[Chem. Pharm. Bull.
15(4) 490~498 (1967)]

UDC 547.759.02.07 : 541.653

62. Shun-ichi Yamada and Takehisa Kunieda: Studies on Optical Rotatory Dispersion and Circular Dichroism. I. Absolute Configuration of Cyclic α-Amino-ketones and Octant Rule.

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*1])

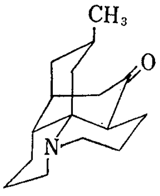
The absolute configurations of cyclic amino-ketones, hexahydro-1(5*H*)-indolizinone (Ⅲ), hexahydro-2*H*-quinolizin-1(6*H*)-one (Ⅳ), 3,4,11,11a-tetrahydro-2*H*-benzo[*b*]quinolizin-1(6*H*)-one (Ⅴ) and 3,4,11,11a-tetrahydro-1*H*-benzo[*b*]quinolizin-2(6*H*)-one (XIX) were determined by the chemical correlation with indolizidine (Ⅸ), 1-methylenequinolizidine (Ⅹ), 1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizine (Ⅻ) and phenylalanine, respectively.

A good agreement of the octant rule predictions with the experimental results was observed in the cases of hexahydro-1*H*-pyrrolizin-1-one (Ⅱ), Ⅲ and XIX, while the reverse result to the predictions was obtained in Ⅳ and Ⅴ.

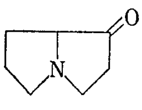
(Received July 4, 1966)

The octant rule[1)] has been successfully applied to a considerable number of the structural, configurational and conformational studies in the compounds containing cyclohexanone ring systems and proved to be one of the rules with very few exceptions. However, careful considerations must be paid on the application of this rule to the compounds whose molecular constructions largely differ from that of the cyclohexanone ring systems. For example, recent communication by Ayer, *et al.*[2)] described that the optical rotatory dispersion (ORD) curves of cyclic amino-ketone, lycopodine (I), showed the positive Cotton effect in the state of free base, while the negative Cotton effect in hydrochloride salt. They ascribed this phenomenon to the charge of the nitrogen atom in the molecule. Similar unexpected findings were also observed in the alkaloid field[3)] and the other.[4)] There seems to be no report concerning about the systematic studies on the application of the octant rule to such systems containing a nitrogen atom near the carbonyl group in cyclic compounds.

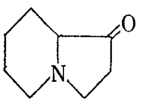
The present investigation was undertaken to examine the applicability of the octant rule to such bi- and tri-cyclic α-amino-ketones as hexahydro-1*H*-pyrrolizin-1-one (Ⅱ), hexahydro-1(5*H*)-indolizinone (Ⅲ), hexahydro-2*H*-quinolizin-1(6*H*)-one (Ⅳ) and 3,4,11,11a-tetrahydro-2*H*-benzo[*b*]quinolizin-1(6*H*)-one (Ⅴ).



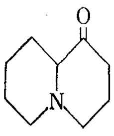
I



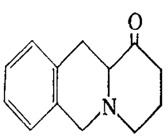
Ⅱ



Ⅲ



Ⅳ



Ⅴ

[*1] Hongo 7, Tokyo (山田俊一, 国枝武久).
[1)] W. Moffitt, R.B. Woodward, A. Moscowitz, W. Klyne, C. Djerassi: J. Am. Chem. Soc., **83**, 4013 (1961).
[2)] W.A. Ayer, J.A. Berezowsky, D.A. Law: Can. J. Chem., **41**, 649 (1963).
[3)] Private communication from Dr. T. Onaka of this Faculty.
[4)] O.F. Morrow, M.E. Brokke, G.W. Moersch, M.E. Butler, C.F. Klein, W.A. Neuklis, E.C.Y. Huang: J. Org. Chem., **30**, 212 (1965).

Determination of Absolute Configuration——The absolute configuration of (−)II is already known by the correlation with L-proline.5,6) The absolute configurations of (−)III, (+)IV and (+)V, obtained by resolution by means of *d*-3-bromo-8-camphorsulfonic acid were chemically determined as shown in Charts 1 and 2.

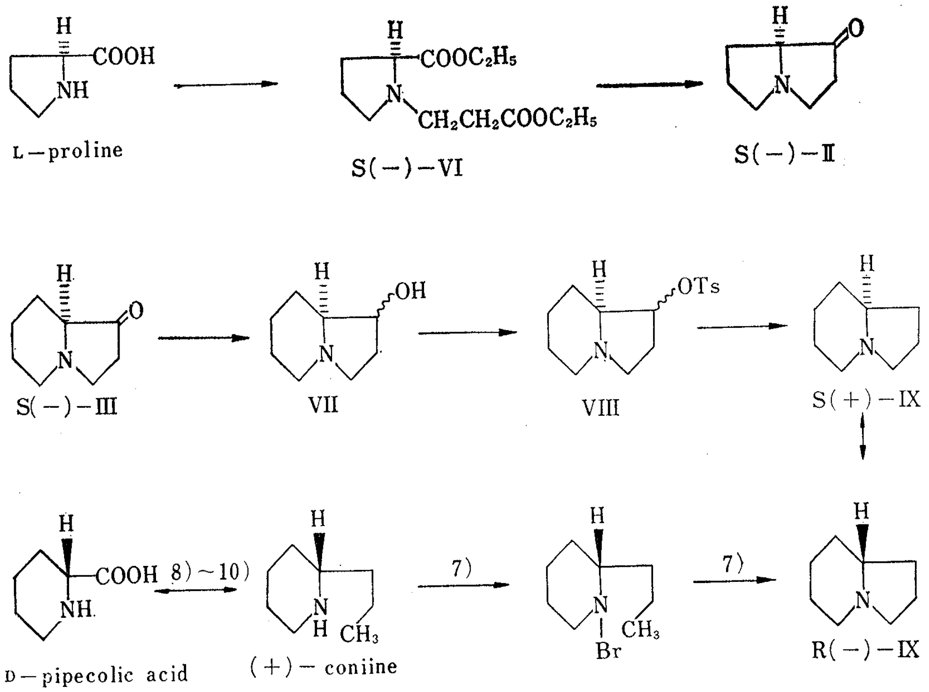


Chart 1.

