Studies on the Asymmetric Synthesis of α-Amino Acids. I. A New Approach

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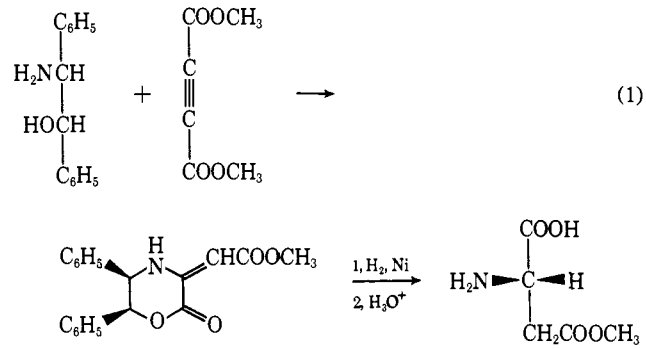
Abstract: A new approach has been demonstrated for the asymmetric synthesis of α-amino acids from α-keto acids using chiral reagents which are regenerated by the synthesis. The chiral reagents used were the N-amino-2-hydroxymethylindolines (*S*)-**9** and (*S*)-**16**. The synthesis, resolution, and assignment of absolute configuration for these reagents is described. The application of (*S*)-**9** and (*S*)-**16** to the asymmetric synthesis of α-amino acids depends on their combination with α-keto acids to form chiral hydrazono lactones (see Chart IX). Reduction of the C=N unit in these lactones (**23**, **24**, and **25**) affords the corresponding hydrazino lactones (**29**, **30**, and **31**) which are transformed to α-amino acids by hydrogenolysis of the N–N linkage and ester hydrolysis. By this process D-alanine and D-butyrine have been synthesized from pyruvic acid and α-ketobutyric acid using the reagent (*S*)-**9** in optical purities of 80 and 90%, respectively. As a result of these studies, a solid basis exists for the design of chiral indoline reagents of still greater efficiency in the asymmetric synthesis of α-amino acids.

The problem of devising general methods for the asymmetric synthesis of chiral, optically active organic structures which are efficient both with regard to optical and material yield remains a major challenge despite extensive studies in this area for many years.[1] The studies reported in this and the following article have been carried out, commencing in 1958, with the specific objective of developing an asymmetric synthesis of α-amino acids which would produce either antipode of an α-amino acid in high (>95%) optical yield *without* destruction of the reagent used to induce chiral selectivity.

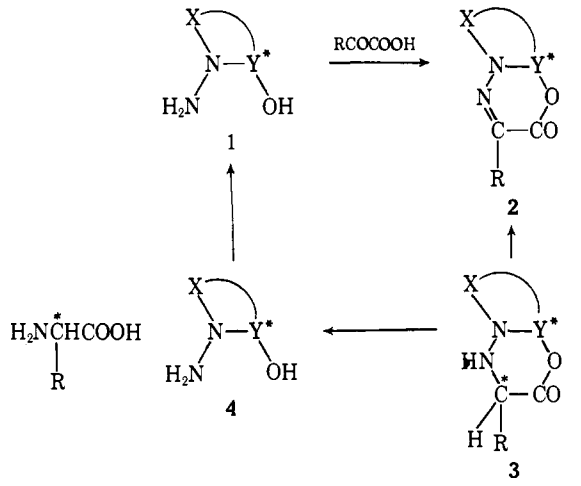
A number of methods for the asymmetric synthesis of α-amino acids have been investigated previously. These include (a) the reduction of β-substituted α-acylaminoacrylyl units attached to chiral directing moieties[2–7] such as arginine,[2] L-α-methylbenzylamine,[5] (+)-borneol,[4] and (+)-menthol;[6] (b) the hydrogenation of acylhydrazones[7] or Schiff bases[8,9] derived from α-keto acids and a chiral amino-bearing component; (c) the Strecker sequence starting from the reaction of hydrogen cyanide, an aldehyde and optically active α-methylbenzylamine;[10] (d) the hydroxyalkylation of one antipode of the complex $[Co(en)_2\ glycine]^{2+}$ using an aldehyde (*e.g.*, acetaldehyde) in the presence of base;[11] and (e) hydrogenation of α-amino acid derivatives using palladium catalyst supported on silk.[12] In most cases where it is possible to assess the optical purity of the amino acid resulting from asymmetric synthesis (and before any fractionation procedures), the chiral specificity has been low,[5,7,8,11,12] although there are a few notable exceptions.[8–10] Outstanding among these is a recently reported synthesis of aspartic acid with an optical purity of 98%,[9] which is both rational and efficient.[13] The approach used in this case (eq 1)[9] is in certain respects similar to that described in this series of papers but suffers from the fact that the asymmetric reagent is sacrificed. In addition, the extension to the other α-amino acids appears uncertain.



The derivation of the present approach to asymmetric synthesis was based on conditions: (1) that the precursor of the α-amino acid antipode be the corresponding α-keto acid, (2) that the α-keto acid be combined with a chiral reagent to form a ring of minimal size containing the α-carbon and carboxyl functions of the keto acid, (3) that the α-carbon be doubly bonded to nitrogen as part of a cyclic hydrazone function, (4) that the ring contain one or two chiral centers, (5) that the cyclic intermediate be convertible by reduction to chiral α-amino acid and a chiral secondary amino alcohol, and finally (6) that the chiral secondary amino alcohol be convertible to original chiral reagent. These conditions are formulated schematically by the cycle **1** → **2** → **3** → **4** → **1** shown in Chart I. The conversion **4** → **1**, which corresponds synthetically to the N-nitrosation

(1) For a recent review, see D. R. Boyd and M. A. McKervey, *Quart. Rev.* (London), **22**, 95 (1968).
(2) M. Bergmann and J. E. Tietzman, *J. Biol. Chem.*, **155**, 535 (1944).
(3) A. Pedrazzoli, *Chimia* (Switz.), **10**, 260 (1956).
(4) A. Pedrazzoli, *Helv. Chim. Acta*, **40**, 80 (1951).
(5) J. C. Sheehan and R. E. Chandler, *J. Am. Chem. Soc.*, **83**, 4795 (1961).
(6) S. Yamada, T. Shioiri, and T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **10**, 688 (1962).
(7) S. Akabori and S. Sakurai, *Nippon Kagaku Zasshi*, **78**, 1629 (1957).
(8) R. G. Hiskey and R. C. Northrop, *J. Am. Chem. Soc.*, **83**, 4798 (1961); **87**, 1753 (1965).
(9) J. P. Vigneron, H. Kagen, and A. Horeau, *Tetrahedron Lett.*, 5681 (1968).
(10) K. Harada, *Nature*, **200**, 1201 (1963).
(11) M. Murakami and K. Takahashi, *Bull. Chem. Soc. Jap.*, **32**, 308 (1959).
(12) S. Akabori, S. Sakurai, Y. Izumi, and Y. Fujii, *Nature*, **178**, 323 (1956).
(13) For another asymmetric synthesis of aspartic acid (optical purity *ca.* 88%), involving the addition of α-methylbenzylamine to maleic acid followed by catalytic hydrogenolysis, see A. P. Terent'ev, R. A. Gracheva, L. F. Titova, and T. F. Dedenko, *Dokl. Chem. Akad. Nauk SSSR*, **154**, 1406 (1964).

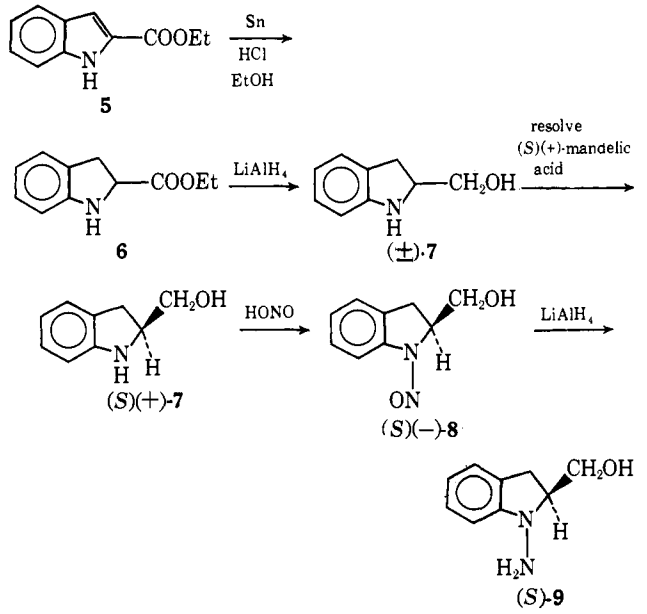
Chart I[a]



[a] Asterisk signifies a chiral group or center.

and >N–NO to >N–NH_2 reduction sequence, is essential for the regeneration of the chiral reagent. The transformation **3** → **4**, involving N–N hydrogenolysis and ester hydrolysis, liberates the α-amino acid and the precursor of chiral reagent **1**. The realization of this conversion is in practice highly dependent on the structure of X, since it has been found[14] that N–N hydrogenolysis proceeds poorly or not at all if X is attached to N–N by a saturated carbon, but smoothly if X includes an N-benzenoid substituent. An additional and specific structural requirement on the reagent thereby results. The choice of hydrazone unit as in **3** was dictated by the need to fix the prochiral center in a fairly rigid chiral environment having a minimum of conformational alternatives so that the critical conversion **2** → **3** would be subject to rational planning and control. The first two specific reagents selected for study were based on 2-hydroxymethylindoline (**7**) and 2-methyl-2-hydroxymethylindoline (**18**) (Charts II and V).

