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Amino Acids and Peptides. XIII.[1] A New Approach to the Biogenetic-type, Asymmetric Synthesis of Indole and Isoquinoline Alkaloids by 1,3-Transfer of Asymmetry[2]

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A new approach to the synthesis of optically active indole and isoquinoline alkaloids is described. The key reactions are: (i) the biogenetic-type, asymmetric Pictet-Spengler reaction of optically active α-amino acids (I) with aldehydes (II) (1,3-asymmetric induction), and (ii) the elimination of the chiral center derived from α-amino acids (1,3-transfer of asymmetry), shown in Chart 1. To achieve (ii), laboratory simulation of decarboxylative processes of α-amino acids was investigated by oxidative and reductive methods. The former did not give any fruitful results, as shown in Table I. However, the reduction of α-amino nitriles, easily prepared from α-amino acids, by means of sodium borohydride gave the satisfactory result, as shown in Table II.

By this new method, two simple indole alkaloids, (*S*)-(−)-tetrahydroharman (XXIV) and (*S*)-(−)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (XXIX) could be obtained from L-tryptophan in a satisfactory manner.

A central problem in the synthesis of optically active compounds is how to introduce the asymmetry. The one method employed very frequently is the optical resolution, through which the synthesis of the desired enantiomer could be achieved in only 50% yield even at maximum. The second is the transformation of optically active starting materials, by which it may be possible to obtain the desired enantiomer in 100% yield. However, this method may lack the generality because the selection of the starting, optically active compounds is not easy. The third method is the asymmetric synthesis which controls the reaction under suitable asymmetric moieties. The generality of the last method may be much higher, and the desired enantiomer could be obtained in 100% yield.

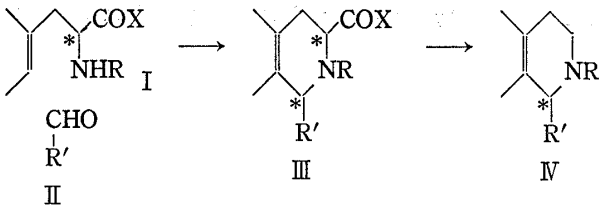


Chart 1

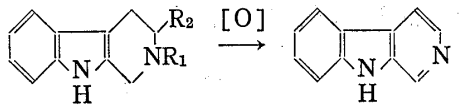
In general, many indole and isoquinoline alkaloids are optically active, and produced *in vivo* from L-tryptophan and L-phenylalanine, L-tyrosine or L-dopa with concomitant decarboxylation at some biosynthetic stage. Our efforts have been directed to the synthesis of optically active alkaloids from readily available α-amino acids following the biosynthetic route. The key reaction for this project are as follows: i) the biogenetic-type, asymmetric Pictet-Spengler reaction of optically active α-amino acids (I) with aldehydes (II) will give the cyclized products (III) in preference of one of diastereoisomers (1,3-asymmetric induction), and ii) the elimination of the chiral center derived from α-amino acids will result in 1,3-transfer of asymmetry to afford optically active compounds (IV), shown in Chart 1.

1) Part XII: K. Ninomiya, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 1795 (1974).
2) Preliminary communication; S. Yamada and H. Akimoto, *Tetrahedron Letters*, **1969**, 3105. Presented in part at the 16th Symposium on the Chemistry of Natural Products, Osaka, October 20, 1972, Symposium Papers, p. 264.
3) Location: *Hongo, Bunkyo-ku, Tokyo, 113, Japan.*

The first step, the Pictet-Spengler reaction,[4] is a well-known process and will produce no trouble. However, laboratory simulation of decarboxylative process of α-amino acids of type III, which may occur *in vivo* very easily, will be a difficult task, though there are two known methods to achieve the chemical decarboxylation: thermal[4a] and oxidative[5] methods. The former method was already tried by our group[6] in the case of some 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids, resulting in decarboxylation accompanied by aromatization.

We next tried the latter oxidative method in the case of DL-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (V) and its derivatives (VI and VII). The acid (V) was subjected to decarboxylation under various oxidative conditions, such as lead tetraacetate in acetic acid, sodium periodate, and sodium hypochlorite. The only product identified was norharman (VIII), an aromatized product. After our work had been finished, van Tamelen and his coworkers[7] reported a similar result of the oxidative decarboxylation of V with sodium hypochlorite. Attempted glycol-type cleavage of 1,2,3,4-tetrahydro-β-carboline-3-methanol (VI), prepared from V by esterification with methanolic hydrogen chloride followed by sodium borohydride reduction, also resulted in the formation of VIII. The 2-benzoyl derivative (VII) of V furnished VIII by means of lead tetraacetate in acetic acid. Oxidation of the 2-tosyl derivatives of V under similar reaction conditions did not give any fruitful results. These aromatization reactions, summarized in Table I, will be due to easy oxidation of the plausible intermediate (IX), and will make the synthesis of the optically active alkaloids impossible.

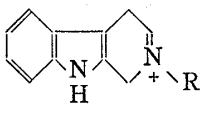
TABLE I



V—VII VIII

Compound	R_1	R_2	Reagent	Yield (%)
V	H	CO_2H	$Pb(OAc)_4$ in AcOH	23.5
			$NaIO_4$ in aq. NaOH	11
			aq. NaOCl	53
VI	H	CH_2OH	$Pb(OAc)_4$ in AcOH	52
			$NaIO_4$in aq. MeOH	87
			HIO_4 in aq. diglyme	41
VII	COPh	CO_2H	$Pb(OAc)_4$ in AcOH	18.5

Ph=phenyl



X

These unfavorable results of thermal and oxidative decarboxylation led us to investigate methods for removal of C_1-unit without aromatization of the tetrahydro ring and epimerization of the chiral center newly formed. During the development of "Chemistry of Diborane and Sodium Borohydride,"[8] we found 2-cyanoquinoline (X) and 3-cyanoisoquinoline (XI) were respectively reduced with sodium borohydride to the tetrahydro derivatives (XII and XIII) accompanying decyanization. The apparent intermediates were presumed to be α-amino nitriles (XIV and XV), as shown in Chart 2.