(−)III, $[\alpha]_D$ −113° (EtOH), was reduced with lithium aluminum hydride to the corresponding alcohol VII. This alcohol was tosylated with tosylchloride in pyridine, and the resulting tosylate VIII was reduced with lithium aluminum hydride in tetrahydrofuran to afford (+)indolizidine (IX), α_D^{20} +0.24° (l=1 cm., neat). Since (−)indolizidine was obtained from (+)coniine,7) which was correlated with D-pipecolic acid,8~10) it follows that (+)IX and hence (−)III have the *S*-configuration.

(+)IV, $[\alpha]_D$ +21.8° (EtOH), was subjected to the Wittig reaction11) using methyltriphenylphosphonium iodide and sodium amide. 1-Methylenequinolizidine (X), obtained in 73% yield, showed $[\alpha]_D$ +23.3° (EtOH), $[\alpha]_D$+ 2,787° (l=1 cm., neat), which gave a picrate, m.p. 156° and a chloroaurate, m.p. 143°. As (−)X, α_D −11.57° (l=2.5 cm, neat),12) was derived from (−)lupinine of the known absolute configuration,13,14) (+)IV must be the *S*-configuration, contrary to the Mason's assignment15) by the application of the octant rule on (−)IV. Furthermore, although Collins and Hammond16) reported

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5) A.M. Likhosherstov, A.M. Krytsin, N.K. Kochetkov : Doklady Akad. Nauk. S.S.S.R., **141**, 361 (1961).
6) T. Kunieda, K. Koga, S. Yamada : This Bulletin, **15**, 337 (1967).
7) E. Lellmann : Ber., **23**, 2141 (1890).
8) L. Marion : "The Alkaloids. Chemistry and Physiology." edited by R.H.F. Manske, H.L. Holmes, Academic Press, Inc., New York, N.Y., Vol. I, 215, 217, 225, 226 (1950).
9) W. Leithe : Ber., **65**, 927 (1932).
10) A. Neuberger : Advances in Protein Chemistry, **4**, 297 (1948).
11) G. Wittig, H. Eggersu, P. Duffner : Ann., **619**, 10 (1958).
12) P. Karrer, A. Vogt : Helv. Chim. Acta, **13**, 1073 (1930).
13) R.C. Cookson : Chem. & Ind. (London), **1953**, 3337.
14) S. Okuda, H. Kataoka, K. Tsuda : This Bulletin, **13**, 487 (1965).
15) S.F. Mason, K. Schofield, R.J. Wells : Proc. Chem. Soc., **1963**, 337.
16) C.H. Collins, G.S. Hammond : J. Org. Chem., **25**, 1434 (1960).

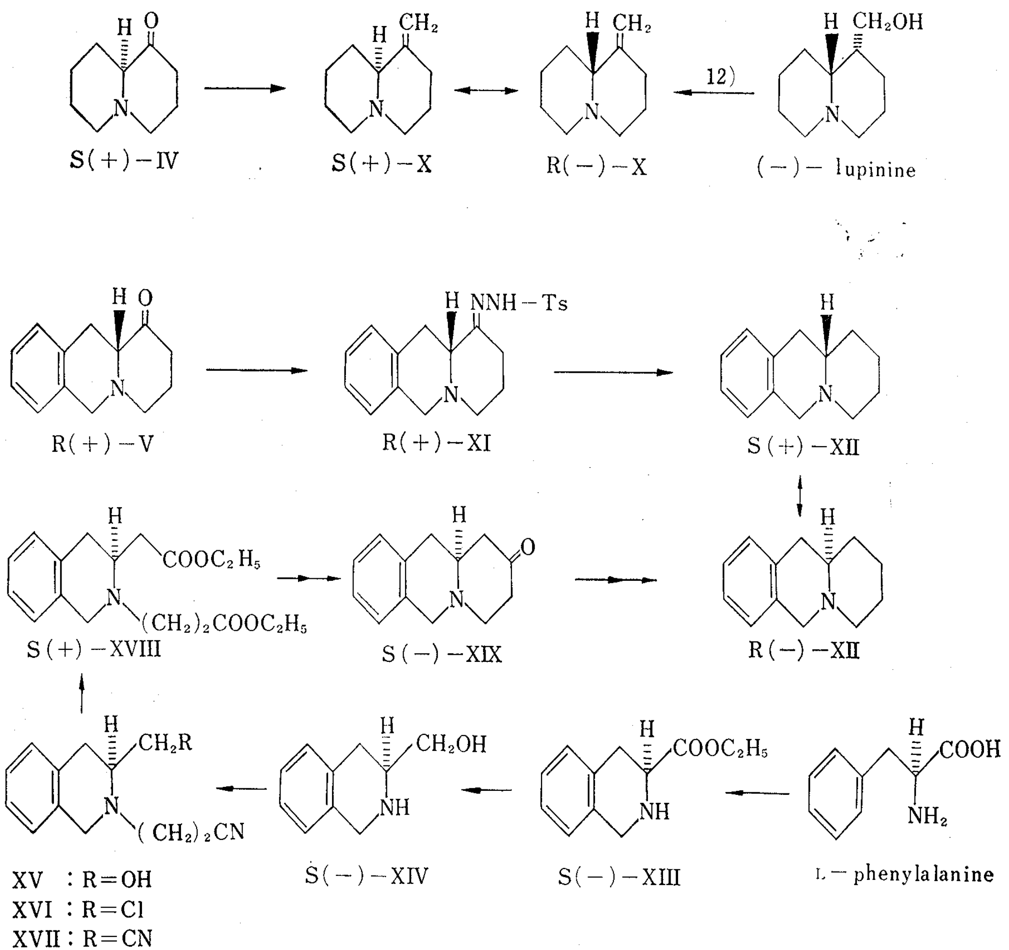

Chart 2.

that a considerable difficulty was encountered in the use of methyltriphenylphosphonium iodide instead of the corresponding bromide in the Wittig reaction to cyclopentanone, and indeed the iodide has not yet been successfully employed in this reaction, the above result seems to indicate that the iodide is not an essential obstacle in this reaction.