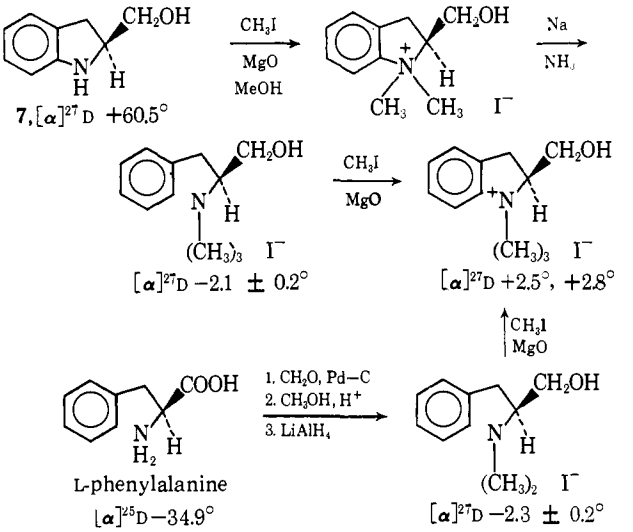
Chart II. Synthesis of (*S*)-2-Hydroxymethylindoline and the N-Amino Derivative



(14) Unpublished results of E. J. Corey and P. Schudel at the University of Illinois, Urbana, Ill., 1957.

Synthesis and Absolute Configuration of Chiral Reagents. Reduction of ethyl 2-indolecarboxylate (**5**)[15] with tin in ethanolic hydrogen chloride afforded a tin complex of ethyl (±)-2-indolinecarboxylate which when treated with anhydrous ammonia gave the free ester **6**. Lithium aluminum hydride reduction of **6** produced (±)-2-hydroxymethylindoline **7**. Resolution of (±)-**7** was accomplished *via* a crystalline salt with (*S*)(+)-mandelic acid containing a 2:1 molar ratio of acid to indoline (Chart II). The dextrorotatory indoline **7** thus obtained, $[\alpha]^{27}D$ +60.5° in ethanol, was shown to have the *S* configuration by means of the chemical correlation outlined in Chart III.

Chart III. Configurational Correlation of (+)-**7** with L(−)-Phenylalanine



Nitrosation of (*S*)(+)-**7** afforded the crystalline levorotatory N-nitroso derivative, (*S*)(−)-**8**, which by reduction using lithium aluminum hydride in ether gave the corresponding N-amino derivative, (*S*)-**9**, as an air sensitive oil (can be stored under nitrogen at −20° without appreciable decomposition). Racemic **9** could be conveniently prepared from the (±)-indoline ester **6** by nitrosation followed by lithium aluminum hydride reduction.

The synthesis of *R* and *S* forms of N-amino-2-methyl-2-hydroxymethylindoline was carried out as indicated in Chart IV. Ethyl (±)-2-indolinecarboxylate (**6**) was transformed to the imidazolidinedione **11** *via* the phenylurethan **10** and then methylated to give **12**. Saponification of **12** and subsequent nitrosation furnished the racemic acid **13** from which the *levo* (*R*) and *dextro* (*S*) forms could be obtained by the use of the resolving agents brucine and ephedrine, respectively. Esterification of the nitroso acids with diazomethane and ester reduction ($LiBH_4$) followed by nitroso reduction ($LiAlH_4$)[16] produced the (*R*)- and (*S*)-N-amino indolines **15** and **17**. The absolute configurations of these reagents were established by the chemical correlation of the *d*-nitroso acid **16** with (*S*)(−)-α-methylphenylalanine[17,18] as out-

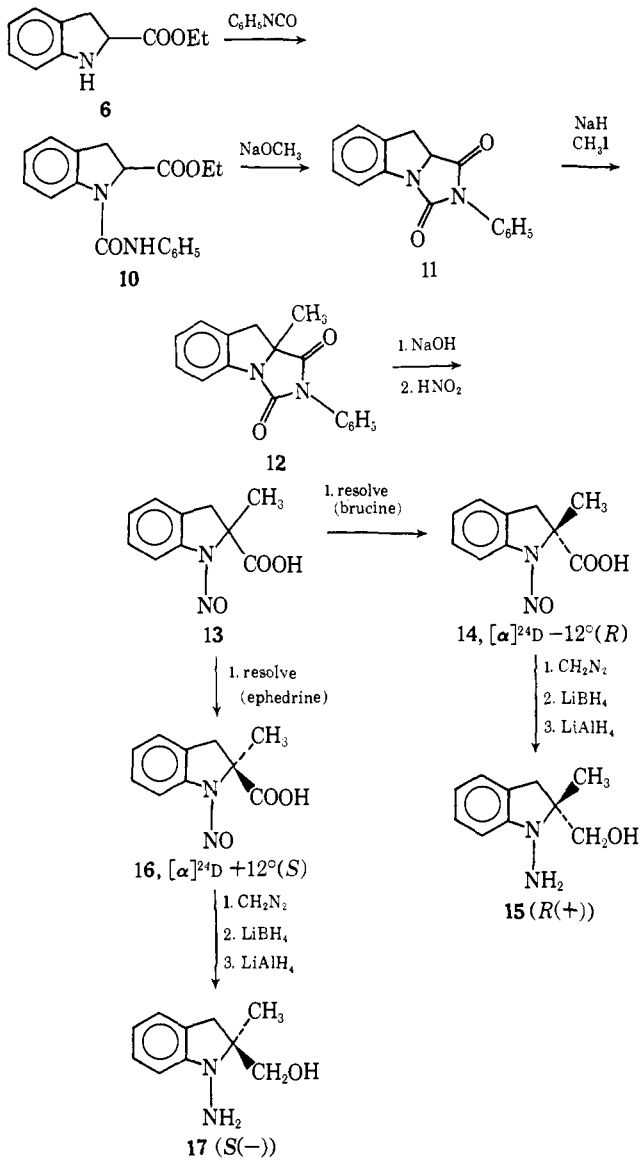
(15) W. E. Noland and F. J. Baude, *Org. Syn.*, **43**, 40 (1963).

(16) This two-stage reduction sequence to **15** and **17** was found to be much more effective than direct reduction of the nitroso acid or ester with lithium aluminum hydride.

(17) For absolute configuration of this amino acid, see S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 1138 (1966).

(18) We are indebted to Dr. E. W. Tristram, Merck, Sharp and Dohme, Research Laboratories, for a generous sample of *S*(−)-α-methylphenylalanine.

Chart IV. Synthesis of (*R*)- and (*S*)-N-Amino-2-methyl-2-hydroxymethylindoline



lined in Chart V. Both substances were transformed into the same dextrorotatory amino alcohol (**20**) having the same rotation within experimental error. The methiodides derived from the two samples of **20** were likewise identical.

In connection with the assignment of absolute configuration in the 2-hydroxymethylindoline and 2-methyl-2-hydroxymethylindoline series, use was also made of enzymic specificity to afford independent evidence. The experiments are outlined in Charts VI and VII. Chymotrypsin-catalyzed hydrolysis of the (±)-nitroso ester **21** (Chart VI) would be expected to result in selective conversion of the *R* antipode of the nitroso ester **21** corresponding acid and to leave the *S* antipode unchanged on the basis of a number of previous observations on chymotrypsin-catalyzed hydrolysis of closely analogous structures, some of which are recorded in Chart VIII.[19-21] The observed selective hydrolysis of one antipode of **21**, together with the analogies indicated in Chart VIII, leads to the correlation shown in Chart

(19) G. Hein, R. B. McGriff, and C. Niemann, *J. Am. Chem. Soc.*, **82**, 1830 (1960).
(20) W. B. Lawson, *J. Biol. Chem.*, **242**, 3397 (1967).
(21) M. S. Silver and T. Sone, *J. Am. Chem. Soc.*, **89**, 457 (1967).