This strongly suggested us that the decyanization of α-amino nitriles would promise a successful removal of the C_1-unit from α-amino acids. As α-amino nitriles can be easily

4) *a*) A. Pictet and T. Spengler, *Ber.*, **44**, 2030 (1911); *b*) W.M. Whaley and T.R. Govindachari, *Org. Reactions*, **6**, 151 (1951).
5) *Cf.* I.D. Spenser, *Can. J. Chem.*, **37**, 1851 (1959).
6) S. Tachibana, H. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 414 (1968).
7) E.E. van Tamelen, V.B. Haarstad, and R.L. Orvis, *Tetrahedron*, **24**, 687 (1968).
8) Y. Kikugawa, M. Kuramoto, I. Saito, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 1927 (1973).

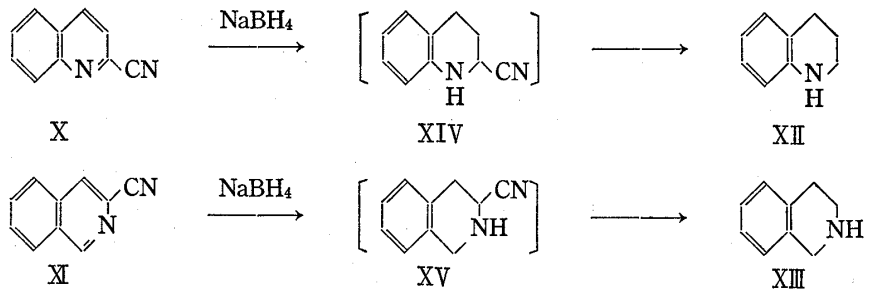
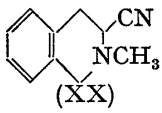
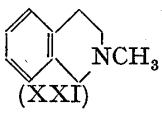
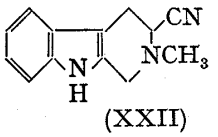
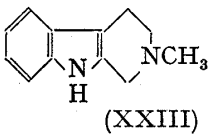


Chart 2

prepared by esterification of α-amino acids, amidation, followed by dehydration of amides, we investigated the reductive decyanization of α-amino nitriles by means of sodium borohydride.[9]

First, DL-α-acetamidohydrocinnamonitrile (XVI) was reduced with sodium borohydride in diglyme to give the expected decyanized product (XVII) in good yield. DL-α-N,N-Dimethylaminohydrocinnamonitrile (XVIII), prepared from DL-phenylalanine methyl ester, was quantitatively converted to N,N-dimethyl-2-phenylethylamine (XIX) with sodium borohydride in ethanol. The borohydride reduction of DL-3-cyano-2-methyl-1,2,3,4-tetrahydroisoquinoline (XX) in various solvents revealed the combination of sodium borohydride and ethanol afforded the best results, as shown in Table II. The β-carboline derivative (XXII) was also smoothly reduced to give the decyanized product (XXIII).

TABLE II

Starting material	Solvent	Temp. (°C)	Time (hr)	Product	Yield(%)[a]	mp or bp (mmHg) (°C)	Reported mp or bp (mmHg) (°C)
$PhCH_2CH(CN)NHCOCH_3$ (XVI)	diglyme	60	24	$PhCH_2CH_2NHCOCH_3$	9		
	diglyme	100	24	(XVII)	88(85)	49—50	51[b]
$PhCH_2CH(CN)N(CH_3)_2$ (XVIII)	EtOH	35	20	$PhCH_2CH_2N(CH_3)_2$	100(93)	95—96(20)	97—98(22)[c]
	pyridine	60	24	(XIX)	87		
 (XX)	EtOH	35	20	 (XXI)	97(92)	81—84(8)	98—100(12)[d]
	pyridine	60	24		81		
	DMF	60	24		73		
	diglyme	100	24		85(82)	80—83(8)	98—100(12)[d]
 (XXII)	EtOH–pyridine	35	24	 (XXIII)	(91)	213—215	208—210[e]

Ph=phenyl

a) By GLC analysis. Numbers in parentheses are isolated yields.
b) A. Michaelis, *Ber.*, **26**, 2162 (1893)
c) R.N. Icke, B.B. Wisegarver, and G.A. Alles, *Org. Synth.*, Coll. Vol. **3**, 723 (1955)
d) L.G. Yudin, A.N. Kost, Yu.A. Berlin, and A.E. Shipov, *Zhur. Obsheč. Khim.*, **27**, 3021 (1957) [*C.A.*, **52**, 8142b (1958)]
e) B. Witkop and S. Goodwin, *J. Am. Chem. Soc.*, **75**, 3371 (1953)

To check the possible epimerization at the newly formed chiral center during the above removal processes and to open the way for the biogenetic-type, asymmetric synthesis of indole and isoquinoline alkaloids, we attempted the synthesis of optically active tetrahydro-

9) G. Charvière, B. Tchoubor, and Z. Walvart (*Bull. Soc. Chim. France*, **1963**, 1428) and P. Rajagopalan and B.G. Advani (*Tetrahedron Letters*, **1965**, 2197) reported α-amino nitriles can be decyanized with lithium aluminum hydride, but satisfactory results are limited to special cases because of easier reduction of nitriles to amines. See also K. Schreiber and C. Horstmann, *Chem. Ber.*, **99**, 3183 (1966).