(+)V, $[\alpha]_D$ +89.6° (EtOH), was correlated with L-phenylalanine as shown in Chart 2. For the direct conversion of the carbonyl group to the methylene group under the mild condition,[17] the tosylhydrazone XI, m.p. 191°, $[\alpha]_D$ +42.7° ($CHCl_3$) of (+)V was reduced with sodium borohydride in dioxane. The product was purified by chromatography on neutral alumina to afford (+)-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizine (XII), m.p. 42~47°, $[\alpha]_D$ +29.3° (EtOH), which gave the hydrochloride, m.p. 258°, $[\alpha]_D$ + 25.5° (EtOH). On the other hand, L-phenylalanine was converted to (−)ethyl 1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (XIII) by the application of the Pictet-Spengler reaction[18] followed by esterification, using formaldehyde in conc. hydrochloric acid. The ester XIII was reduced with lithium aluminum hydride to the corresponding alcohol XIV, $[\alpha]_D$ −101.4° (EtOH) which was reacted with acrylonitrile in the presence of acetic acid to give the nitrile XV. (+)Ethyl 3-ethoxycarbonylmethyl-1,2,3,4-tetrahydro-2-isoquinolinepropionate (XVIII), $[\alpha]_D$ +9.9° (EtOH), obtained from XV in 48% overall yield *via* the chloride XVI and subsequently the dinitrile XVII, was subjected to the Dieckmann

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[17] L. Caglioti, P. Grasselli: Chem. & Ind. (London), **1964**, 153.
[18] A. Pictet, Th. Spengler: Ber., **44**, 2030 (1911).

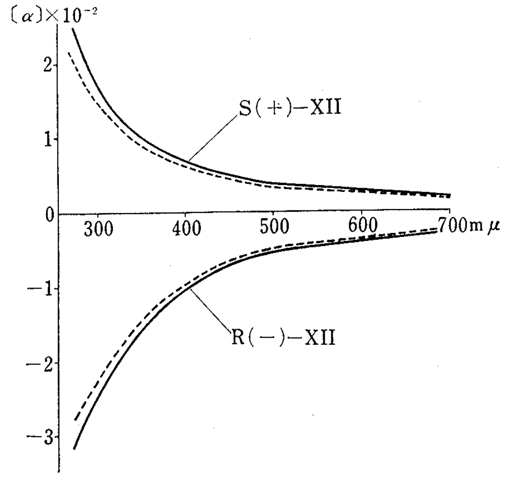


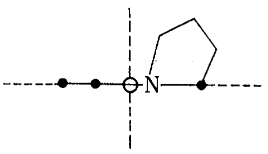
Fig. 1. Optical Rotatory Dispersion Curves of S(+)- and R(−)-1,3,4,6,11,11a-Hexahydro-2*H*-benzo[*b*]quinolizine (XII) in EtOH

——— : free base
- - - - : hydrochloride

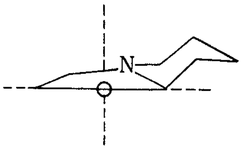
cyclization reaction using sodium hydride as a condensing agent followed by saponification and decarboxylation to yield (−)-3,4,11,11a-tetrahydro-1*H*-benzo[*b*]quinolizin-2(6*H*)-one (XIX), m.p. 119.5∼120.5°, $[\alpha]_D -91.0°$ (EtOH), which gave the oxime hydrochloride of m.p. 253°, $[\alpha]_D -65.1°$ (H_2O). The reduction of the tosylhydrazone of XIX with sodium borohydride and subsequent purification with chromatography as above afforded (−)XII, m.p. 42∼44°, $[\alpha]_D$ −41.2° (EtOH), which gave the hydrochloride of m.p. 253°, $[\alpha]_D -40°$ (EtOH). (+)XII and (−)XII obtained as mentioned above were proved to be identical in their infrared spectra in the solid state, showed to be optically antipodal in their ORD curves (Fig. 1), and therefore the absolute configuration of (+)V was established to be *R*-configuration as shown in Chart 2.

Application of the Octant Rule——Although an application of the octant rule to the five-membered cyclic ketones is, in general, difficult due to the uncertainty of their precise conformations, Klyne[19] reported that the good agreement of the experimental results with the octant predictions was observed in such five-membered ring ketones having fairly predictable conformation as hydrindanones and steroidal D-ring ketones.

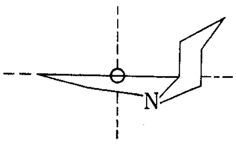
The most important conformer in S(−)II is considered to be XX, due to the strong rigidity of the molecule and the absence of Bohlmann band[20] in the infrared spectrum (chloroform), while in S(−)III, the three conformers, XXI, XXII and XXIII, must be taken into account because of the possible inversion at the bridge-head tri-covalent nitrogen, although XXI would be the predominant according to the distinct presence of the Bohlmann absorption band[20] in its infrared spectrum (chloroform).



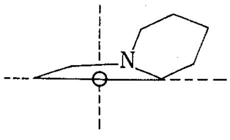
XX



XXI



XXII



XXIII

An application of the octant rule to these conformers suggests that both S(−)II and S(−)III should give the markedly negative Cotton effect. The agreement of predictions with the experimentally determined results is observed as shown in Figs. 2 and 3.

In the case of six-membered cyclic α-amino-ketones (IV,V), the situation is not so simple. Possible conformations must be a mixture of *cis*- and *trans*-1-decalone type conformers due, also in this case, to the possible inversion of configuration at the bridge-head nitrogen atom. As a result, conformers XXIV, XXV and XXVI for R(−)IV and XXIV′, XXV′ and XXVI′ for R(+)V are important. Judging from the presence of the Bohlmann band[20] in their infrared spectra (chloroform), XXIV and XXIV′ appear to be predominant among these conformations. The octant rule predicts that

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[19] W. Klyne: Tetrahedron, **13**, 29 (1961).
[20] F. Bohlmann: Ber., **91**, 2157 (1958).