Chart V. Configuration Correlation of (+)-**16** with *S*(−)-α-Methylphenylalanine

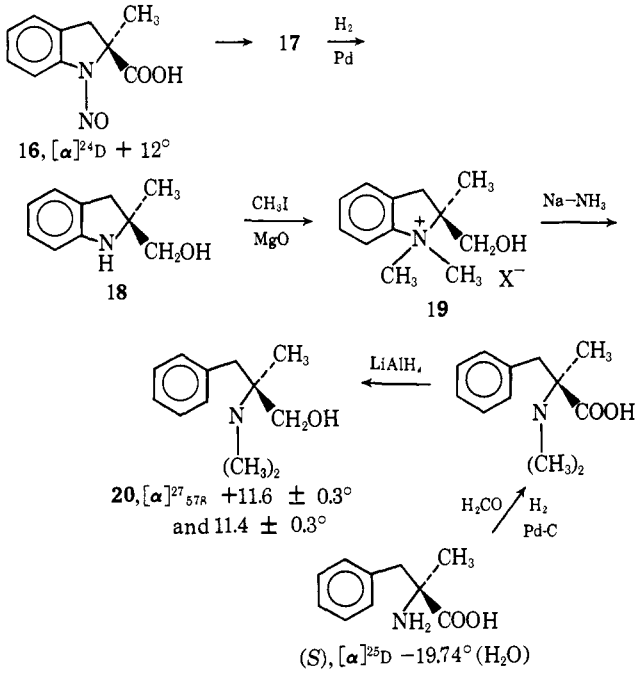
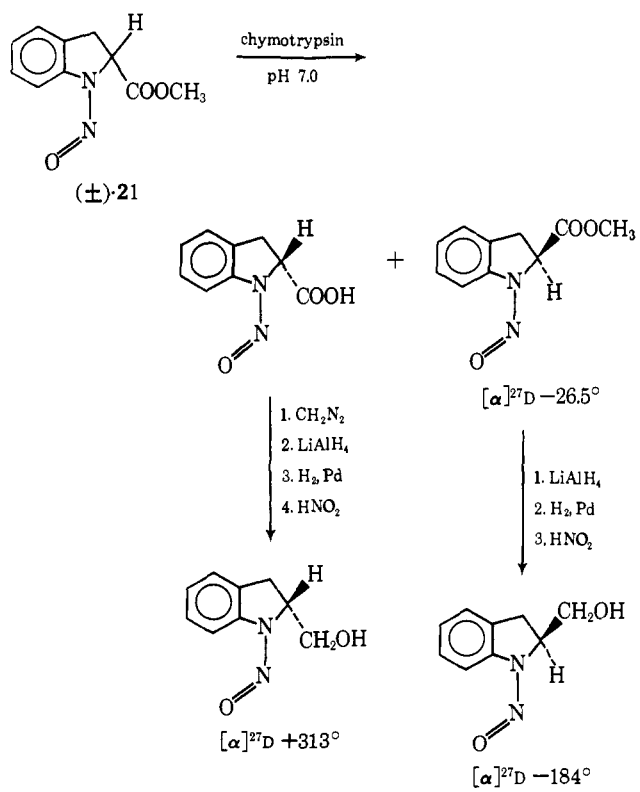


Chart VI. Selective Hydrolysis of *d*-**21** (*R*) Catalyzed by Chymotrypsin



VI which is in agreement with the chemical correlation outlined in Chart III for the 2-hydroxymethylindoline series. Similarly, the assignment of absolute configuration in the 2-methyl-2-hydroxymethylindoline series on the basis of the observed stereospecificity of chymotrypsin action on the (±)-nitroso ester **22** (Chart VII) agrees with the independent chemical correlation indicated in Chart V.

Chart VII. Selective Hydrolysis of *l*-**22** (*R*) Catalyzed by Chymotrypsin

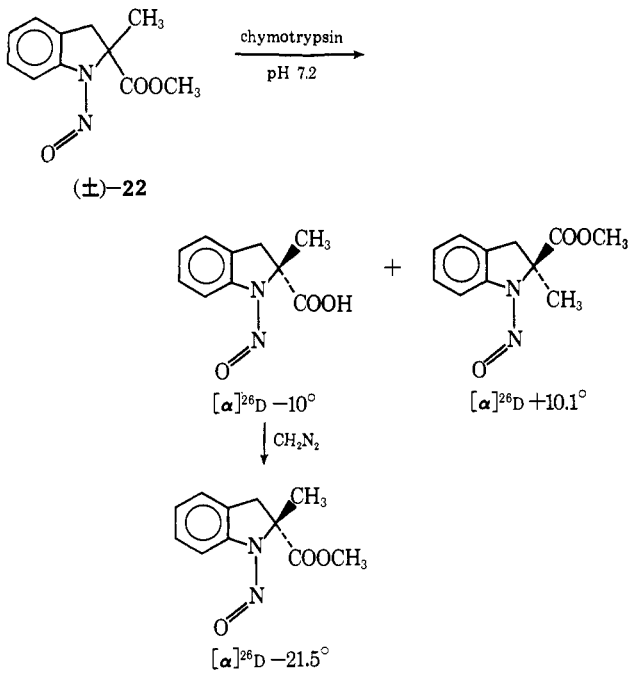
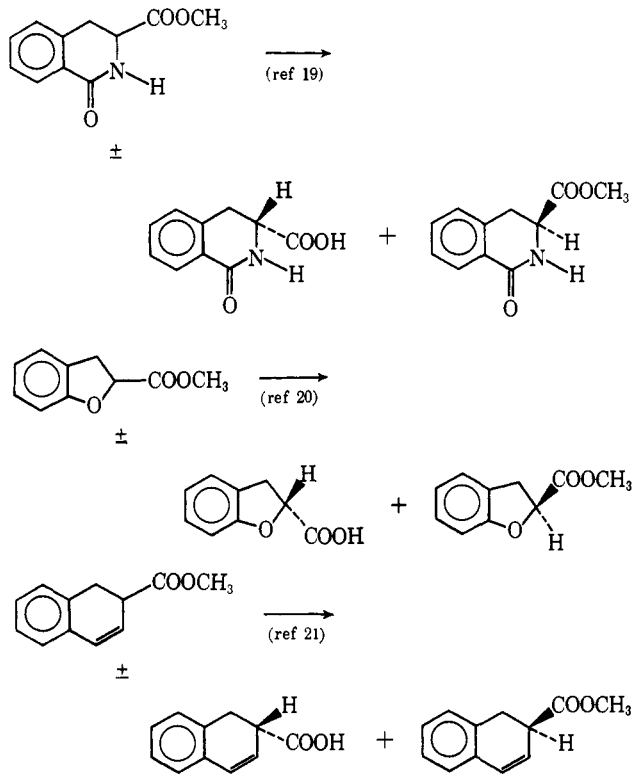


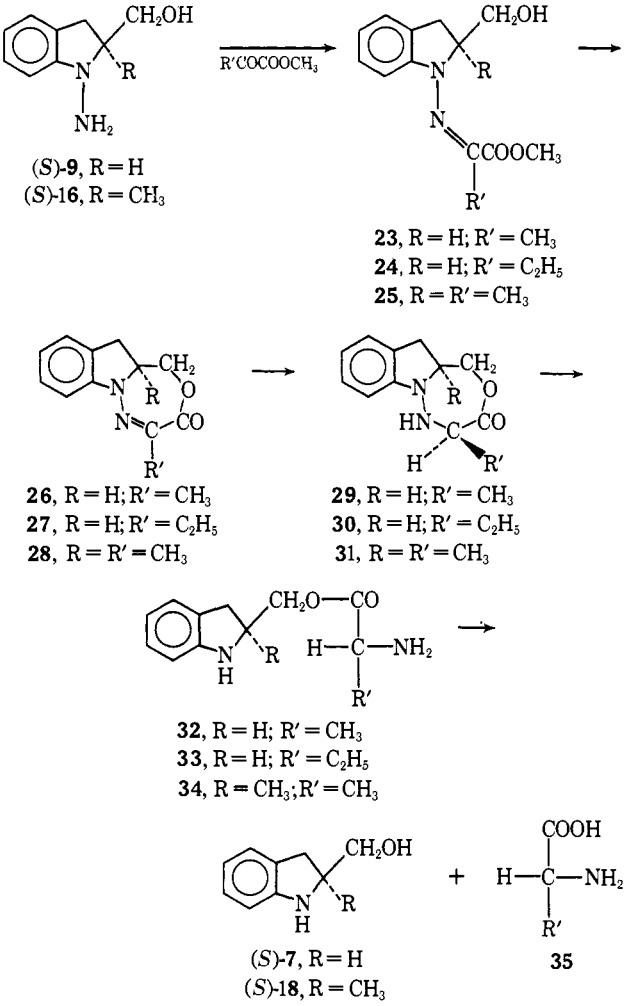
Chart VIII. Selective Chymotrypsin-Catalyzed Hydrolysis of Bicyclic Esters at pH *ca.* 8



Asymmetric Synthesis of α-Amino Acids from the Chiral N-Amino-2-hydroxymethylindolines (*S*)-9 and (*S*)-16. The pathway for the asymmetric synthesis of α-amino acids from α-keto acids and the hydroxy hydrazine derivatives (*S*)-**9** and (*S*)-**16** is indicated in Chart IX.