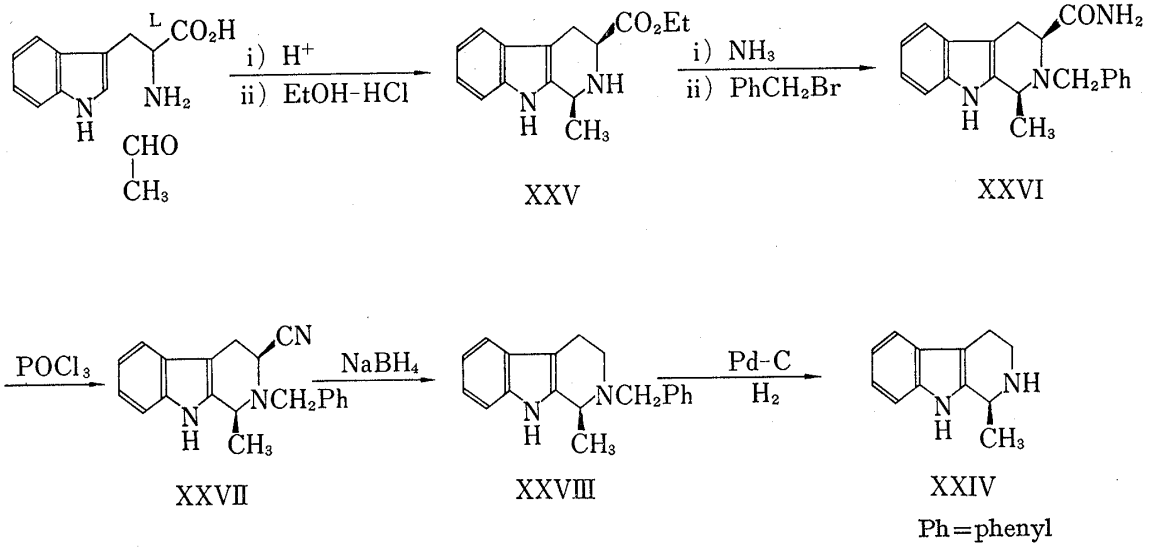


Chart 3

harman (XXIV), a simple indole alkaloid. The Pictet-Spengler reaction of L-tryptophan and acetaldehyde gave the cyclized product, which was converted to the (−)-ethyl ester (XXV).[10] Treatment of XXV with methanolic ammonia, followed by benzylation with benzyl bromide afforded the (+)-Nb-benzyl amide (XXVI). Dehydration of XXVI with phosphorus oxychloride in a mixture of pyridine and dimethylformamide furnished the (−)-α-amino nitrile (XXVII) in 47% yield calculated from the ethyl ester (XXV). The α-amino nitrile (XXVII) was subjected to reductive decyanization with sodium borohydride in a mixture of ethanol and pyridine to give the decyanized product (XXVIII) in 94% yield. The hydrochloride of XXVIII was hydrogenated over palladium-carbon, followed by treatment with alkali to give the desired optically active tetrahydroharman (XXIV), $[\alpha]_D^{25}$ −52° (c=2.0, ethanol), which is presumed to be optically pure.[11]

This series of experiments demonstrates that no epimerization occurs during the removal processes, and since (−)-tetrahydroharman (XXIV) has (*S*)-configuration,[11] the main product

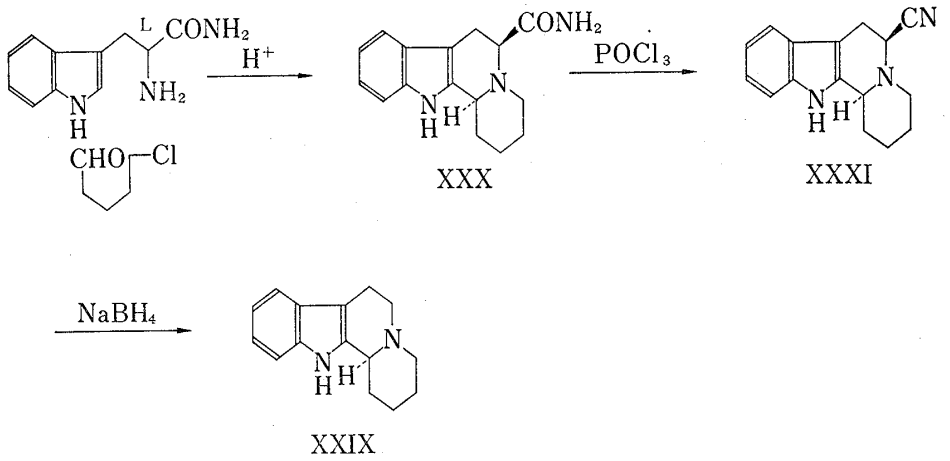


Chart 4

10) J. Le Men and M.C. Fan, *Bull. Soc. Chim. France*, **1959**, 1866.

11) *a*) J. Trojánek, Z. Koblicová, and K. Bláha (*Chem. Ind.*, **1965**, 1261) obtained (+)-XXIV, [α]D +24°, by optical resolution. Since the optical rotation of D-alanine derivative obtained by degradation of this (+)-XXIV was a half of the rotation of the pure sample,[11b] the optical rotation of the optically pure XXIV will presumably be *ca.* 48°; *b*) A.R. Battersby and T.P. Edwards, *J. Chem. Soc.*, **1960**, 1214.

from the asymmetric Pictet-Spengler reaction has 1,3-*cis*-configuration which will be thermodynamically more stable than 1,3-*trans*-configuration.[12]

Next, (−)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (XXIX), a main alkaloid of *Dracontomelum mangiferum* Bl. (Anacardiaceae),[13] was synthesized from L-tryptophan by 1,3-transfer of asymmetry.

L-Tryptophanamide hydrochloride, easily prepared from L-tryptophan,[14] was condensed with 5-chloropentanal[15] to give the (−)-tetracyclic amide (XXX) in 71% yield, which was dehydrated with phosphorus oxychloride to furnish the (−)-α-amino nitrile (XXXI) in 45% yield. Reductive decyanization of XXXI by means of sodium borohydride in a mixture of ethanol and pyridine afforded (−)-XXIX in 64% yield, whose physical constants coincide with those of the optically pure (−)-XXIX,[16] as shown in Experimental. As the absolute configuration of (−)-XXIX was already determined as (*S*)-configuration,[17] the product (XXX) of the asymmetric Pictet-Spengler reaction proved to have 1,3-*cis*-configuration.

An extension of the above new method to the synthesis of the other optically active indole and isoquinoline alkaloids is now under way.[18]

Experimental

Unless otherwise stated, melting and boiling points were uncorrected; infrared (IR) spectra were measured either in nujol mulls (for crystals) or in liquid films (for oils); ultraviolet (UV) spectra were measured in 95% aqueous ethanol.

