-tartaric acid. D-Pipecolic acid bi-*d*-tartrate was obtained from EtOH as colorless prisms, m.p. 191～193°(decomp.), $[\alpha]^{25}_{\mathrm{D}}$ +20.0°(c=6.5, H_2O) (lit.,9,10) m.p. 182°, $[\alpha]_{\mathrm{D}}$ +20.3°(c=6.4, H_2O); m.p. 192～193°, $[\alpha]^{20}_{\mathrm{D}}$ +22.3°(c=6.4, H_2O)). D-Pipecolic acid was recovered from the salt in the usual manner, m.p. 267～269°, $[\alpha]^{23}_{\mathrm{D}}$ +25.3°(c=1.05, H_2O) (lit.,9,10) m.p. 264～267°, $[\alpha]_{\mathrm{D}}$ +25.4°, $[\alpha]_{\mathrm{D}}$ +26.2°(H_2O)).

The IR spectrum (KBr) was identical with that of an authentic sample.12) From the mother liquor was also obtained L-isomer with less optical purity, $[\alpha]^{25}_{\mathrm{D}}$ −21.5°(c=2, H_2O).

(−)-Ethyl 2-Ethoxycarbonyl-1-piperidinepropionate (VII)——A solution of 3.5 g. (0.002 mole) of L-pipecolic acid ethyl ester,[*7] b.p$_{15}$ 90～100°, $[\alpha]^{29}_{\mathrm{D}}$ −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. (60%) of diester Ⅶ as a colorless liquid, b.p$_{0.5}$ 127～132°, $[\alpha]^{27}_{\mathrm{D}}$ −26.7°(c=2.1). *Anal.* Calcd. for $C_{13}H_{23}O_4N$: C, 60.68; H, 9.01; N, 5.44. Found : C, 60.87; H, 8.96; N, 5.51.

[*6] All melting points were not corrected. Optical rotations were measured in EtOH unless otherwise stated.

[*7] This was prepared according to the Likhosherstov's method.1)

8) F. Bohlmann : Ber., **91**, 2157 (1958).

9) R. Lukes, J. Kloubek, K. Blaha, J. Kovar : Collection Czechoslov. Chem. Communs., **22**, 286 (1957).

10) H.C. Beyerman : Rec. trav. chim., **78**, 134 (1959).

11) Org. Syntheses : Coll. Ⅲ, 740.

12) J.P. Greenstein, M. Winitz : "Chemistry of the Amino Acids." John Wiley & Sons, Inc., New York, London, Vol. Ⅲ, 2557 (1961).

Hexahydro-1(5*H*)-indolizinone (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$_{1-2}$ 65\~70°, $[\alpha]_D^{25}$ ±0°(c=5.8) (lit.,[13] b.p$_3$ 85°) was afforded.

The oxime was recrystallized from isopropyl alcohol-isopropyl ether as colorless prisms, m.p. 115\~116°. *Anal.* Calcd. for $C_8H_{14}ON_2$: C, 62.30; H, 9.15; N, 18.17. Found : C, 62.45; H, 8.97; N, 17.90.

The picrate was recrystallized from acetone as yellow needles, m.p. 170\~171° (lit.,[13] m.p. 175\~176°). *Anal.* Calcd. for $C_{14}H_{16}O_8N_4$: C, 45.65; H, 4.38; N, 15.21. Found : C, 45.74; H, 4.55; N, 15.47.

The picrolonate was prepared from EtOH as yellow prisms, m.p. 174\~175°. *Anal.* Calcd. for $C_{18}H_{21}O_6N_5$: C, 53.59; H, 5.25; N, 17.36. Found : C, 53.64; H, 5.39; N, 17.57.

(−)-Hexahydro-1(5*H*)-indolizinone (II)*8——A solution of 5.0 g. (0.036 mole) of *dl*-ketone Ⅱ and 11.5 g. (0.037 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(5*H*)-indolizinone 3-bromo-8-camphorsulfonate as colorless prisms, m.p. 160\~161.5°, $[\alpha]_D^{15}$ +38.7°(c=1.25, H_2O). *Anal.* Calcd. for $C_{18}H_{28}O_5NBrS$: C, 48.00; H, 6.22; N, 3.11. Found : C, 48.17; H, 6.10; N, 3.12.

Two grams of the salt was dissolved in 5 ml. of H_2O, the solution was made strongly basic with K_2CO_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$_{1-2}$ 68\~70°, $[\alpha]_D^{24}$ −105°(c=4.6), $[\alpha]_D^{24}$ −107.3°(c=0.8, dioxane).