Starting from the hydrazine reagent (*S*)-**9** and methyl pyruvate, the hydrazone **23** was prepared simply by reaction in methanol solution at room temperature, and this was cyclized by heating under anhydrous conditions

Chart IX. Asymmetric Synthesis of α-Amino Acids



in benzene containing sodium methoxide to form the hydrazono lactone **26**, a crystalline, levorotatory substance. The reduction of the hydrazono lactone **26** to the hydrazino lactone **19**, the next step in the desired sequence, proved to be unexpectedly difficult and complex using hydrogen and a wide variety of hydrogenation catalysts. The desired product **29** could not be obtained using palladium, platinum, or rhodium catalysts (on a number of supports) or Raney nickel at pressures from 1 to 70 atm. Success was achieved, however, using "chemical" reduction with aluminum amalgam as reagent under carefully controlled conditions.[22] These conditions involve the use of an excess of aluminum amalgam at 0° with *ca.* 12% water in purified dimethoxyethane under an inert atmosphere. The hydrazino lactone could be purified by recrystallization and obtained as a single diastereomer which could be converted further to alanine. Alternatively, the total reduction product of the hydrazono lactone **26** which contained mainly **29** could be used without recrystallization or other fractionation in the steps to form alanine. In this way the optical efficiency of the asymmetric synthesis could be determined unambiguously. The stereochemical course of the reduction of **26** to **29** could also be determined by an independent, but approximate,

(22) Attempts to effect the conversion of **26** to **29** using other chemical reducing agents were without success. The following reagents were tried: zinc–acetic acid, zinc–copper couple in ethanol, diborane, sodium borohydride, tributyltin hydride, hydrogen sulfide, lithium aluminum tri-*t*-butoxy hydride, and aluminum isopropoxide trimer.

method involving nuclear magnetic resonance (nmr) measurements.[23] This method is based on the fact that the major diastereomer produced by reduction shows a methyl signal due to the grouping $CHCH_3$ as a doublet centered at 1.51 ppm,[24] whereas the minor diastereomeric product exhibits the corresponding doublet centered at 1.33 ppm. The results of the nmr and optical methods were in good agreement, although the latter were more precise.

The hydrazino lactone **29** which had been purified by recrystallization was converted to the amino acid ester **32** by hydrogenolysis using palladium-on-charcoal catalyst in dimethoxyethane–water containing hydrochloric acid. The ester **32** so formed was subjected to acid-catalyzed hydrolysis in one experiment and base-catalyzed hydrolysis in another, and the resulting alanine was isolated by procedures which do not fractionate the antipodes (see Experimental Section).[25] The alanine obtained under acidic and basic hydrolysis procedures exhibited optical rotation indicating an optical purity of 99 ± 1 and 98 ± 2%, respectively.

The total aluminum amalgam reduction product of **26** (unpurified **29**), when converted to α-amino acid by the same procedure, yielded D(−)-alanine (*R* configuration) of 78–82% optical purity.

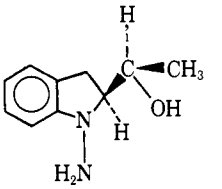
Starting with the hydrazine reagent (*S*)-**9** and methyl α-ketobutyrate and using conditions comparable to those described above for the synthesis of D(−)-alanine, D(−)-butyrine (**35**, R = C_2H_5) of 89–90% optical purity was obtained by the analogous sequence **24** → **27** → **30** → **33** → **35** without any purification of intermediates.

The hydrolysis of the amino acid esters **32** and **34** produced, as expected, (*S*)-2-hydroxymethylindoline (**7**) as well as alanine and butyrine. The indoline **7** was easily isolated in good yield, thereby fulfilling the original objective that the chiral reagent for asymmetric amino acid be recoverable and reusable.

Using the second chiral reagent, (*S*)-2-methyl-2-hydroxymethylindoline ((*S*)-**16**), and methyl pyruvate, the process of asymmetric synthesis leading to alanine *via* intermediates **25**, **28**, **31**, and **34** (Chart IX) was carried out without purification of **28**, **31**, or **34**. The D(−) form of alanine was obtained in 75% optical purity, and again the chiral indoline reagent **18** was recovered for reuse. When the intermediate hydrazino lactone **31** was purified by recrystallization and used in the process, 99 ± 0.8% optically pure D(−)-indoline was produced.

The formation of the D(−) form of alanine and/or butyrine from the reagents (*S*)-**9** and (*S*)-**16** as indicated in Chart IX shows that the hydrogen transfer which generates the newly created asymmetric center occurs mainly from the direction *cis* to the hydrogen or methyl substituent α to the indoline nitrogen. The effect of replacing hydrogen at the chiral center of the reagent (*S*)-**9** by methyl as in (*S*)-**16**, which diminishes somewhat the stereochemical efficiency of alanine synthesis (from 80 to 75%), is easily reconciled with the observed stereochemistry for the hydrazono lactone → hydrazino lactone transformation as a simple steric or bulk effect. However, a detailed explanation of this difference certainly must await the understanding of the mechanism of the aluminum amalgam reduction. In this respect it is somewhat unfortunate that the catalytic hydrogenation or hydride reduction procedures for the hydrazono lactone → hydrazino lactone transformation were inoperative, since these processes are much better known in terms of stereochemical characteristics and mechanism.

In any event these first studies pointed to the desirability of designing a chiral indoline reagent which would be more effective in directing asymmetric synthesis and specifically suggested the reagent **36**, whose synthesis and application is described in the accompanying paper.[26]



In conclusion, it can be reported that the discovery of a chemical process for the asymmetric synthesis of α-amino acids which allows preservation of the chiral reagent has been realized. Further, two basic chiral reagents for the process have been synthesized, resolved, and characterized with respect to absolute configuration. These reagents, (*S*)-**9** and (*S*)-**16**, have been evaluated with regard to the over-all stereochemical course of the asymmetric synthesis and efficiency in the critical conversion of a prochiral to a chiral center.

Experimental Section

General. Melting points are corrected unless otherwise indicated. Optical rotations were measured using either a Bendix automatic polarimeter Type 143A adapted for greater sensitivity with a Leeds and Northrop K potentiometer or a Perkin-Elmer Model 141 polarimeter (1-dm cell). Infrared spectra were recorded using a Perkin-Elmer Model 137 spectrometer, and ultraviolet spectra were obtained by means of a Cary 14 spectrometer. A Varian A-60 spectrometer was used for most nuclear magnetic resonance measurements.[24] High resolution mass spectra were determined using an AEI MS-9 double focusing spectrometer. Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All chemical reactions involving indoline derivatives were conducted under an inert atmosphere.

(±)-Ethyl 2-Indolinecarboxylate (6) (Chart II). Ethyl 2-indolecarboxylate (**5**)[15] (45.2 g, 0.238 mol) in a 1-l. polyethylene container containing 450 ml of absolute ethanol was chilled in a Dry Ice–ethanol bath and saturated with dry hydrogen chloride until the liquid volume reached 875 ml. Granular tin metal (84.2 g, 0.710 mol) was added to the slurry, and the container was sealed in a prechilled 1.4-l. autoclave, which had all surfaces coated with silicone oil. After standing at room temperature for 36 hr, the vessel was vented and the contents were filtered through sintered glass and allowed to stand at −15° overnight. The yellow crystalline tin complex (73.6 g), mp 108.0–117.6°, which separated was dissolved in 750 ml of absolute ethanol, chilled, and treated with a stream of anhydrous ammonia until the pH of the solution reached 8 (Hydrion paper). The crystalline residue, obtained by evaporation of the ethanol, was slurried in 700 ml of ether, filtered, and washed with several portions of ether. The combined ether filtrates were vigorously extracted with 300 ml of a 1:1 water–saturated salt solution whereupon most of the basic tin salts were suspended and separated in the water phase. The ether was dried over magnesium sulfate and evaporated to 33.82 g of oil, which spontaneously crystallized to a semisolid mass. The ethyl 2-indolinecarboxylate was re-

(23) Using either racemic or optically active **26**.

(24) All nmr data are expressed as parts per million shifts (δ) upfield from tetramethylsilane as internal standard.

(25) It was also shown in control experiments that the optical rotation of a number of samples of alanine of differing optical purity was unchanged by the procedure used for the isolation (absorption on Dowex SOW-X8 resin (acid form), elution with dilute ammonium hydroxide, concentration and sublimation *in vacuo*).

(26) E. J. Corey, H. S. Sachdev, J. Z. Gougoutas, and W. Saenger, *J. Am. Chem. Soc.*, **92**, 2488 (1970).

crystallized from 15 ml of hexane, giving 28.5 g (62.5%), mp 54.1–56.9°. The analytical sample was recrystallized to constant melting point, 56.5–57.0°; ultraviolet absorption (EtOH) at 238 mμ (ε 5800) and 293 mμ (ε 2130); infrared absorption due to C=O at 5.74 μ (CCl_4).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.88; H, 6.90; N, 7.31.