Oxidative Removal of C_1-Unit

DL-1,2,3,4-Tetrahydro-β-carboline-3-carboxylic Acid (V)——Prepared from DL-tryptophan and formalin according to the literature.[19]

Oxidation of V——(i) With Lead Tetraacetate in Acetic Acid: A stirred mixture of V (0.50 g, 2.3 mmoles) and lead tetraacetate (1.02 g, 2.3 mmoles) in glacial acetic acid (10 ml) was warmed under nitrogen at 100° for 1.5 hr. The mixture was evaporated *in vacuo*, and the residue was treated with aqueous sodium carbonate and diethyl ether. The ethereal extracts were washed with saturated aqueous sodium chloride, and dried over sodium sulfate. Evaporation gave a slightly yellow needles (0.09 g, 23.5%), mp 198—199° (recrystallized from methanol) (lit.[19] 200°), identified as norharman (VIII) by IR and UV spectral and thin-layer chromatographic comparisons with the authentic sample prepared by dichromate oxidative decarboxylation of V.[19]

(ii) With Sodium Periodate in Aqueous Sodium Hydroxide: To a solution of V (1.08 g, 5 mmoles) in 0.1 N aqueous NaOH (53 ml, 5.3 mmoles) was added 0.3 M aqueous sodium periodate (60 ml, 18 mmoles). The mixture was allowed to stand in a dark place at room temperature for 24 hr to afford dark yellow precipitates. After filtration, the precipitates were treated with aqueous sodium hydroxide and ethyl acetate. The ethyl acetate extracts were washed with saturated aqueous sodium chloride and dried over sodium sulfate. Evaporation gave VIII (0.06 g), identified by comparisons with the authentic sample.[19] The above filtrate was basified with sodium hydroxide, and extracted with ethyl acetate. Work-up as above afforded VIII (0.05 g). Total yield of VIII was 0.11 g (11%).

(iii) With Aqueous Sodium Hypochlorite: To the acid (V) (300 mg. 1.39 mmoles) dissolved in water (10 ml) and 10% aqueous sodium hydroxide (0.8 ml) was added under nitrogen 10% hydrochloric acid till crystals just appeared. After dilution with water to 30 ml (total amount, pH *ca.* 10), diethyl ether (25 ml) was added to the stirred solution, followed by the addition of aqueous sodium hypochlorite (6 ml, 10% available chlorine). The mixture was stirred at room temperature for 2 hr. After separation of the ethereal layer, the water layer was extracted with diethyl ether. The combined extracts were washed with water and saturated aqueous sodium chloride. Drying over sodium sulfate followed by evaporation afforded VIII (124 mg, 53%).

12) A. Brossi, A. Focella, and S. Teitel, *J. Med. Chem.*, **16**, 418 (1973).
13) S.R. Johns, J.A. Lamberton, and J.L. Occolowitz, *Chem. Comm.*, **1966**, 421; *idem, Aust. J. Chem.*, **19**, 1951 (1966).
14) E.L. Smith and W.J. Polglase, *J. Biol. Chem.*, **180**, 1209 (1949).
15) Y. Ban and T. Oishi, *Chem. Pharm. Bull.* (Tokyo), **11**, 411 (1963).
16) J. Pospišek, Z. Koblicová, and J. Trojánek, *Chem. Ind.*, **1969**, 25.
17) S. Yamada and T. Kunieda, *Chem. Pharm. Bull.* (Tokyo), **15**, 499 (1967).
18) A preliminary account of a biogenetic type synthesis of *S*(+)-laudanosine from L(−)-dopa was already communicated; S, Yamada. M. Konda, and T. Shioiri, *Tetrahedron Letters*, **1972**, 2215.
19) D.G. Harvey, E.J. Miller, and W. Robson, *J. Chem. Soc.*, **1941**, 153.

DL-Methyl 1,2,3,4-Tetrahydro-β-carboline-3-carboxylate Hydrochloride——A mixture of V (20 g, 0.92 moles) and 10 w/v% methanolic hydrogen chloride (400 ml) was refluxed for 8 hr. Concentration of the mixture to 50 ml afforded crystals (19.2 g), which was washed with cold methanol and diethyl ether. From the combined filtrates, a further crop (2.1 g) of crystals was obtained. The total yield was 21.3 g (91%). For analysis, a sample was recrystallized from methanol to give colorless needles, mp 222—235° (decomp.), IR 2680, 2622, 2520, 2480, 1742, 1567, 732 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{15}O_2N_2Cl$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.34; H, 5.77; N, 10.57.

DL-1,2,3,4-Tetrahydro-β-carboline-3-methanol (VI)——To a stirred suspension of the above methyl ester hydrochloride (2 g, 7.5 mmoles) in 75% aqueous ethanol (20 ml) was added sodium borohydride (1.20 g, 30 mmoles) in 75% aqueous ethanol (20 ml). The mixture was stirred at reflux for 5 hr, and evaporated to the residue, which was dissolved in water. The aqueous solution was extracted with ethyl acetate. The organic extracts were washed with water and saturated aqueous sodium chloride. Drying over sodium sulfate followed by evaporation gave a white form (0.75 g, 50%), which crystallized by tritulation with diethyl ether. For analysis, a sample was recrystallized from ethanol to give colorless prisms of VI, mp 185—186° (lit.[20] 189°), IR in chloroform 3480 cm^{-1}. *Anal.* Calcd. for $C_{12}H_{14}ON_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.20; H, 6.82; N, 14.08.

Oxidation of VI——(i) With Lead Tetraacetate in Acetic Acid: To a stirred VI (0.60 g, 2.9 mmoles) in glacial acetic acid (40 ml) was added lead tetraacetate (1.50 g, 3.4 mmoles) in glacial acetic acid (40 ml) during 30 min with ice-cooling under nitrogen. The mixture was stirred at room temperature for 5 hr. Water (300 ml) was added to the mixture, which was made alkaline with sodium hydroxide. Extraction with ethyl acetate, washing the extracts with water and saturated aqueous sodium chloride, drying over sodium sulfate, followed by evaporation afforded a yellow solid, which was chromatographed over silica gel with a mixture of chloroform and ethanol (8: 1) to give norharman (VIII) (0.01 g, 2%).