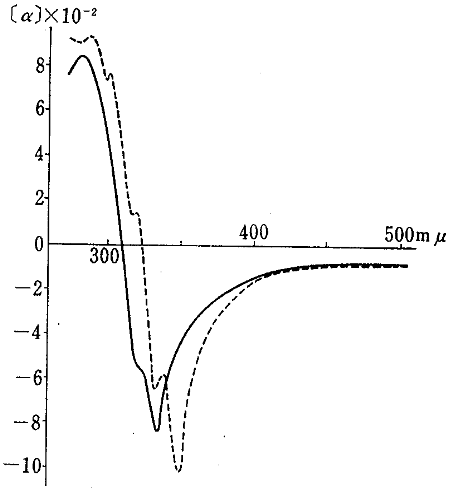


Fig. 2. Optical Rotatory Dispersion Curves of S(−)-Hexahydro-1*H*-pyrrolizin-1-one (II)

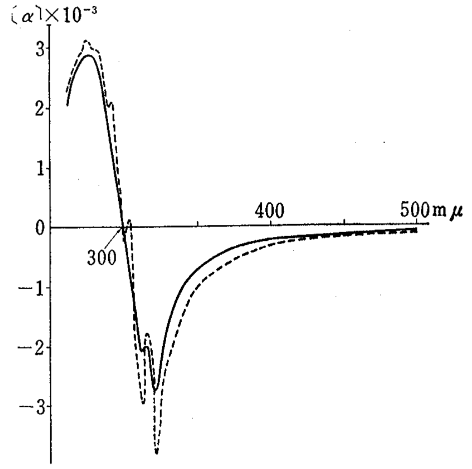
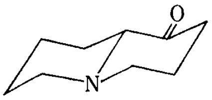
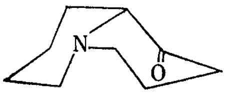


Fig. 3. Optical Rotatory Dispersion Curves of S(−)-Hexahydro-1(5*H*)-indolizinone (III)

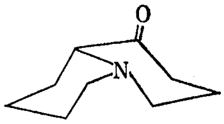
———: in EtOH -------: in isooctane



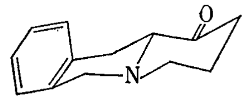
XXIV



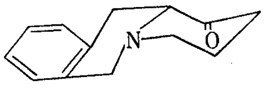
XXV



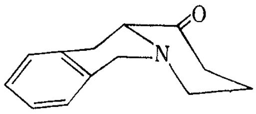
XXVI



XXIV′



XXV′



XXVI′

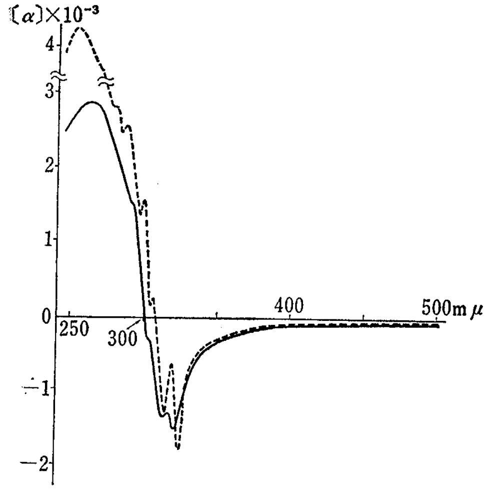


Fig. 4. Optical Rotatory Dispersion Curves of R(−)-Hexahydro-2*H*-quinolizin-1(6*H*)-one (IV)

———: in EtOH
-------: in isooctane

conformers XXIV and XXV would give the strong, positive Cotton effect and conformer XXVI the weak, positive Cotton effect. Consequently, the strong, positive Cotton effect is the octant prediction for R(−)IV. The experimentally determined ORD curves of R(−)IV in EtOH and in isooctane, however, are the opposite to the prediction as shown in Fig. 4. The consideration of the other possible conformers having boat and flexible form does not change the sign of the prediction. The same disagreement of the prediction with the observed data is also encountered in (+)V, although, in conformation XXV′, a part of phenyl group belongs to the near octant, which makes an opposite contribution in sign (Fig. 5). However, the prediction of the octant rule in (−)XIX, *β*-amino-ketone, agreed well with the observed data as shown in Fig. 6.

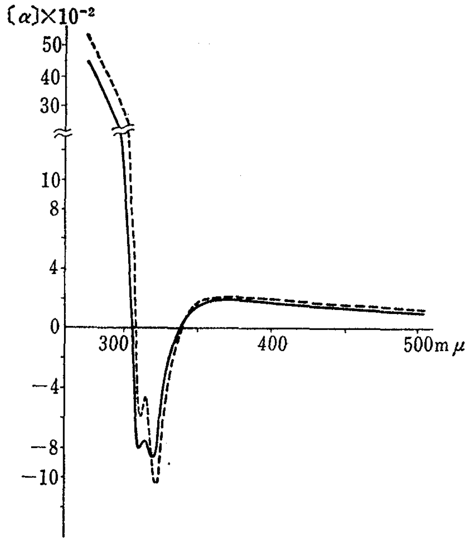


Fig. 5. Optical Rotatory Dispersion Curves of R(+)-3,4,11,11a-Tetrahydro-2*H*-benzo[*b*]quinolizin-1(6*H*)-one (V)

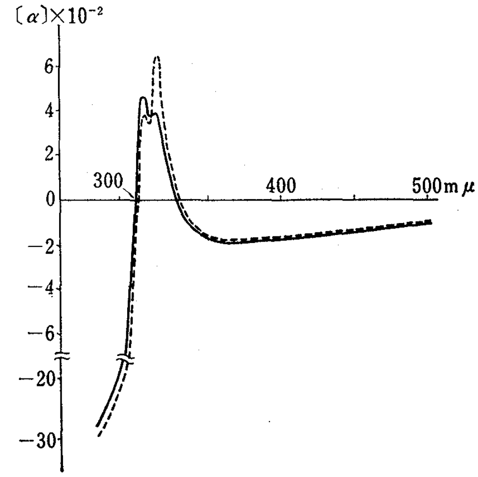


Fig. 6. Optical Rotatory Dispersion Curves of S(−)-3,4,11,11a-Tetrahydro-1*H*-benzo[*b*]quinolizin-2(6*H*)-one (XIX)

———— : in EtOH -------: in dioxane

These results indicate that the octant rule appears to be successfully applicable when the nitrogen atom of the amino-ketone lies on the axis of the octant projection, while the disagreement will be encountered when the nitrogen atom is on the octant space.

As shown in Figs. 2, 3, 4, and 5, the solvent-dependent Contton effect curves having fine structures are observed in II, III, IV and V, just as in the case of β,γ-unsaturated ketones investigated in detail by Moscowitz, *et al.*[21] Since this phenomenon may reflect the result of the intramolecular interacion between a nitrogen atom and the carbonyl group, α-amino-ketone function might be taken as a dissymmetric chromophore.