(±)-2-Hydroxymethylindoline (7). Ethyl 2-indolinecarboxylate (22.0 g, 0.115 mol) dissolved in 500 ml of ether was added over 0.75 hr to a slurry of 10.0 g (0.264 mol) of lithium aluminum hydride in 800 ml of ether which had been refluxed for 6 hr prior to the reaction. The reaction mixture was maintained at reflux during the addition and then stirred at room temperature for 14 hr before chilling on ice and treating dropwise with 19.0 g of water. The slurry was heated at reflux for 1 hr, filtered through a Super Cel, and triturated six times with a total of 300 ml of ether. The combined ether filtrates were dried over magnesium sulfate and evaporated to a colorless oil. The oil was taken up in *ca.* 20 ml of ether, treated with 30 ml of hexane, and seeded to give 11.5 g (67%) of (±)-2-hydroxymethylindoline as colorless cubic crystals, mp 57.7–59.1°. The infrared and nmr spectra were consistent with the assigned structure.[27]

(*S*)(+)-2-Hydroxymethylindoline-(+)-dimandelate. (*S*)(+)-Mandelic acid (51.0 g, 0.336 mol) dissolved in a hot mixture of 400 ml of benzene and 40 ml of methanol was treated with a solution of 25.0 g (0.168 mol) of (±)-2-hydroxymethylindoline in 70 ml of benzene. The resulting solution was heated to remove the methanol and then allowed to cool slowly to room temperature. Upon seeding, the salt separated as colorless needles, mp 107.5–109.5°. The salt was recrystallized from benzene–methanol, and the progress of the resolution was followed by optical rotation. After two recrystallizations material of mp 111.5–112.0°, $[\alpha]^{23}D$ +119 ± 0.5°, was obtained. Complete resolution was indicated by the constancy of these properties over several additional recrystallizations. Yields of optically pure salt after reworking mother liquors amounted to *ca.* 90%. A sample of the salt was dried *in vacuo* for 24 hr at 56° for elemental analysis, which showed the ratio of mandelic acid to indoline as 2:1.

Anal. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00; N, 3.09. Found: C, 66.26; H, 6.06; N, 3.17.

(*S*)(+)-2-Hydroxymethylindoline (7). (*S*)(+)-2-Hydroxymethylindoline-(+)-dimandelate (23.1 g, 0.051 mol) dissolved in 150 ml of cold water was treated with a cold solution of 6.74 g (0.120 mol) of potassium hydroxide in 10 ml of water. The mixture was extracted with five 50-ml portions of ether. The ether was washed with saturated salt solution and dried over magnesium sulfate. The ether was evaporated, leaving a colorless oil, which crystallized upon seeding, mp 57.0–59.5°. Several recrystallizations from ether–hexane gave 6.3 g (83%) of (+)-2-hydroxymethylindoline, mp 67.8–69.3°, $[\alpha]^{27}D$ +60.5° (*c* 0.89, 95% ethanol). The infrared spectrum (in $CHCl_3$) was identical with the spectrum of the racemic compound.

(*S*)(−)-1-Nitroso-2-hydroxymethylindoline (8). A cold solution of 2.60 g (0.0174 mol) of (*S*)(+)-2-hydroxymethylindoline in 50 ml of water containing 7.3 ml of 10% hydrochloric acid was treated dropwise with a solution of 1.32 g (0.0191 mol) of sodium nitrite in 10 ml of water. The thick, white crystalline mass was stirred for an additional 20 min and then extracted four times with chloroform. The chloroform extract was washed with saturated salt solution and dried by passage through magnesium sulfate over cotton. The chloroform was evaporated, leaving 2.95 g (95%) of (*S*)(−)-1-nitroso-2-hydroxymethylindoline (**8**) as light yellow needles, mp 130.0–133.0°. The analytical sample was recrystallized from ether and methanol to constant melting point, 131.3–133.4°, $[\alpha]^{25}D$ −345.2 (*c* 1.0, ethanol). The infrared and nmr spectra were consistent with structure **8**.[27]

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.66; H, 5.72; N, 15.74.

(*S*)-1-Amino-2-hydroxymethylindoline (9). To a slurry of 6.8 g (0.179 mol) of lithium aluminum hydride in 450 ml of ether, which had been refluxed for 2 hr, was added dropwise a solution of 6.8 g (0.0382 mol) of (*S*)(−)-1-nitroso-2-hydroxymethylindoline in 1100 ml of ether over 1.25 hr. The light gray slurry was stirred for 17.5 hr at room temperature and for 1 hr at reflux. After the mixture had been cooled to room temperature, 7.8 ml of water was added dropwise over 20 min, and the mixture was refluxed for 1.75 hr to ensure hydrolysis. The precipitate of aluminum hydroxide was removed by filtration and thoroughly washed with three portions of ether. The combined ether filtrates were dried over magnesium sulfate and evaporated to afford 5.27 g oil that crystallized spontaneously upon cooling in the freezer. An additional 0.55 g of product could be obtained by extracting the aluminum hydroxide residue in a Soxhlet extractor for 18 hr, thus giving a total of 5.82 g (93%) of (*S*)-1-amino-2-hydroxymethylindoline. This product, which was used for asymmetric synthesis without further purification, is quite air sensitive and had to be stored under nitrogen or argon at −20° to guard against decomposition. The infrared and nmr spectra were identical with those of racemic material prepared as described below.

(±)-Ethyl 1-Nitroso-2-indolinecarboxylate. Ethyl 2-indolinecarboxylate (24.6 g, 0.129 mol) dissolved in 100 ml of water and 16 ml of concentrated hydrochloric acid was treated dropwise with a solution of 14.45 g of sodium nitrite dissolved in 50 ml of water over a period of 0.5 hr at room temperature. The deep yellow oily mixture was stirred for 1 additional hr before extracting it with three 125-ml portions of ether. The combined ether extracts were washed with 10% sodium bicarbonate solution and saturated salt solution and dried over magnesium sulfate. Evaporation of the ether left 28.1 g (99%) of a yellow oil that crystallized spontaneously giving the product as yellow prisms, mp 58.0–59.0°. The analytical sample was recrystallized several times from cyclohexane to a constant melting point, 60.4–61.0°.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.99; H, 5.66; N, 12.91.

(±)-1-Amino-2-hydroxymethylindoline. To a slurry of 27.25 g (0.719 mol) of lithium aluminum hydride in 1150 ml of ether that had been refluxed for 4.5 hr was added dropwise a solution of 27.2 g (0.124 mol) of ethyl 1-nitroso-2-indolinecarboxylate dissolved in 300 ml of ether. The solution of ester was added over 1 hr at a rate such as to maintain mild refluxing. The reaction mixture was heated at reflux for 2 hr and stirred at room temperature for an additional 11 hr. Water (52 ml) was added dropwise over 1.5 hr, and the mixture was heated at reflux for 3 hr. After filtering the aluminum hydroxide on a Super Cel cake, and thorough trituration of the residue with four 150-ml portions of ether, the combined ether filtrates were dried over magnesium sulfate. Evaporation of the ether left 14.08 g of light amber oil, which crystallized upon cooling. Extraction of the alumina residue in a Soxhlet extractor gave an additional 1.44 g of material to make a total of 15.52 g (76%) of (±)-1-amino-2-hydroxymethylindoline, mp 79.5–82.0°. The material was recrystallized from ether–methanol to constant melting point, 81.5–82.7°.

Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.62; H, 7.39; N, 17.19.

Methiodide of (*S*)(+)-7 (Chart III). To a solution of (*S*)(+)-2-hydroxymethylindoline (**7**) ($[\alpha]^{27}D$ +60.5° (*c* 0.9, ethanol)) (0.149 g, 1 mmol) in 4 ml of dry methanol was added magnesium oxide (0.2 g, 5 mmol) followed by methyl iodide (0.705 g, 5 mmol), and the mixture was stirred at 30° for 16 hr. The mixture was filtered through Celite 545, and the filtrate was taken to dryness *in vacuo* to give a solid residue which upon one crystallization from methanol–ethyl acetate mixture furnished 210 mg of colorless crystals, mp 142.5–143.5°, $[\alpha]^{27}D$ −0.8 ± 0.2°, $[\alpha]^{27}_{365}$ −7 ± 0.15° (*c* 0.77, methanol). The infrared spectrum (KBr) showed 2.97 (strong, OH), 6.74 (medium), 6.86 (strong), 7.0 (medium), 7.17 (medium), 7.2 (medium), 8.84 (medium), 9.43 (strong), 9.62 (strong), 10.34 (strong), 10.69 (strong), 12.8 (strong), 13.07 (strong), and 13.85 μ (strong).

The methiodide prepared from (±)-2-hydroxymethylindoline melted at 165–166° and showed identical infrared absorption.