(ii) With Sodium Periodate in Aqueous Methanol: To a stirred VI (50 mg, 0.25 mmoles) in methanol (50 ml) was added sodium periodate (64 mg, 0.30 mmoles) in water (2.5 ml). The mixture was stirred at room temperature for 30 hr. After addition of water, methanol was evaporated. The aqueous solution was made alkaline with sodium hydroxide, and extracted with ethyl acetate. The extracts were washed with water and saturated aqueous sodium chloride and dried over sodium sulfate. Evaporation gave yellow crystals of VIII (36 mg, 87%).

(iii) With Periodic Acid in Aqueous Diglyme: To a cooled VI (0.50 g, 2.5 mmoles) in diglyme (20 ml) was added periodic acid (0.56 g, 2.5 mmoles) in water (3 ml) with stirring. The mixture was stirred at room temperature for 24 hr to give yellow precipitates from which the starting VI (0.15 g) was recovered by dissolving in alkaline solution and extraction with ethyl acetate. The mother liquor was diluted with water (50 ml), and washed with ethyl acetate. The aqueous layer was made alkaline with sodium carbonate, and extracted with ethyl acetate. The organic extracts were treated as usual to give VIII (0.17 g, 41%).

DL-2-Benzoyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (VII)——To a stirred acid (V) (20 g, 0.09 moles) dissolved in aqueous sodium hydroxide (sodium hydroxide, 3.9 g, 0.09 moles) was added aqueous sodium carbonate (25.5 g, 0.24 moles) (total amount of water was 500 ml), followed by the addition of benzoyl chloride (17 g, 0.12 moles) at room temperature during 40 min. After 3 hr stirring, benzoyl chloride (2 g, 0.014 moles) was added. After 7 hr, benzoyl chloride (5 g, 0.036 moles) and sodium carbonate (6 g, 0.057 moles) in water (100 ml) was added to the reaction mixture, which was stirred for 3 hr to give yellow precipitates. The precipitates were dissolved in water (500 ml), acidified with hydrochloric acid, and extracted with ethyl acetate. The extracts were washed with water and saturated aqueous sodium chloride. Drying over sodium sulfate followed by evaporation afforded a yellow solid, which was washed with hot water to furnish VII (13 g). The first mother liquor was acidified with hydrochloric acid, and treated as above to give VII (9 g). The total yield of VII was 22 g (74%). A sample was recrystallized from aqueous methanol to give colorless prisms, mp 224—226° (decomp), IR 3340, 1745, 1641, 1630, 758 cm^{-1}. *Anal.* Calcd. for $C_{19}H_{16}O_3N_2$: C, 71.24; H, 5.03; N, 8.75. Found: C, 71.37; H, 5.24; N, 8.91.

Oxidation of VII——A mixture of VII (50 mg, 0.16 mmoles) and lead tetraacetate (90 mg, 0.20 mmoles) in glacial acetic acid (7 ml) was stirred at room temperature for 3 hr, made alkaline with sodium hydroxide, and treated as usual to give VIII (5 mg, 18.5%).

DL-2-(*p*-Toluenesulfonyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid——To a stirred acid (V) (10 g, 0.046 moles) in 0.2 N NaOH (500 ml) was added *p*-toluenesulfonyl chloride (10 g, 0.052 moles) in diethyl ether (70 ml). The mixture was vigorously stirred at room temperature. After 5 hr, *p*-toluenesulfonyl chloride (3 g, 0.016 moles) in diethyl ether (20 ml) was added to the mixture, which was stirred for 2 hr. After the addition of *p*-toluenesulfonyl chloride (3 g, 0.016 moles) in diethyl ether (20 ml), the mixture was further stirred for 5 hr. The aqueous layer was separated, acidified with hydrochloric acid, and extracted with diethyl ether. The ethereal extracts were washed with water and saturated aqueous sodium chloride. Drying over sodium sulfate followed by evaporation afforded pale yellow crystals (13.3 g, 77%). Re-

20) T. Hino, K. Uoji, and S. Akaboshi, *Chem. Pharm. Bull.* (Tokyo), **18**, 384 (1970).

peated recrystallization from 95% aqueous ethanol afforded colorless prisms, mp 234.5—235.5° (decomp.). *Anal.* Calcd. for $C_{19}H_{18}O_4N_2S$: C, 61.61; H, 4.90; N, 7.56. Found: C, 61.73; H, 4.70; N, 7.38.

Attempted oxidation of the tosyl derivative failed to give any identifiable products.

Reductive Decyanization of α-Amino Nitriles

DL-α-Acetamidohydrocinnamonitrile (XVI)——Prepared from DL-α-acetamidohydrocinnamamide in 69% yield according to the method[21] for the preparation of L-isomer. Recrystallization of the crude product from a mixture of benzene and *n*-hexane gave colorless needles, mp 96—97°, IR 3300, 2280, 1660 cm^{-1}. *Anal.* Calcd. for $C_{11}H_{12}ON_2$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.25; H, 6.60; N, 14.69.