Experimental*2

S(−)-Hexahydro-1*H*-pyrrolizin-1-one (II)[5,6]——The procedure was modified from the method of Likhosherstov, *et al.*[5] L-Poline was converted to ethyl (−)-2-ethoxycarbonyl-1-pyrrolidinepropionate (VI) in 87% yield, which was subjected to the Dieckmann reaction using NaOEt as a condensing agent, followed by decarboxylation with dil. HCl to yield (−)-II in 39% yield as an unstable colorless liquid, b.p$_{4\sim5}$ 65°, $[\alpha]_D^9$ −49.7°(c=2.5), (lit.,[5] $[\alpha]_D^{21}$ −22.4°(c=1.25)); $[\alpha]_D^9$ −59.2° (c=2.3, dioxane). UV λ_{max}^{EtOH} mμ (log ε): 307 (1.48); $\lambda_{max}^{dioxane}$: 310 (1.65); $\lambda_{max}^{isooctane}$: 303 (1.66), 314 (1.68), 327 (1.62), 342 (inf.) (1.43). ORD: (c=0.51 in EtOH), $[\alpha]_{332}$ −850, $[\alpha]_{320}$ −600, $[\alpha]_{308}$ ±0, $[\alpha]_{280}$ +820 (Fig. 2); (c=0.55 in dioxane), $[\alpha]_{345}$ −1000, $[\alpha]_{330}$ −600, $[\alpha]_{322}$ ±0, $[\alpha]_{290}$ +1030; (c=0.58 in isooctane), $[\alpha]_{348}$ −1020, $[\alpha]_{337}$ −600, $[\alpha]_{333}$ −660, $[\alpha]_{324}$ ±0, $[\alpha]_{318}$ +140, $[\alpha]_{308}$ +660, $[\alpha]_{296}$ +900 (Fig. 2).

(−)-Hexahydro-1(5*H*)-indolizinone (III)——This was obtained by resolution using BCS*3 in the same way as described before.[6] The base recovered from the BCS salt was distilled to yield an unstable colorless liquid, b.p$_{1\sim2}$ 68~70°, $[\alpha]_D^{24}$ −105°(c=4.6), $[\alpha]_D^{24}$ −107.3°(c=0.81, dioxane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2785, 2715, 1680, 1758. UVλ_{max}^{EtOH} mμ (log ε): 293 (1.46); $\lambda_{max}^{dioxane}$: 291 (1.51), 302 (1.48), 313 (1.38); $\lambda_{max}^{isooctane}$: 283 (1.43), 293 (1.46), 304 (1.45), 316 (1.30). ORD: (c=0.46 in EtOH), $[\alpha]_{318}$ −2800, $[\alpha]_{311}$ −2280, $[\alpha]_{307}$ −2340, $[\alpha]_{297}$ ±0, $[\alpha]_{275}$ +2930 (Fig. 3); (c=0.43 in dioxane), $[\alpha]_{319}$ −3600, $[\alpha]_{312}$ −1930, $[\alpha]_{307}$ −2300, $[\alpha]_{302}$ ±0, $[\alpha]_{300}$ +460, $[\alpha]_{275}$ +3450; (c=0.35 in isooctane), $[\alpha]_{320}$ −3800, $[\alpha]_{315}$ −1800, $[\alpha]_{309}$ −3000, $[\alpha]_{303}$ +170, $[\alpha]_{299}$ −210, $[\alpha]_{290}$ +2000, $[\alpha]_{275}$ +3000 (Fig. 3).

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*2 All melting points were uncorrected. Optical rotations were determined in EtOH, unless otherwise stated.

*3 *d*-3-bromo-8-camphorsulfonic acid.

21) A. Moscowitz, K. Mislow, M.A.W. Glass, C. Djerassi: J. Am. Chem. Soc., **84**, 1945 (1962).

(−)-Octahydro-1-indolizinol (VII)——With 1.0 g. (0.03 mole) of $LiAlH_4$ was reduced 1.6 g. (0.012 mole) of (−)III, $[\alpha]^{27}_{\mathrm{D}}$ −113°(c=1.28), in abs. ether. Distillation of the product yielded 1.1 g. (68%) of a colorless liquid, b.p$_3$ 90~95°, $[\alpha]^{30}_{\mathrm{D}}$ −24°(c=0.84). IR $\nu^{\mathrm{cap.}}_{\mathrm{max}}$ cm^{-1}: 3350 (ν_{OH}), 1140 (δ_{OH}). The IR spectrum (cap.) was identical with that of *dl*-VII, which gave picrate, m.p. 155~159° (lit.,[22] m.p. 156~157°).

(−)-Octahydro-1-indolizinol Tosylate (VIII)——Under cooling, 2.0 g. (0.01 mole) of tosyl chloride was added to a solution of 1.1 g. (0.008 mole) of the above alcohol VII in 30 ml. of dry pyridine and the mixture was kept at room temperature for 3 days. The solvent was distilled off not high above 40°, the resulting residue was treated with aqueous K_2CO_3 and it was extracted with ether. The extract was dried and the solvent was evaporated *in vacuo*. The oily residue was chromatographed on neutral alumina (Woelm activity III) to yield 1.4 g. (60%) of a viscous colorless liquid, $[\alpha]^{24}_{\mathrm{D}}$ −23°(c=0.89). The IR spectrum (cap.) was superimposal with that of *dl*-VIII, which gave a picrate as yellow needles from EtOH, m.p. 181~183°. *Anal.* Calcd. for $C_{21}H_{23}O_{10}N_4S$: C, 48.18; H, 4.40; N, 10.71. Found: C, 48.24; H, 4.57; N, 10.86.