The oxime hydrochloride was obtained from EtOH-isopropyl ether as colorless prisms, m.p. 193\~194°, $[\alpha]_D^{24}$ −22.0°(c=1, H_2O). *Anal.* Calcd. for $C_8H_{15}ON_2Cl$: 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$_5$ 80°, $[\alpha]_D^{20}$ +30°(c=1.28), was also obtained on the similar treatment of mother liquor.

Ethyl Octahydro-1-oxo-2-indolizinecarboxylate (VIII)——To a suspension of NaOEt prepared from 0.7 g. (0.03 atom) of metallic sodium in 80 ml. of abs. 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_2O, the aqueous solution was adjusted to neutral by adding either dry-ice or AcOH and it was extracted with ether and CH_2Cl_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 β-ketoester Ⅷ as a viscous colorless liquid, b.p$_{0.6}$ 105\~107°, $[\alpha]_D^{27}$ ±0°(c=3.8). *Anal.* Calcd. for $C_{11}H_{17}O_3N$: C, 62.54; H, 8.11; N, 6.63. Found : C, 62.56; H, 8.20; N, 6.88. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2790, 2720, 2680, 1770 (s), 1730 (s), 1680 (w), 1630 (w).

(−)-Ethyl 2-Ethoxycarbonyl-1-pyrrolizinebutyrate (IX)——A solution of 19 g. (0.133 mole) of L-proline ethyl ester and 30 g. (0.154 mole) of ethyl 4-bromobutyrate[14,15] prepared from γ-butyrolactone in 60 ml. of acetone was stirred under reflux for 3.5 hr. in the presence of 20 g. of anhydrous K_2CO_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_2CO_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$_{0.1}$ 132°, $[\alpha]_D^{13}$ −63.7°(c=0.54). *Anal.* Calcd. for $C_{13}H_{23}O_4N$: C, 60.68; H, 9.01; N, 5.44. Found : C, 60.56; H, 8.54; N, 5.40.

(−)-Ethyl Octahydro-8-oxo-7-indolizinecarboxylate (X)——Starting with 15 g. of the above diester Ⅸ, this was prepared analogously to the procedure described for Ⅷ. Distillation of the product under N_2 atmosphere afforded 3.0 g. (34% based on unrecovered starting material) as a pale yellow liquid, b.p$_{0.05}$ 99\~102°, $[\alpha]_D^{19}$ −25.1°(c=2.7). *Anal.* Calcd. for $C_{11}H_{17}O_3N$: C, 62.54; H, 8.11; N, 6.63. Found : C, 62.64; H, 7.80; N, 6.51. IR $\nu_{max}^{CHCl_3}$ 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$_{0.6}$ 130\~138°, $[\alpha]_D^{16}$ −46°(c=3.88). This indicated that racemization was somewhat occurred.

Hexahydro-8(5*H*)-indolizinone(III)——Three grams of the above β-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_2CO_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$_5$ 65\~67°, α_D^{16} ±0°(l=1 cm, neat).

The oxime was recrystallized from isopropyl ether as colorless prisms, m.p. 117\~118°. *Anal.* Calcd. for $C_8H_{14}ON_2$: C, 62.30; H, 9.15; N, 18.17. Found : C, 62.44; H, 9.04; N, 17.81.

The picrate was formed in ether and recrystallized from EtOH as yellow needles, m.p. 147\~148°, (lit.,[12] 144\~145°). *Anal.* Calcd. for $C_{14}H_{16}O_8N_4$: C, 45.65; H, 4.35; N, 15.21. Found : C, 45.70; H, 4.40; N, 15.48.

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*8 We thank Mr. H. Horiguchi for his assistance in this experimental procedure.

13) N. J. Leonard, S. Swann, J. Figueras : J. Am. Chem. Soc., **74**, 4620 (1952).

14) A. W. D. Avison, A. L. Morrison : J. Chem. Soc., **1950**, 1471.

15) W. A. Recknow, D. S. Tarbell : J. Am. Chem. Soc., **74**, 496 (1952).