DL-α-N,N-Dimethylaminohydrocinnamonitrile (XVIII)——i) From Phenylacetaldehyde: The nitrile (XVIII) was prepared from phenylacetaldehyde according to the literature,[22] a colorless oil, bp 132—137° (24 mmHg).

ii) From DL-Phenylalanine Methyl Ester Hydrochloride: a) DL-α-N,N-Dimethylaminohydrocinnamic Acid Methyl Ester: A mixture of DL-phenylalanine methyl ester hydrochloride (21.6 g, 0.1 mole), formic acid (200 ml), and formalin (120 ml) was warmed on a water bath for 5 hr. After the addition of concentrated hydrochloric acid (20 ml), the mixture was evaporated to dryness. The residue was dissolved in water (200 ml), basified with potassium carbonate, and extracted with chloroform. Drying over potassium carbonate followed by evaporation afforded a pale yellow oil, which was distilled at 114—115° (8 mmHg) to give a slightly yellow oil (14.5 g, 70%), IR 2760, 1730 cm^{-1}. *Anal.* Calcd. for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.74; H, 8.06; N, 6.86.

b) DL-α-N,N-Dimethylaminohydrocinnamide: A solution of the above ester (14.5 g, 0.07 moles) in dry methanol (100 ml) containing a catalytic amount of sodium was saturated with ammonia. The mixture was allowed to stand in a closed bottle at room temperature for 18 days, and evaporated to the residue which was solidified by tritulation with diethyl ether. Recrystallization from ethanol afforded colorless needles (11.3 g, 84%), mp 120—122°, IR 3280, 1680, 1625 cm^{-1}. *Anal.* Calcd. for $C_{11}H_{16}ON_2$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.75; H, 8.40; N, 14.57.

c) DL-α-N,N-Dimethylaminohydrocinnamonitrile (XVIII): To a stirred mixture of the above amide (3.84 g, 0.02 moles) and dry pyridine (13 ml, 0.16 moles) in dry chloroform (100 ml) was added phosphorus oxychloride (3.68 g, 0.024 moles) in dry chloroform (20 ml) below 5° and the mixture was refluxed for 10 min. After cool, 10% aqueous sodium carbonate (80 ml) was added to separate organic layer. The aqueous layer was extracted with chloroform (2×50 ml). The combined organic layer was dried over magnesium sulfate, and evaporated to give a reddish brown oil. Distillation at 122—124° (11 mmHg) afforded a pale yellow oil (2.7 g, 78%), IR 2780, 2240 cm^{-1}. *Anal.* Calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.76; H, 8.08; N, 15.96.

DL-3-Cyano-2-methyl-1,2,3,4-tetrahydroisoquinoline (XX)——i) By Hydrocyanation of 2-Methyl-1,2-dihydroisoquinoline: To a stirred 2-methyl-1,2-dihydroisoquinoline[23] (2.2 g, 0.015 moles) in ethanol (5 ml) was added with cooling a mixture of concentrated hydrochloric acid (4.5 ml, 0.045 moles) and ethanol (10 ml), followed by the addition of potassium cyanide (4.9 g, 0.075 moles) in water (15 ml). The mixture was stirred at room temperature for 15 min, basified with saturated aqueous sodium bicarbonate (15 ml), and extracted with diethyl ether (50 ml, 3×25 ml). The ethereal extracts were dried over magnesium sulfate, and evaporated. The residue was purified over silica gel (100 g) with a mixture of methylene chloride and diisopropyl ether (2: 1) to give a colorless solid (1.3 g, 50%). Recrystallization from a mixture of benzene and *n*-hexane afforded colorless needles, mp 71—72°, IR 2780, 2240 cm^{-1}. *Anal.* Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.80; H, 7.01; N, 16.21.

ii) From DL-Ethyl 1,2,3,4-Tetrahydroisoquinoline-3-carboxylate: a) DL-Ethyl 2-Methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate: A mixture of hydrochloride of DL-ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate[24] (9.66 g, 0.04 moles), formic acid (120 ml), and formaline (120 ml) was warmed on a water bath for 5 hr. After cool, 10% hydrochloric acid (50 ml) was added to the mixture, which was evaporated to dryness. The residue was dissolved in water (200 ml), basified with potassium carbonate, and extracted with chloroform (100 ml, 2×50 ml). The combined extracts were dried over potassium carbonate, and evaporated to give a pale yellow oil, which was distilled at 140—142° (6.5 mmHg) to furnish a slightly yellow oil (7.7 g, 88%). *Anal.* Calcd. for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.78; H, 7.89; N, 6.36.

The methiodide was prepared as usual, colorless needles (recrystallized from ethanol), mp 186—188°. *Anal.* Calcd. for $C_{14}H_{20}O_2NI$: C, 46.55; H, 5.58; N, 3.88. Found: C, 46.88; H, 5.70; N, 3.78.

b) DL-2-Methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide: The above ester (2.8 g, 0.013 moles) in dry methanol (300 ml) containing a catalytic amount of sodium was saturated with ammonia, and the mixture was allowed to stand in a closed bottle at room temperature for 10 days. Evaporation of the methanol, followed by recrystallization of the residue from ethanol afforded colorless prisms (2.1 g, 90%), mp

21) D.W. Woolley, J.W. Hershey, and H.A. Jodlowski, *J. Org. Chem.*, **28**, 2012 (1963).
22) T.S. Stevens, J.M. Cowan, and J. Mackinnon, *J. Chem. Soc.*, **1931**, 2568.
23) H. Smith and P. Karrer, *Helv. Chim. Acta*, **32**, 960 (1949).
24) G.R. Clemo and S.P. Popli, *J. Chem. Soc.*, **1951**, 1406.

158—159°, IR 3300, 3200, 2760, 1670 cm^{-1}. *Anal.* Calcd. for $C_{11}H_{14}O_2N_2$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.22; H, 7.41; N, 14.66.

c) DL-3-Cyano-2-methyl-1,2,3,4-tetrahydroisoquinoline (XX): To a stirred mixture of the above amide (1.90 g, 0.01 mole) and dry pyridine (6.4 ml, 0.08 moles) in dry chloroform (100 ml) was added phosphorus oxychloride (1.84 g, 0.012 moles) in dry chloroform (10 ml) during 15 min below 5°, and the mixture was refluxed for 15 min. After cool, 10% aqueous sodium carbonate (60 ml) was added to separate the organic layer. The aqueous layer was extracted with chloroform (2×50 ml). The combined organic extracts were dried over magnesium sulfate, and evaporated to furnish a pale brown solid, which was recrystallized from a mixture of benzene and *n*-hexane to give colorless needles (1.58 g, 92%), mp 72—73°, identified with the sample obtained in i). *Anal.* Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.73; H, 7.05; N, 16.18.