(+)-Octahydroindolizine (Indolizidine) (IX)——To a suspension of 1.0 g. (0.026 mole) of $LiAlH_4$ in 60 ml. of abs. THF was added 1.4 g. (0.005 mole) of the above tosylate VIII. After being refluxed for 21 hr., the mixture was cooled in ice and a mixture of 2 ml. of water, 10 ml. of THF and 2.5 ml. of 10% NaOH was added carefully to give a loose precipitation. The filtrate was acidified with dil. HCl and evaporated *in vacuo*. The residue was basified with K_2CO_3 and it was extracted with ether. The extract was dried and evaporated *in vacuo*. Distillation of the resulting oil under N_2 stream afforded 130 mg. (22%) of (+)-octahydroindolizine (IX) as a colorless liquid, b.p$_{10\sim15}$ 50~60° (lit.,[23] b.p$_{18}$ 58~59°), $[\alpha]^{25}_{\mathrm{D}}$ +3.2°(c=1.76), α^{20}_{D} +0.24°(l=1 cm., neat). This showed a positive plain ORD curve in the state of pure liquid, α_{300} +0.62° (l=5 mm.). The gas chromatogram on a 7% SE-30 column at 113° showed just one component. The picrate was obtained as yellow needles from EtOH, m.p. 230~232° (lit.,[7] 226°). *Anal.* Calcd. for $C_{14}H_8O_7N_4$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.30; H, 4.97; N, 15.99.

(−)-Hexahydro-2*H*-quinolizin-1(6*H*)-one (IV)——This was obtained by resolution using BCS as previously described.[6] This was unstable in air and had b.p$_8$ 93~95°, $[\alpha]^{10}_{\mathrm{D}}$ −37° (c=5.5), $[\alpha]^{22}_{\mathrm{D}}$ −31.7° (c=3.3, isooctane) (lit.,[15] $[\alpha]^{21}_{\mathrm{D}}$ −32.9°(c=1.5, isooctane)). IR $\nu^{\mathrm{CHCl_3}}_{\mathrm{max}}$ cm^{-1}: 2800, 2750, 1725. UV $\lambda^{\mathrm{EtOH}}_{\mathrm{max}}$ mμ (log ε): 294 (1.46); $\lambda^{\mathrm{dioxane}}_{\mathrm{max}}$: 298 (1.58), 3.07 (1.58); $\lambda^{\mathrm{isooctane}}_{\mathrm{max}}$: 298 (1.52), 308 (1.49), 318 (inf.) (1.36). ORD: (c=0.47 in EtOH), $[\alpha]_{322}$ −1500, $[\alpha]_{316}$ −1280, $[\alpha]_{314}$ −1350, $[\alpha]_{301}$ ±0, $[\alpha]_{265}$ +2860 (Fig. 4); (c=0.22 in isooctane), $[\alpha]_{324}$ −1700, $[\alpha]_{319}$ −670, $[\alpha]_{314}$ −1290, $[\alpha]_{307}$ +380, $[\alpha]_{304}$ +90, $[\alpha]_{297}$ +1500, $[\alpha]_{287}$ +2480, $[\alpha]_{255}$ +4350 (Fig. 4).

Methyltriphenylphosphonium Iodide——To a solution of 15 g. (0.057 mole) of triphenylphosphine in 20 ml. of benzene was added 10 g. (0.07 mole) of methyl iodide and the mixture was allowed to stand for 4 days at room temperature. The precipitated salt was collected and washing with benzene gave sufficiently purified compound for the use. It afforded 23 g. (100%) of colorless solid, m.p. 183~184° (lit.,[11] 181~184).

(+)-1-Methyleneoctahydroquinolizine (X)——One gram (0.04 atom) of sodium was dissolved portionwise in 250 ml. of liquid ammonia containing a few grains of ferric nitrate. After stirring for 30 min., 17.8 g. (0.044 mole) of methyltriphenylphosphonium iodide was added portionwise and the mixture was stirred for 30 min. The ammonia was displaced with 300 ml. of abs. ether, the last traces being removed by refluxing in a stream of nitrogen for half an hour. To the cooled ether solution was added 2.3 g. (0.015 mole) of (+)-hexahydro-2*H*-quinolizin-1(6*H*)-one (IV), $[\alpha]^{28}_{\mathrm{D}}$ +21.8 (c=1.9),[6] which gave the oxime hydrochloride, $[\alpha]^{20}_{\mathrm{D}}$ +38.6° (c=1.04, H_2O). The reaction mixture was refluxed for 2 hr. and allowed to stand at room temperature for 2 days. Upon removal of precipitates by filtration, the filtrate was acidified with 10% HCl, the aqueous solution separated was made basic with aqueous saturated potassium carbonate and extracted with benzene. The extract was dried and evaporated under N_2 atmosphere. The residue was washed with *n*-hexane-ether to remove triphenylphosphine oxide and the organic layer was distilled off. The resulting product was distilled *in vacuo* to afford the fraction boiling at 90°/20 mm. Redistillation yielded 1.65 g. (73%) of (+)-1-methylenequinolizidine (X) as a colorless liquid, b.p$_{10}$ 78° (lit.,[12] b.p$_{15}$ 85°), $[\alpha]^{26}_{\mathrm{D}}$ +23.3°(c=2.22), α^{26}_{D} +2.787° (l=1 cm., neat). The purity was checked by glpc analysis using a 7% SE-30 column at 160°. IR $\nu^{\mathrm{cap.}}_{\mathrm{max}}$ cm^{-1}: 3090, 1790, 1647, 1125, 894. ORD: (c=2.22 in EtOH), $[\alpha]^{\mathrm{peak}}_{275}$ +100, $[\alpha]_{240}$ ±0. *Anal.* Calcd. for $C_{10}H_{17}N$: N, 9.26. Found: N, 9.02.

The picrate was obtained as yellow needles from AcOEt-ether, m.p. 155~156°. *Anal.* Calcd. for $C_{16}H_{20}O_7N_4$: C, 50.52; H, 5.30; N, 14.73. Found: C, 50.59; H, 5.14; N, 15.09.

The chloroaurate was obtained as yellow prisms from aq. EtOH, m.p. 142~143°. *Anal.* Calcd. for $C_{10}H_{18}NAuCl_4$: C, 24.45; H, 3.69; N, 2.85. Found: C, 24.56; H, 3.67; N, 3.03.

(+)-3,4,11,11a-Tetrahydro-2*H*-benzo[*b*]quinolizin-1(6*H*)-one (V)——The mixture of 4.0 g. (0.02 mole) of *dl*-V, prepared according to the reported method,[24] and 6.4 g. (0.02 mole) of BCS in 20 ml. of acetone was kept in the refrigerator overnight. Colorless crystals separated with an aid of a little amount of ether were collected, weighing 2.4 g. Recrystallization from EtOH yielded colorless prisms, m.p. 187~190°, $[\alpha]^{29}_{\mathrm{D}}$ +87.5°

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(c=0.8, H_2O). *Anal.* Calcd. for $C_{23}H_{30}O_5NBrS$: C, 53.91; H, 5.86; N, 2.73. Found : C, 54.08; H, 5.82; N, 2.95.