Anal. Calcd for $C_{11}H_{16}INO$: C, 43.27; H, 5.42; N, 4.60. Found: C, 43.34; H, 5.28; N, 4.47.

Reductive Cleavage of the Methiodide of (*S*)(+)-7. A three-necked 100-ml round-bottomed flask containing 50 ml of dimethoxyethane and 220 mg of sodium metal was provided with an inlet for ammonia, a Dry Ice condenser, a mercury seal, and an inlet for nitrogen. Ammonia (*ca.* 20 ml) was distilled into the flask causing the sodium metal to float as a shining bronze liquid. To this vigorously stirred suspension 110 mg of the optically active methiodide of (*S*)(+)-7 ($[\alpha]^{27}D$ −0.8 ± 0.2° (*c* 0.77, methanol)) was added, and stirring was continued for 1 hr and 20 min. A positive pressure of nitrogen was maintained to ensure anhydrous conditions. The excess ammonia was evaporated by warming the mixture to 30°, which caused the sodium metal to float as a ball. Saturated ammonium chloride solution was then injected to the suspension, and it was stirred for *ca.* 5 min, when all the sodium was

(27) See R. McCaully, Ph.D. Dissertation, Harvard University, 1964.

consumed. The reaction mixture was filtered through Celite 545, and the filtrate was evaporated under reduced pressure to give a colorless thick oil. It was extracted with carbon tetrachloride (*ca.* 50 ml). The extract on evaporation furnished 60 mg of a colorless oil which was chromatographed on basic alumina (prepared by treating Woelm basic alumina, activity grade I, with 6 ml of 2% sodium hydroxide solution per 100 g). Elution with a benzene–ether mixture (9:1) gave 26 mg (42.5%) of (*S*)-2-dimethylamino-3-phenylpropanol, mp 50–51°, $[\alpha]^{27}D$ −2.1 ± 0.2° (*c* 1.56, ethanol), $[\alpha]^{27}_{365}$ −14.8 ± 0.2° (*c* 1.56, ethanol). The melting point of this sample was unchanged on admixture with an authentic sample of this compound (*vide infra*). Also the infrared and nmr spectra of the two were superimposable.

Methiodide of (*S*)-2-Dimethylamino-3-phenylpropanol. To a solution of 20 mg (0.11 mmol) of (*S*)-2-dimethylamino-3-phenylpropanol (obtained in the above experiment) in 1 ml of dry methanol was added 31 mg (0.22 mmol) of methyl iodide and 50 mg of anhydrous magnesium oxide. The mixture was stirred at 30° overnight, after which it was filtered through Celite 545, and the residue was washed with methanol. The filtrate on evaporation gave a solid which on crystallization from methanol–ether mixture furnished 30 mg (86%) of colorless crystals, mp 168–169°, $[\alpha]^{27}D$ +2.5 ± 0.2°, $[\alpha]^{27}_{365}$ +8.0 ± 0.3° (*c* 1.39, methanol). An authentic sample prepared starting from L-phenylalanine ($[\alpha]^{20}D$ −34.9° (*c* 2, water)) (*vide infra*) showed no change in melting point on admixture. Also the infrared spectra (KBr) of the two samples were superimposable.

N,N-Dimethyl-L-phenylalanine Methyl Ester. N,N-Dimethyl-L-phenylalanine, mp 218° ($[\alpha]^{25}D$ +75° (*c* 2, water) prepared from L-phenylalanine ($[\alpha]D$ −34.9° (*c* 2, water)) (CP grade, Mann Research Laboratory), according to the procedure of Bowmann and Stroud[28] was transformed in 80% yield into its methyl ester by refluxing for 8 hr in reagent grade methanol saturated with hydrogen chloride. The ester was obtained after the usual workup as a colorless oil, bp 256–258°, $[\alpha]^{26}D$ +29.2 ± 0.5° (*c* 2.9, ethanol). The infrared spectrum had $\lambda^{CCl_4}_{max}$ 5.75 (strong, C=O), 6.24 (weak, C=C), 6.7 (weak), 6.89 (medium), and 8.6 μ (strong, C—O—C). The nmr spectrum (CCl_4) exhibited peaks at ppm 2.28 (6 H, singlet) due to the protons of $N(Me)_2$ group, 2.65–3.32 (3 H, multiplet) due to the benzylic protons and the tertiary proton, 3.62 (3 H, singlet) due to the protons of $-OCH_3$ group, and 7.12 (5 H, singlet) due to the aromatic protons.

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.40; H, 8.24; N, 6.63.

(*S*)-2-Dimethylamino-3-phenylpropanol (from L-Phenylalanine). The (+)-methyl ester prepared above (193 mg, 1 mmol) dissolved in 5 ml of ether was added dropwise into a slurry of lithium aluminum hydride (76 mg, 2 mmol) in 25 ml of ether. The mixture was refluxed for 4 hr. The excess hydride was destroyed by the addition of *ca.* 0.7 ml of saturated aqueous sodium sulfate solution and the mixture allowed to stir for 1.5 hr, when the inorganic salts looked white and granular. The mixture was filtered through Celite 545, and the filter cake was washed with ether. The extract after drying (magnesium sulfate) on evaporation furnished 150 mg (83%) of a thick colorless oil which crystallized on refrigeration, mp 50–51°. An analytical sample[29] (mp 51°) was prepared by recrystallization from ethanol–pentane mixture, $[\alpha]^{27}D$ −2.34 ± 0.2°, $[\alpha]^{27}_{365}$ −14.7 ± 0.2° (*c* 3.2, ethanol). The infrared spectrum showed $\lambda^{CCl_4}_{max}$ 2.86 (medium, OH), 6.26 (weak, C=C), 6.71 (medium), 6.9 (strong), 7.12 (medium), and 9.6 μ (strong). The nmr spectrum (CCl_4) exhibited a singlet (6 H) at ppm 2.28 due to protons of $N(Me)_2$ group, a multiplet (3 H) at 2.47–3.0 due to the benzylic protons and the tertiary proton, a doublet centered at 3.24 (3 H, J = 6.5 cps) due to methylene protons and the hydroxyl proton (the signal due to the latter overlapped the high field component of the doublet due to the former), and a singlet at 7.12 (5 H) due to aromatic protons.

The molecular weight determined mass spectrometrically was 179.1313 (calcd for $C_{11}H_{17}NO$: 179.1310).

Methiodide of (*S*)-2-Dimethylamino-3-phenylpropanol (L-Phenylalanine Route). The amino alcohol obtained in the above experiment (from L-phenylalanine) was transformed into its methiodide,[29] mp 168–169°, according to the procedure used for the amino alcohol obtained on metal ammonia reduction of the methiodide of **7**. It had $[\alpha]^{27}D$ +2.87 ± 0.2°, $[\alpha]^{27}_{365}$ +8.7 ± 0.2° (*c* 1.15, methanol). The infrared spectrum showed λ^{KBr}_{max} 2.95 (strong, OH), 6.26 (weak, C=C), 6.34 (weak), 6.74 (strong), 6.83 (strong), 6.91 (medium), 7.28 (medium), 8.44 (medium), 9.18 (medium), 9.25 (medium), 9.57 (strong), 10.41 (strong), 11.23 (medium), 12.03 (medium), 13.18 (medium), and 13.12 μ (strong).

Anal. Calcd for $C_{12}H_{20}INO$: C, 44.86; H, 6.23; N, 4.36. Found: C, 44.57; H, 6.38; N, 4.45.

1,2,3,9a-Tetrahydro-2-phenyl-9H-imidazo[1,5-*a*]indole-1,3-dione (11) (Chart IV). A solution of ethyl 2-indolinecarboxylate (**6**) (19.9 g, 0.1 mol) and phenyl isocyanate (11.9 g, 0.1 mol) in toluene (50 ml) was heated under reflux for 1 hr. Sodium methoxide (0.7 g, 0.013 mol) was then added after cooling to room temperature. The stirred mixture was heated under gentle reflux in a flask fitted with a Soxhlet extractor carrying molecular sieves (Linde Type 4A). A white solid separated during refluxing. The solvent was evaporated under reduced pressure in a rotary evaporator. The solid residue was triturated with 50 ml of cold water and acidified with acetic acid. It was collected on a filter and washed with water. One crystallization from ethanol gave 24 g (91%) of **11** as colorless needles, mp 167–168°. The infrared spectrum showed $\lambda^{CHCl_3}_{max}$ 5.59 (medium, C=O), 5.76 (strong, C=O), 6.25 (weak, C=C), 6.65 (medium), 6.75 (medium), and 7.2 μ (strong). The nmr spectrum ($CDCl_3$) exhibited peaks at ppm 3.3 (2 H, doublet, J = 10 cps, benzylic protons), 4.92 (1 H, doublet of doublets, J_1 = 9.5 cps, J_2 = 10 cps, tertiary proton), 7.2–8 (multiplet), and 7.4 (broad singlet) (9 H, aromatic protons).

Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.11; H, 4.57; N, 10.87.