(+)-Hexahydo-8(5*H*)-indolizinone (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°, $[\alpha]_D^{17}$ +56.8°(c=2.07, H_2O). *Anal.* Calcd. for $C_{18}H_{28}O_5NBrS \cdot H_2O$: 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$_{15}$ 90~93°, $[\alpha]_D$ ±0°(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. and 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 (+)-hexahydro-8(5*H*)-indolizinone 10-camphorsulfonate monohydrate as colorless prisms, m.p. 97~101°, $[\alpha]_D^{15}$ +16.0°(c=2, H_2O). *Anal.* Calcd. for $C_{18}H_{29}O_5NS \cdot H_2O$: 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 $[\alpha]_D^{13}$ +0.93°(c=4.3). The oxime hydrochloride was obtained from EtOH as colorless prisms, m.p. 176°, $[\alpha]_D^{14}$ +7.9°(c=1.7, H_2O). *Anal.* Calcd. for $C_8H_{15}ON_2Cl$: C, 50.39; H, 7.93; N, 14.69. Found : C, 50.50; H, 8.08; N, 14.87.

(+)-Ethyl 2-Ethoxycarbonyl-1-piperidinebutyrate (XI)——Starting with 10.2 g. of D-pipecolic acid ethyl ester,[*7] b.p$_{17}$ 100°, $[\alpha]_D^{28}$ +13.3°(c=3.12), this was obtained in the same way as IX. The product was distilled under the reduced pressure to afford 13 g. (74%) of XI as a colorless liquid, b.p$_{0.05}$ 120~130°, $[\alpha]_D^{30}$ +46.0°(c=2.34). *Anal.* Calcd. for $C_{14}H_{25}O_4N$: C, 61.96; H, 9.29; N, 5.16. Found : C, 62.19; H, 8.82; N, 5.11.

Hexahydro-2*H*-quinolizin-1(6*H*)-one (IV)——This was prepared in 50% yield starting with 4.0 g. of the above diester XI in the similar procedure described for I. A colorless unstable liquid, b.p$_{3-5}$ 80~90°, $[\alpha]_D^{30}$ ±0°(c=10), was afforded (lit.,[13] b.p$_4$ 94°).

The picrate from EtOH as yellow needles, m.p.166~167° (lit.,[13] 167~168°). The semicarbazone from EtOH as colorless prisms, m.p. 214° (lit.,[13] 214°). The oxime hydrochloride from EtOH-isopropyl ether as colorless needles, m.p. 214° (lit.,[7] 215~216°).

(+)-Ethyl Octahydro-1-oxo-2-quinolizinecarboxylate (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 VIII. Distillation of the product afforded 0.85 g. (26%) of XII as a viscous pale yellow liquid, b.p$_{0.15}$ 109~115°, $[\alpha]_D^{32}$ +38.6°(c=3.0).[*9] *Anal.* Calcd. for $C_{12}H_{19}O_3N$: C, 63.97; H, 8.50; N, 6.22. Found : C, 63.97; H, 8.38; N, 6.49. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2790, 2640, 1740 (m), 1723 (m), 1658 (s), 1620 (s).

(−)-Hexahydro-2*H*-quinolizin-1(6*H*)-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 (−)-hexahydro-2*H*-quinolizin-1(6*H*)-one 3-bromo-8-camphorsulfonate as colorless prisms, m.p. 195~196°, $[\alpha]_D^{20}$ +61.2°(c=2, H_2O). *Anal.* Calcd. for $C_{19}H_{30}O_5NBrS$: C, 49.13; H, 6.46; N, 3.01. Found : C, 49.18; H, 6.63; N, 3.17. α-amino-ketone IV recovered from the salt in the same way as (−)-II had b.p$_8$ 93~95°, the rotation $[\alpha]_D^{10}$ −37°(c=5.5), $[\alpha]_D^{22}$ −31.7°(c=3.3, isooctane) (lit.,[16] $[\alpha]_D^{21}$ −32.9°(c=1.5, isooctane)).

The oxime hydrochloride was obtained from EtOH-isopropyl ether as colorless needles, m.p. 218~219°, $[\alpha]_D^{13}$ −62.1°(c=1.2, H_2O). *Anal.* Calcd. for $C_9H_{17}ON_2Cl$: 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°, $[\alpha]_D^{34}$ −62.4°(c=0.8). *Anal.* Calcd. for $C_9H_{16}ON_2$: C, 64.24; H, 9.59; N, 16.65. Found : C, 64.31; H, 9.42; N, 16.41.

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

(−)-Ethyl 1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (XIII)——According to the reported method,[17] L-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 (XIII) in 60% yield as a pale yellow liquid, b.p$_{0.2}$ 115~121°, $[\alpha]_D^{20}$ −76.8°(c=0.7).