The suspension of 2.3 g. of the above salt in 10 ml. of H_2O was made alkaline with aqueous saturated K_2CO_3 and extracted with benzene. The extract was dried and evaported ***in vacuo*** under N_2 stream to leave 0.9 g. of orange crystals. Upon the recrystallization from a little volume of EtOH-*n*-hexane it formed small yellow prisms, m.p. 62~64°, $[\alpha]_D^{28}$ +89.6°(c=0.77). The IR spectrum ($CHCl_3$) was identical with that of *dl*-V prepared by the Clemo's method,[24] which had m.p. 103~104°. *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. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2796, 2750, 1722. UV λ_{max}^{EtOH} mμ (log ε) : 265 (2.66), 272 (2.65), 290 (inf.) (1.76). $\lambda_{max}^{dioxane}$: 257 (inf.) (2.92), 265 (inf.) (2.87), 273 (2.78), 358 (2.67). ORD : (c=0.062 in EtOH), $[\alpha]_{\sim400}$ +160, $[\alpha]_{338}$ ±0, $[\alpha]_{320}$ −860, $[\alpha]_{315}$ −780, $[\alpha]_{310}$ −800, $[\alpha]_{305}$ ±0, $[\alpha]_{280}$ +4000 (Fig. 5); (c=0.20 in dioxane), $[\alpha]_{\sim400}$ +200, $[\alpha]_{339}$ ±0, $[\alpha]_{320}$ −1030, $[\alpha]_{314}$ −450, $[\alpha]_{311}$ −600, $[\alpha]_{307}$ ±0, $[\alpha]_{280}$ +5000 (Fig. 5); (c=0.214 in benzene), $[\alpha]_{400}$ +160, $[\alpha]_{345}$ ±0, $[\alpha]_{322}$ −1260, $[\alpha]_{315}$ −500, $[\alpha]_{312}$ −720, $[\alpha]_{308}$ ±0, $[\alpha]_{280}$ +5000. CD : $[\theta]_{296}^{29}$ −4040 (EtOH).

(+)-3,4,11,11a-Tetrahydro-2*H*-benzo[*b*]quinolizin-1(6*H*)-one Tosylhydrazone (XI)——A solution of 0.6 g. (0.003 mole) of the above (+)V and 0.6 g. (0.003 mole) of tosylhydrazine in 20 ml. of MeOH was heated under reflux for 1 hr. and kept in the refrigerator. Colorless prisms were collected, weighing 0.6 g. Recrystallization from EtOH formed colorless prisms, m.p. 190~191°(decomp.), $[\alpha]_D^{26}$ +42.6 (c=0.82, $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{23}O_2N_3S$: C, 65.02; H, 6.28; N, 11.38. Found : C, 65.09; H, 6.44; N, 11.63.

(+)-1,3,4,6,11,11a-Hexahydro-2*H*-benzo[*b*]quinolizine (XII)——To a solution of 1 g. (0.0027 mole) of the above tosylate XI in 60 ml. of abs. dioxane was added 3 g. (0.08 mole) of $NaBH_4$ and the mixture was boiled with stirring under reflux for 10 hr. Excess $NaBH_4$ was decomposed carefully with an addition of dil. HCl. The precipitation was removed by filtration and the filtrate was evaporated to dryness ***in vacuo***. The resulting residue was dissolved in a little volume of water, made alkaline with K_2CO_3 and it was extracted with benzene. The extract was dried and evaporated ***in vacuo***. After the purification by chromatography on neutral alumina (Woelm activity III) 80 mg. (16%) of (+)XII was obtained as colorless crystals, m.p. 42~47°, $[\alpha]_D^{14}$ +29.3°(c=0.28), $[\alpha]_{280}$ +250°(c=0.28) (Fig. 1). *Anal.* Calcd. for $C_{13}H_{17}N$: N, 7.48. Found : N, 7.64.

The hydrochloride was obtained as colorless needles from EtOH-isopropyl ether, m.p. 255~258°, $[\alpha]_D^{15}$ +25.5° (c=0.22), $[\alpha]_{280}$ +200 (Fig. 1). *Anal.* Calcd. for $C_{13}H_{18}NCl$: C, 69.78; H, 8.11; N, 6.26. Found: C, 69.84; H, 7.83; N, 6.24.

(−) Ethyl 1,2,3,4-Tetrahydro-3-isoquinolinecarboxylate (XIII)——Being analogous to the procedure reported,[25] L-phehylalanine in place of *dl*-phenylalanine was subjected to the Pictet-Spengler reaction[18] using formaline in conc. HCl to afford 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid hydrochloride in 80% yield. This acid was esterified with $SOCl_2$-EtOH to ethyl 1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (XIII), which was distilled to give a pale yellow liquid, $b.p_{0.08}$ 130~135°, $[\alpha]_D^{30}$ −92.4°(c=1.22).

The hydrochloride was recrystallized from EtOH as colorless pillars, m.p. 203~205°, $[\alpha]_D^{28}$ −92.1°(c=1.1, 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 EtOH and recrystallized from EtOH as yellow needles, m.p. 198~200° (decomp.). *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.

(−)-1,2,3,4-Tetrahydro-3-isoquinolinemethanol (XIV)——This was obtained in 90% yield by the reduction of the above (−)-XIV with $LiAlH_4$ in abs. ether. The product was recrystallized from benzene as colorless prisms, m.p. 118~119°, $[\alpha]_D^{18}$ −101.4°(c=2). *Anal.* Calcd. for $C_{10}H_{13}ON$: C, 73.59; H, 8.03; N, 8.58. Found : C, 73.55; H, 7.81; N, 8.64.

3-Hydroxymethyl-1,2,3,4-tetrahydro-2-isoquinolinepropionitrile (XV)——The mixture of 10 g. (0.061 mole) of the alcohol XIV, 20 g. (0.38 mole) of the freshly distilled acrylonitrile and 2 ml. of acetic acid was heated under reflux for 10.5 hr. After the removal of the low boiling materials, the residue was extracted with dil. HCl and the acidic layer was made basic with K_2CO_3 and extracted with benzene. The extract was dried and the solvent was removed. It gave 11 g. of XV as an orange oil, which was almost decomposed to the alcohol XV on distillation at 150°/0.05 mm. The IR spectrum showed the presence of a nitrile at 2280 cm^{-1} and a hydroxyl group at 3450 cm^{-1}.