1,2,3,9a-Tetrahydro-2-phenyl-(9a-methyl)-9H-imidazo[(1,5-*a*]-indole-1,3-dione (12). To a suspension of sodium hydride (6.8 g, 0.1 mol; 53% oil dispersion washed with pentane) in dry tetrahydrofuran (900 ml) was added **11** (26.4 g, 0.1 mol) followed by methyl iodide (28.2 g, 0.2 mol). The mixture was stirred at 27–28° for 36 hr under nitrogen, when it became a clear solution. It was then warmed to 55–60° for 48 hr, which caused a white precipitate of sodium iodide to separate. After cooling the mixture, excess sodium hydride was destroyed by the addition of 2 ml of acetic acid and the solid was filtered. The filtrate was taken to dryness on a rotary evaporator, yielding a light pale solid which on one crystallization from ethanol furnished 22.4 g (80.6%) of **12** as colorless crystals, mp 152°. The infrared spectrum had $\lambda^{CHCl_3}_{max}$ 5.59 (medium, C=O), 5.77 (strong, C=O), 6.2, 6.25 (shoulder) (weak, C=C), 6.66 (medium), 6.75 (medium), and 7.19 μ (strong). The nmr spectrum ($CDCl_3$) showed peaks at ppm 1.62 (3 H, singlet; methyl protons), 2.98 (1 H, doublet, J = 16.5 cps; benzylic proton), 3.5 (1 H, doublet, J = 16.5 cps; benzylic proton), and 7.3 (9 H, multiplet; aromatic protons).

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.36; H, 5.14; N, 9.98.

(±)-N-Nitroso-2-methylindoline-2-carboxylic Acid (13). A suspension of **12** (22 g) in 15% sodium hydroxide and methanol (60 ml) was heated under reflux for 10 hr with stirring. The clear reaction mixture was concentrated *in vacuo* to *ca.* one-third of its original volume. The concentrate was cooled and acidified with hydrochloric acid to pH 4–5 causing a white solid to separate; total volume at this stage was *ca.* 100 ml. The solid was collected with suction and washed with 10 ml of ice water. The solid thus obtained was contaminated with inorganic material. It was dried *in vacuo* and extracted with cold dry ethanol (50 ml). Evaporation of the solvent gave 12 g (85.6%) of the acid **12** as a colorless solid which deteriorated on keeping. The infrared spectrum in potassium bromide showed bands at 2.9 (broad, NH), 3.5–4.3 (broad, strong, N^+H_2), 5.86 (medium, COOH), 6.02 (shoulder), 6.09 (shoulder), 6.18 (strong, COO^-), 6.72 (medium), 6.83 (medium), 7.1 (medium), and 7.3 μ (medium). It was used in the next step without any further purification.

To a stirred solution of (±)-2-methylindoline-2-carboxylic acid (3.54 g, 20 mmol) in 30 ml of 1 *N* hydrochloric acid, cooled in ice, was added dropwise a solution of sodium nitrite (1.38 g, 20 mmol) in water (15 ml). A light pale solid separated which was filtered, washed with water, and dried *in vacuo* to give 3.45 g (86%) of the (±)-nitroso acid **13**, mp 119°. The infrared spectrum showed $\lambda^{CHCl_3}_{max}$ 5.78 (strong, C=O), 6.25 (weak, C=C), 6.75 (weak), 6.83 (medium), 7.05 (strong, NO), 7.74 (strong), and 8.48 μ (strong). The molecular weight determined mass spectrometrically was 206.0698 (calcd for $C_{10}H_{10}N_2O_3$: 206.0691).

The free nitroso acid deteriorates at room temperature but can be stored at −25° for weeks without decomposition. It was transformed into its stable methyl ester by treatment with diazomethane. The ester was recrystallized from ethanol–pentane to give light yellow plates, mp 74–75°. The infrared spectrum had $\lambda^{CHCl_3}_{max}$

(28) R. E. Bowmann and H. H. Stroud, *J. Chem. Soc.*, 1342 (1950).

(29) For data on (±) form see P. Karrer, *Helv. Chim. Acta*, **4**, 96 (1921).

5.68 (strong, C=O) 6.23 (weak, C=C), 6.7 (weak), 6.76 (medium), 7.0 (strong, NO), and 7.68 μ (strong, C—O—C).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.04; H, 5.66; N, 12.40.

Resolution of (±)-1-Nitroso-2-methylindoline-2-carboxylic Acid (13) with (−)-Ephedrine. Isolation of (*S*)(+)-16. To a solution of 15 g (0.073 mol) of the nitroso acid **13** in ethyl acetate (100 ml) was added 12 g (0.073 mol) of (−)-ephedrine dissolved in 30 ml of the same solvent. In a few minutes a light yellow solid crystallized which was collected on filter and washed with ethyl acetate to give 11 g of the salt, mp 155–158°. One recrystallization from methanol–ethyl acetate mixture followed by another from methanol–benzene mixture furnished 8 g (60%) of light pale crystals, mp 165–166°, $[\alpha]^{24}D$ −44.7° (*c* 1.3, ethanol).

Anal. Calcd for $C_{20}H_{25}N_3O_4$: C, 64.47; H, 6.78; N, 11.31. Found: C, 65.05; H, 7.00; N, 11.22.

To obtain (*S*)(+)-**16**, the ephedrine salt (8 g) was dissolved in 200 ml of 1% sodium hydroxide solution and extracted with three 50-ml portions of ether to remove ephedrine. The aqueous solution was acidified with hydrochloric acid to pH 4 and extracted with four 50-ml portions of ether. The organic solution was washed with water (20 ml), dried (magnesium sulfate), and evaporated *in vacuo* to furnish 4 g (91%) of pale crystals, mp 115–116°, $[\alpha]^{24}D$ +12° (*c* 2, ethanol). The infrared spectrum was identical with that of the racemic sample.

Resolution of (±)-13 with Brucine. Isolation of (*R*)(−)-14. Following the above procedure, the mother liquor gave 7.5 g of **13** enriched in the (−)-antipode. To a solution of this in ethyl acetate (100 ml) was added brucine (18 g) dissolved in 50 ml of the same solvent, and the mixture was warmed for a few minutes. A crystalline solid separated which was filtered after cooling to give 13 g of the salt, mp 160–165°. Two crystallizations from methanol–ethyl acetate mixture furnished 9.5 g (45%) of the salt of (*R*)(−)-**14** as a glistening solid, mp 175–176°, $[\alpha]^{24}D$ −55.1° (*c* 1.3, ethanol).

Anal. Calcd for $C_{33}H_{36}N_4O_7$: C, 65.99; H, 6.04; N, 9.33. Found: C, 65.92; H, 6.23; N, 9.24.

To obtain the free acid (*R*)(−)-**14**, the above salt (9.5 g) was suspended in 200 ml of 1% sodium hydroxide and stirred well. The insoluble liberated base was filtered and washed with water. The alkaline filtrate was repeatedly extracted with ether to remove traces of the alkaloid. The basic solution was acidified with hydrochloric acid to pH 4–5, and the liberated acid was extracted into three 100-ml portions of ether. The washed and dried (magnesium sulfate) extract on evaporation *in vacuo* gave 3 g (88%) of the acid (*R*)(−)-**14**, mp 114–115°, $[\alpha]^{24}D$ −12° (*c* 2, ethanol). Its infrared spectrum was identical with that of the antipode (*S*)(+)-**16**.

(*S*)(−)-N-Amino-2-hydroxymethyl-2-methylindoline (17). A solution of 1.03 g (5 mmol) of (*S*)(+)-**16** ($[\alpha]^{24}D$ +12° (*c* 2, ethanol)) in ether (100 ml) was treated with excess diazomethane in ether solution. The mixture was evaporated to give 1.1 g (100%) of the ester **16** as a thick light brown gum. The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 5.72 (strong, CO), 6.27 (weak, C=C), 6.76 (medium), 6.83 (medium), 7.08 (strong, NO), 7.3 (medium), 7.41 (weak), 7.72 (shoulder, strong), 7.8 (strong), 7.97 (medium), 8.5 (strong), and 8.89 μ (medium, C—O—C). This product was used for the reduction processes described below without further purification. The conversion to **17** by attempted reduction of both carboxyl and N-nitroso groups using lithium aluminum hydride appeared to be complicated by unknown side reactions. These were circumvented by carrying out the reduction in two stages: (1) reduction of the carboxyl function ($LiBH_4$) and (2) reduction of the nitroso group ($LiAlH_4$).