DL-Methyl 1,2,3,4-Tetrahydro-β-carboline-3-carboxylate——The corresponding hydrochloride (25 g, 0.093 moles) obtained as above was suspended in a mixture of 20% aqueous sodium carbonate (500 ml) and ethyl acetate (3 *l*), and the mixture was vigorously shaken. The ethyl acetate layer was washed with water and saturated aqueous sodium chloride. Drying over sodium sulfate followed by evaporation afforded colorless needles (18 g, 84%), mp 214—218°, IR 1750 cm^{-1}. This was used for the next step without further purification.

DL-1,2,3,4-Tetrahydro-β-carboline-3-carboxamide——A mixture of the above free ester (16 g) and 16 w/v% methanolic ammonia (880 ml) was allowed to stand at room temperature for 3 days. Evaporation followed by recrystallization from methanol afforded colorless crystals (13.5 g, 90%). For analysis, a sample was recrystallized from ethanol to give colorless small prisms, mp 216—219° (lit.[25] 222°), IR 3430, 3300, 3158, 1675, 747 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{13}ON_3$: C, 66.95; H, 6.09; N, 19.52. Found: C, 66.72; H, 5.94; N, 19.35.

DL-2-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide——A mixture of the above amide (3.0 g, 0.014 moles), sodium bicarbonate (2.5 g, 0.033 moles), and methyl iodide (2.5 g, 0.016 moles) in methanol (350 ml) was stirred at room temperature for 2 days. Evaporation gave the crude product, which was purified by column chromatography over alumina (400 mg) with a mixture of chloroform and ethanol (8: 1) to give a pale yellow solid (1.5 g, 47%). Recrystallization from aqueous ethanol afforded pale green crystals, mp 228—230°, IR 3340, 1680 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{15}ON_3$: C, 68.10; H, 6.59; N, 18.33. Found: C, 67.91; H, 6.52; N, 18.51.

DL-3-Cyano-2-methyl-1,2,3,4-tetrahydro-β-carboline (XXII)——To a stirred mixture of the above amide (0.57 g, 2.5 mmoles) and dry pyridine (2 g, 25 mmoles) in dry dimethylformamide (50 ml) was added phosphorus oxychloride (0.46 g, 3 mmoles) during 20 min below 5°. The mixture was stirred at room temperature for 2 hr, diluted with chloroform (300 ml), poured into ice-water, followed by the addition of 10% aqueous sodium carbonate (20 ml). The separated chloroform layer was washed with saturated aqueous sodium chloride, dried over potassium carbonate, and evaporated. The residue was purified by column chromatography over alumina (50 g) with a mixture of benzene and ethanol (9: 1) to furnish pale brown crystals (0.34 g, 65%). Recrystallization from methylene chloride afforded pale yellow prisms, mp 145—147°, IR 2780, 2240 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{13}N_3$: C, 73.90; H, 6.20; N, 19.89. Found: C, 73.78; H, 6.11; N, 20.05.

General Procedure for Decyanization of α-Amino Nitriles——To an α-amino nitrile (0.5 mmoles) in a solvent (5 ml) shown in Table II was added sodium borohydride (2.5 mmoles), and the mixture was stirred at various temperature (35—100°) for 20—24 hr. After evaporation, saturated aqueous sodium chloride (20 ml) was added to the residue, which was extracted with diethyl ether (50 ml, 2×25 ml). The extracts were dried over potassium carbonate or magnesium sulfate, and concentrated. The yield of each decyanized product was determined by gas chromatography (SE-30, 2 m, at 206 or 226°) using methyl β-naphthyl ether (0.5 mmoles) as an internal standard.

For a preparative purpose, each decyanization reaction was carried out using 10 times amounts of the reagents except in the case of XXII (twice), and the crude products were purified by silica gel column chromatography. The yields were given in Table II. The products were identified with the authentic samples prepared according to the literatures (see footnotes of Table II).

Synthesis of *S*(—)-Tetrahydroharman (XXIV)

(—)-1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide——(—)-Ethyl 1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylate (XXV) (4.2 g, 0.016 moles) (mp 116°, $[\alpha]_D^{24}$ −106° (*c*=0.4, ethanol), prepared from L-tryptophan and acetaldehyde according to the literature,[10] lit.[10] mp 118°, $[\alpha]_D^{20}$ −106.7° (*c*=0.39, 96% ethanol)), in methanol (50 ml) was saturated with ammonia, and the mixture was allowed to stand in a closed bottle at room temperature for 10 days. Evaporation of the methanol, followed by recrystallization of the residue from benzene, afforded pale yellow prisms (3.5 g, 94%), mp 144°, $[\alpha]_D^{25}$ −149° (*c*=0.4, ethanol), IR 1685, 1665 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{15}ON_3$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.01; H, 6.58; N, 18.29.

25) J.R. Geigy, A.-G. (by Frederick Leonard), *Belg.*, 612, 725 (1962) [*C.A.*, **58**, 12521*h* (1963)].

(+)-2-Benzyl-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide (XXVI)——A mixture of the above amide (2.29 g, 0.01 mole), benzyl bromide (2.05 g, 0.012 moles), and sodium bicarbonate (2.01 g, 0.024 moles) in ethanol (100 ml) was stirred at reflux for 10 hr. Filtration and evaporation, followed by alumina column chromatography with a mixture of benzene and ethanol furnished XXVI (2.20 g, 69%), which was recrystallized from a mixture of ethanol and diisopropyl ether afforded colorless prisms, mp 177—178°, $[\alpha]_D^{24}$ +52.8° (c=0.3, chloroform). *Anal.* Calcd. for $C_{20}H_{21}ON_3$: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.17; H, 6.77; N, 12.91.

The starting material (0.72 g, 31%) was recovered by further elution of the column, $[\alpha]_D^{26}$ −153° (c=0.3 ethanol).