(+) Ethyl 3-(Ethoxycarbonylmethyl)-1,2,3,4-tetrahydro-2-isoquinolinepropionate (XVIII)——To a cooled solution of 10 g. of the nitrile XV in 40 ml. of $CHCl_3$ was added 11 g. of $SOCl_2$ dropwise and the mixture was stirred under cooling for 3 hr. with the subsequent reflux for 1 hr. The mixture was treated in the usual manner to give 9.5 g. of 3-chloromethyl-1,2,3,4-tetrahydro-2-isoquinolinepropionitrile (XVI) as a red oil. The IR spectrum showed the absence of a hydroxyl group.

To the warmed mixture of 3.8 g. of NaCN and 20 ml. of DMSO, was added 9.5 g. of the chloride XVI without purification and the mixture was kept at 100° for 2 hr. The mixture was cooled, poured into

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[24] G.R. Clemo, G.A. Swan : J. Chem. Soc., **1946**, 617.

[25] P.L. Julian, W.J. Karpel, A. Magnand, E.W. Meyer : J. Am. Chem. Soc., **70**, 180 (1948); S. Archer : J. Org. Chem., **16**, 430 (1951).

cold water and extracted with benzene. The extract was dried and evaporated ***in vacuo*** to afford 7.5 g. of the dinitrile XVII as an orange oil.

This was alcoholyzed by refluxing for 4.5 hr. in 100 ml. of EtOH saturated with dry HCl. The solvent was removed ***in vacuo***, the resulting oil was dissolved in cold water, made alkaline with aq. K_2CO_3 and extracted with benzene. On removal of the benzene was obtainend 7.5 g. of a red oil, which was distilled under N_2 atmosphere to afford 7.0 g. (48% from XV) of ethyl 3-(ethoxycarbonylmethyl)-1,2,3,4-tetrahydro-2-isoquinolinepropionate (XVIII) as a slightly yellow viscous liquid, b.p$_{0.06}$ 178~184°, $[\alpha]_D^{22}$ +9.9°(c=2). *Anal.* Calcd. for $C_{18}H_{25}O_4N$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.34; H, 7.64; N, 4.71.

(−)-3,4,11,11a-Tetrahydro-1*H*-benzo[*b*]quinolizin-2(6*H*)-one (XIX)——In 80 ml. of abs. dioxane, 7.0 g. (0.022 mole) of the diester XVIII was cyclized using 0.75 g. (0.031 mole) of sodium hydride in the usual manner and the Dieckmann product was hydrolyzed and decarboxylated by heating in 150 ml. of conc. HCl for 10 hr. to give 3.5 g. (80%) of the crude (−)-XIX as a pale yellow solid. The product was roughly chromatographed on alumina with benzene as an eluent followed by the recrystallization from EtOH-hexane to afford the analytical sample of m.p. 119.5~120.5° as colorless prisms, $[\alpha]_D^{24}$ −91.0°(c=0.26). *Anal.* Calcd. for $C_{13}H_{15}ON$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.51; H, 7.44; N, 7.08. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2760, 1725. UV λ_{max}^{EtOH} mμ (log ε): 265 (2.60), 272 (2.68), 293 (inf.) (1.30). $\lambda_{max}^{dioxane}$: 265 (2.58), 272 (2.60), 290 (inf.) (1.40). ORD: (EtOH, c=0.26), $[\alpha]_{370}$ −200, $[\alpha]_{309}$ +450, $[\alpha]_{316}$ +370, $[\alpha]_{276}$ −2660 (Fig. 6); (dioxane, c=0.41), $[\alpha]_{370}$ −210, $[\alpha]_{317}$ +640, $[\alpha]_{308}$ +370, $[\alpha]_{277}$ −2800 (Fig. 6). CD: $[\theta]_{290}^{27}$ +2300 (EtOH), $[\theta]_{294}^{25}$ +2500 (dioxane).

The oxime hydrochloride was obtained as colorless prisms from MeOH-isopropyl ether, m.p. 250~253° (decomp.), $[\alpha]_D^{16}$ −65.1°(c=0.75). *Anal.* Calcd. for $C_{13}H_{17}ON_2Cl$: C, 61.77; H, 6.78; N, 11.09. Found: C, 61.79; H, 6.55; N, 10.90.

(−)-1,3,4,6,11,11a-Hexahydro-2*H*-benzo[*b*]quinolizine (XII)——A solution of 1.5 g. (0.0075 mole) of the above (−)XIX and 1.5 g. (0.008 mole) of tosylhydrazine in 15 ml. of MeOH was boiled under reflux for 3 hr. and the mixture was evaporated to dryness ***in vacuo***. The residue was taken up in 50 ml. of dioxane, 6 g. of $NaBH_4$ added and the mixture was refluxed for 9 hr. After the usual treatment, the product was chromatographed on neutral alumina (Woelm activity III) to yield 180 mg. (13%) of colorless crystals, m.p. 42~44°, $[\alpha]_D^{18}$ −41.2°(c=1.04), $[\alpha]_{280}$ −330 (c=1.04) (Fig. 1). The IR spectrum (KBr) was identical with that of (+)XII.

The hydrochloride was obtained as colorless needles from EtOH-isopropyl ether, m.p. 250~253° $[\alpha]_D^{18}$ −40°(c=0.42), $[\alpha]_{280}$ −310 (c=0.42) (Fig. 1). The IR spectrum (KBr) was identical with that of the hydrochloride of (+)XII.

The picrate was formed in ether and recrystallized from EtOH as yellow prisms, m.p. 156~158°. *Anal.* Calcd. for $C_{19}H_{20}O_7N_4$: C, 54.80; H, 4.84; N, 13.46. Found: C, 54.65; H, 4.92; N, 13.37.

The authors are grateful to the Members of the Central Analysis Room of this Faculty for elemental analyses and spectral data, and also to a donation of L-proline and L-phenylalanine from the Ajinomoto Co., Ltd. and Tanabe Seiyaku Co., Ltd.