The hydrochloride was recrystallized from EtOH as colorless pillars, m.p. 203~205°(decomp.), $[\alpha]_D^{26}$ −85.7°(c=1.2, H_2O). *Anal.* Calcd. for $C_{12}H_{16}O_2NCl$: 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 $C_{18}H_{18}O_9N_4$: C, 49.77; H, 4.15; N, 12.90. Found : C, 49.82; H, 4.40; N, 12.97.

[*9] Racemic compound was reported to be b.p$_1$ 131~134°, G. R. Clemo, T. P. Metcalfe : J. Chem. Soc., **1937**, 1518.

16) S. F. Mason, K. Schofield, R. J. Wells : Proc. Chem. Soc., **1963**, 337. Unfortunately this gave no experimental details.

17) G. R. Clemo, G. A. Swan : J. Chem. Soc., **1946**, 617; P. L. Julian, W. J. Karpel, A. Magnani, E. W. Meyer : J. Am. Chem. Soc., **70**, 180 (1948); S. Archer : J. Org. Chem., **16**, 430 (1951).

(−)-Ethyl 3-Ethoxycarbonyl-1,2,3,4-tetrahydro-2-isoquinolinebutyrate (XIV)——This was prepared from the above ester XIII in 58% yield, according to the modified procedure described for IX. Distillation of the product gave a pale yellow viscous liquid, b.d$_{2-3}$ 180∼190°, $[\alpha]_D^{28}$ −7.4°(c=5). *Anal.* Calcd. for $C_{18}H_{25}O_4N$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.53; H, 7.48; N, 4.35.

(−)-Ethyl 1,3,4,6,11,11*a*-Hexahydro-1-oxo-2*H*-benzo[*b*]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-ketoester XV as yellow needles, m.p. 79∼79.5°, $[\alpha]_D^{28}$ −13.3°(c=1.5). *Anal.* Calcd. for $C_{16}H_{19}O_3N$: C, 70.33; H, 6.96; N, 5.10. Found: C, 69.98; H, 6.83; N, 5.26. UV λ_{max}^{EtOH} mμ (log ε): 253 (4.04), 383 (3.38). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2775, 1660 (s), 1621 (m).

3,4,11,11*a*-Tetrahydro-2*H*-benzo[*b*]quinolizin-1(6*H*)-one (XVI)——1.5 g. of the above β-ketoester 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°, $[\alpha]_D^{25}$ ±0°(c=1.5)(lit.,[17,18]) m.p. 98∼100°). The IR spectrum (KBr) was identical with that of an authentic specimen prepared by the Clemo's method.[17] *Anal.* Calcd. for $C_{13}H_{15}ON$: C, 77.60; H, 7.45; N, 6.96. Found: C, 77.55; H, 7.66; N, 6.80.

TABLE I. Data for Racemizations of Bicyclic α-Amino-ketones (20°±0.1)

Compounds	Solvents	Pseudo first order rate constants (k) min^{-1}	Half-times for racemization ($t\frac{1}{2}$) min.
I	a	8.6×10^{-3}	80
	b	4.9×10^{-2}	10
II	a	1.5×10^{-3}	530
	b	9.2×10^{-2}	6
III	a	7.7×10^{-4}	900
	b	6.6×10^{-2}	10
IV	a	∼0	+∞
	b	2.8×10^{-3}	250

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°±0.1 constant temperature bath. The decrease of the optical rotation (α) at appropriate intervals of time was measured at 589 mμ for I, II and IV and 460 mμ for III. The degree of decomposition was checked by ultraviolet spectroscopic analysis.

In each case the logarithms of α/α_0 was plotted against time t to draw a good straight line (Figs. 1 and 2). The pseudo first order rate constants (k) and half-time ($t\frac{1}{2}$) for racemization were determined graphically, using the expression

$$kt=\ln \alpha_0/\alpha$$

where α_0 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°±0.1.

The authors are grateful to Dr. T. Hino of National Institute of Radiological Sciences for measurement of NMR spectra and the Members of the Central Analysis Room of this Faculty for microanalyses and spectral data. A donation of L-proline and L-phenylalanine from Tanabe Seiyaku, Co., Ltd. and Ajinomoto Co., Ltd., is also gratefully acknowledged.

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[18] N.J. Leonard, S. Swann, G. Fuller: J. Am. Chem. Soc., **76**, 3193 (1954).