(−)-2-Benzyl-3-cyano-1-methyl-1,2,3,4-tetrahydro-β-carboline (XXVII)——To a stirred mixture of XXVI (0.8 g, 2.5 mmoles) and dry pyridine (1.6 ml, 20 mmoles) in dimethylformamide (50 ml) was added phosphorus oxychloride (0.46 g, 3 mmoles) below 5°. The mixture was stirred at room temperature for 4 hr, diluted with chloroform (300 ml), poured into ice-water (150 ml), basified with 10% aqueous sodium carbonate (20 ml), and extracted with chloroform. The extracts were washed with saturated aqueous sodium chloride (2×50 ml), dried over potassium carbonate, and evaporated. The residue was purified by silica gel column chromatography using a mixture of methylene chloride and diisopropyl ether to give a colorless solid (0.54 g, 72%). Recrystallization from diisopropyl ether afforded colorless leaflets, mp 160—161°, $[\alpha]_D^{20}$ −12.6° (c=1.6, pyridine), IR 3380, 2240 cm^{-1}. *Anal.* Calcd. for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94. Found: C, 79.43; H, 6.16; N, 13.73.

(−)-2-Benzyl-1-methyl-1,2,3,4-tetrahydro-β-carboline (XXVIII)——To XXVII (0.331 g, 1.1 mmoles) in a mixture of pyridine (10 ml) and ethanol (20 ml) was added sodium borohydride (0.22 g, 5.5 mmoles), and the mixture was stirred at 35° for 24 hr. After evaporation of the solvent, the residue was diluted with saturated aqueous sodium chloride (15 ml), and extracted with diethyl ether (50 ml, 2×25 ml). The combined extracts were dried over magnesium sulfate, and evaporated to give XXVIII as a pale yellow oil (0.285 g, 94%), $[\alpha]_D^{27}$ −31° (c=0.7, ethanol).

The hydrochloride was prepared by treatment of XXVIII with ethereal hydrogen chloride. Recrystallization from ethanol afforded colorless needles, mp 210°. *Anal.* Calcd. for $C_{19}H_{21}N_2Cl$: C, 73.02; H, 6.77; N, 8.96. Found: C, 72.81; H, 6.61; N, 9.34.

(*S*)-(−)-Tetrahydroharman (XXIV)——The hydrochloride of XXVIII (0.34 g, 1.1 mmoles) in methanol (20 ml) was catalytically hydrogenated over 5% palladium-carbon at room temperature for 3.5 hr (uptake of hydrogen, 26 ml). Filtration and evaporation gave the residue, which was dissolved in water (10 ml), basified with 10% aqueous sodium carbonate, and extracted with diethyl ether (40 ml, 2×20 ml). The ethereal extracts were dried over potassium carbonate, and evaporated to give pale yellow prisms (0.18 g, 90%), $[\alpha]_D^{29}$ −54° (c=1.8, ethanol). Recrystallization from benzene afforded colorless prisms, mp 177°, (lit.[11a] 177—180°), $[\alpha]_D^{25}$ −52° (c=2.0, ethanol). The IR spectrum was virtually identical with that of the racemic authentic sample.[26] *Anal.* Calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.46; H, 7.60; N, 14.98.

Synthesis of (*S*)-(−)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (XXIX)

(−)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine-6-carboxamide (XXX)——A mixture of L-tryptophan amide hydrochloride[14] (10.4 g, 0.048 moles) ($[\alpha]_D^{19}$ +24.5° (c=1.6, water), lit.[14] $[\alpha]_D^{25}$ +24° (c=1.6, water)) and 5-chloropentanal[15] (7.0 g, 0.058 moles) in 50% aqueous methanol (120 ml) was gently refluxed for 9.5 hr. After evaporation, the residual crystals were dissolved in 10% aqueous hydrochloric acid, washed with chloroform (3×70 ml), and made alkaline with 10% aqueous sodium carbonate. The precipitates were collected, washed with water, and dried to give a pale yellow solid (9.1 g, 71%), which was purified by silica gel column chromatography using ethyl acetate to furnish a pale yellow solid (5.5 g, 47%). Recrystallization from acetonitrile afforded pale yellow needles, mp 245—258° (decomp.), $[\alpha]_D^{24}$ −122° (c=1, methanol), IR 3420, 1670 cm^{-1}. *Anal.* Calcd. for $C_{16}H_{19}ON_3$: C, 71.34; H, 7.11; N, 15.60. Found: C, 71.34; H, 7.06; N, 15.68.

(−)-6-Cyano-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (XXXI)——To a stirred mixture of XXX (0.67 g, 2.5 mmoles) and dry pyridine (2 g, 25 mmoles) in dry dimethylformamide (40 ml) was added phosphorus oxychloride (0.46 g, 3 mmoles) below 5°. The mixture was stirred at room temperature for 2 hr, diluted with chloroform (100 ml), poured into ice-water, and basified with 10% aqueous sodium carbonate (20 ml). The separated chloroform layer was washed with saturated aqueous sodium chloride (2×50 ml), dried over potassium carbonate, and evaporated. The residue was purified by silica gel column chromatography using ethyl acetate to furnish a pale brown solid (0.28 g, 45%). Recrystallization from a mixture of benzene and *n*-hexane afforded pale orange needles, mp 153—157°, $[\alpha]_D^{25}$ −173° (c=1.0, ethanol), IR 2250 cm^{-1}. *Anal.* Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.59; H, 6.94; N, 16.51.

(*S*)-(−)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (XXIX)——To XXXI (0.125 g, 0.5 mmoles) in a mixture of pyridine (2.5 ml) and ethanol (5 ml) was added sodium borohydride (0.1 g, 2.5 mmoles). The mixture was stirred at 35° for 24 hr. After evaporation, saturated aqueous sodium chloride (20 ml) was

26) S. Akabori and K. Saito, *Ber.*, 63, 2245 (1930).

added to the residue. Extraction with diethyl ether (50 ml, 3×20 ml), drying the extracts over magnesium sulfate, followed by evaporation afforded a pale yellow oil, which was purified on a silica gel column using ethyl acetate to give pale yellow crystals (0.072 g, 64%). Recrystallization from *n*-hexane afforded colorless crystals, mp 149—152° (lit.[16] 149—151°), $[\alpha]_D^{24}$ −84° (*c*=1, methanol) (lit.[16] −86.5±2° (methanol)). *Anal.* Calcd. for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.88; H, 7.93; N, 12.26.