Stage 1. To a stirred suspension of lithium borohydride (220 mg, 10 mmol) in dimethoxyethane (60 ml) was added dropwise a solution of the ester (1.1 g, 5 mmol) in ether (50 ml). The mixture was heated under reflux for 14 hr. It was chilled in ice, and 2 ml of saturated aqueous sodium sulfate solution was added slowly under nitrogen atmosphere. The mixture was stirred for 2 hr, and the inorganic salts were removed by filtration through Celite 545. The filtrate after drying (magnesium sulfate) was evaporated to give a thick light pale solid which crystallized on refrigeration. It was crystallized from ethanol–pentane mixture to give 8.5 g (88.5%) of *S*(−)-N-nitroso-2-methyl-2-hydroxymethylindoline as a crystalline solid, mp 97–98°, $[\alpha]^{24}D$ −98° (*c* 1, ethanol). The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 2.72 (weak, shoulder) and 2.9 (medium) (OH), 6.27 (weak, C=C), 6.75 (medium), 6.86 (medium), 7.1 (strong, NO), 7.3 (medium), 7.46 (strong), and 7.88 μ (strong). The nmr spectrum ($CDCl_3$) exhibited peaks at (ppm) 1.44 (singlet) and 1.63 (singlet) (3 H, ratio 2:3) due to the protons of the methyl group, 2.7–4.28 (5 H, multiplet) due to benzylic protons, hydroxylic and methylene protons. The aromatic protons were shown as a multiplet centered at 7.1 (3 H), 7.626 (multiplet), and 8.4 (multiplet) (1 H, area ratio 2:3). The latter two resonances are attributed to the aromatic proton (nearest to the ring nitrogen) affected by the anisotropy of the N–O group.

The racemic product prepared in this manner had identical spectral properties and melted at 86–87°.

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.73; H, 6.52; N, 14.27.

Stage 2. A solution of (*S*)(−)-N-nitroso-2-methyl-2-hydroxymethylindoline (1.15 g, 6 mmol) in ether (40 ml) was dropped slowly into a well stirred ice-cooled solution of lithium aluminum hydride (0.684 g, 18 mmol) in 150 ml of the same solvent. The mixture was stirred for 14 hr at 24–25° and then refluxed for 0.5 hr. The excess hydride was destroyed by adding 5 ml of sodium sulfate solution as above. After removal of the inorganic salts the colorless ether solution was first dried over potassium hydroxide and then over magnesium sulfate. Evaporation of the solvent *in vacuo* gave a colorless syrup which solidified and turned pink on keeping. One recrystallization from cyclohexane gave 0.85 g (80%) of (*S*)(−)-N-amino-2-hydroxymethyl-2-methylindoline as light pink needles, mp 88°, $[\alpha]^{25}D$ −25.7° (*c* 1.38, ethanol). The infrared spectrum showed $\lambda_{max}^{CCl_4}$ 2.8–2.95 (broad, strong, OH and NH_2), 6.3 (strong C=C), 6.8 (strong), 6.89 (strong), and 9.55 μ (strong). In the nmr spectrum ($CDCl_3$) methyl protons appeared as a single resonance at (ppm) 1.0 (3 H) while the benzylic protons appeared as a pair of doublets (J = 15 cps) centered at 2.4 (1 H) and 3 (1 H). The exchangeable protons (NH_2 and OH) appeared as a singlet at 3.22 (3 H) and methylene protons showed a doublet each at 3.315 (1 H) and 3.52 (1 H), the J being 10.5 cps; the high-field peak of the former partly overlapped with the singlet due to the exchangeable protons. The aromatic protons exhibited a multiplet centered at 7.2 (4 H).

The nmr spectrum of the uncrystallized sample exhibited an absorption at (ppm) 1.16 (singlet) (area 6% relative to the peak at 1.0) which was attributed to the methyl group of **18** (Chart V), the latter having been formed by hydrogenolysis of N–N bond.

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.31; H, 8.08; N, 15.57.

(*S*)(+)-2-Hydroxymethyl-2-methylindoline (18) (Chart V). A solution of (*S*)(−)-N-amino-2-hydroxymethyl-2-methylindoline (**17**) (0.178 g, 1 mmol) in dimethoxyethane (10 ml) and 0.1 *N* hydrochloric acid (10 ml) was hydrogenated in the presence of 10% palladium-on-carbon catalyst (100 mg). The hydrogenolysis was complete in 1.5 hr. The catalyst was filtered, and the filtrate was evaporated *in vacuo* to *ca.* one-fourth of its original volume. It was treated with 2 g of solid potassium hydroxide. The strongly basic solution was extracted with three 30-ml portions of ether. The ether solution was dried and evaporated to give 155 mg (95%) of **18** as a colorless oil, $[\alpha]^{27}D$ +9.05° (*c* 1.325, ethanol). The nmr spectrum in $CDCl_3$ exhibited peaks at (ppm) 1.2 (3 H, singlet, methyl group protons), 2.62 and 3.03 (2 H, pair of doublets, J = 15 cps, benzylic protons), 3.2 (2 H, broad peak, exchangeable protons), 3.48 (2 H, singlet, methylene protons on the carbon bearing the hydroxyl group) and 6.4–7.1 (4 H, multiplet, aromatic protons). The product was analyzed as hydrochloride, mp 179°, which was recrystallized from ethanol–ether.

Anal. Calcd for $C_{10}H_{14}ClNO$: C, 60.15; H, 7.02; N, 7.02. Found: C, 60.04; H, 7.12; N, 6.86.

(*S*)(+)-2-Hydroxymethyl-2-methyl-N-methylindoline Methiodide (19) (X = I). To a solution of the (*S*)(+)-indoline **18** (147 mg, 0.9 mmol) in a mixture of methanol (10 ml) and methyl iodide (10 ml) was added magnesium oxide (200 mg), and the reaction mixture was held at gentle reflux for 48 hr. It was filtered through Celite 545 and evaporated *in vacuo* to give a solid which was recrystallized from ethanol–ether to give 248 mg (86%) of **19** (X = I) as shining white crystals, mp 180°, $[\alpha]^{27}D$ +9.3° (*c* 0.3, ethanol). The iodide which was quite insoluble was converted to the chloride **19** (X = Cl) as described below.

Anal. Calcd for $C_{12}H_{18}INO$: C, 45.14; H, 5.64; N, 4.39. Found: C, 44.99; H, 5.66; N, 4.38.

(*S*)(+)-2-Hydroxymethyl-2-methyl-N-methylindoline Methochloride (19) (X = Cl). To a well-stirred suspension of freshly prepared silver chloride (5 g) in water (150 ml) was added a solution of the (+)-quarternary methiodide **19** (X = I) (0.224 g, 0.7 mmol) in 10 ml of water. The mixture was stirred in the dark for 1 hr. It was filtered through Celite 545, and the filtrate was evaporated *in vacuo* to give a white solid. This operation was repeated with 2 g of silver chloride. The solid was recrystallized from ethanol–ether to give 0.128 g (82%) of **19** (X = Cl) as white needlelike crystals, mp 202°, $[\alpha]^{26}D$ +19° (*c* 0.11, ethanol). The nmr spectrum in D_2O

(with TMS as external reference) showed peaks at (ppm) 1.55 (3 H, singlet, protons of the methyl group on the indoline ring), 3.3 (2 H, broad singlet, benzylic protons), 3.36 and 3.39 (6 H, overlapping singlets, protons of the methyl on the nitrogen), 4.02 (2 H, AB quartet, J = 14 cps, protons on the carbon bearing oxygen), 4.72 (1 H, singlet, hydroxylic proton) and 7.52 (4 H, unresolved multiplet, aromatic protons).

Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.43; H, 7.93; N, 6.16. Found: C, 63.40; H, 8.00; N, 6.12.

Reduction of (*S*)(+)-2-Hydroxymethyl-2-methyl-N-methylindoline Methochloride (19, X = Cl) to (*S*)(+)-2-Dimethylamino-2-methyl-3-phenylpropanol (20). A three-necked 200-ml round-bottomed flask, equipped with a Dry Ice condenser and provided with a U-tube seal containing mercury and a nitrogen inlet, was charged sequentially with dimethoxyethane (100 ml), sodium metal (0.25 g), and dry ammonia (40 ml). To the well-stirred blue suspension was added 0.1025 g (0.45 mmol) of the quaternary chloride **19** (X = Cl). The mixture was stirred for 3.5 hr. The Dry Ice was removed from the condenser, and the ammonia was allowed to evaporate. Saturated aqueous ammonium chloride solution (1 ml) was then injected into the reaction mixture. In *ca.* 5 min all the sodium metal was consumed. The mixture was filtered through Celite 545, and the filtrate was first dried over potassium hydroxide and then over anhydrous magnesium sulfate. The solvent was evaporated *in vacuo* to give a colorless oil which was chromatographed on a 1 mm thick 20 × 20 cm thin layer chromatography (tlc) plate prepared by slurrying alumina PF_{254} with 0.4 N sodium hydroxide. Ether–benzene (7:3) mixture was used for developing. A spot of the authentic sample was developed side by side for reference. The band (*ca.* 1 cm wide, R_f 0.35) was eluted with 75 ml of methanol–ether (1:4) after addition of 0.2 g of powdered sodium hydroxide to the scraped adsorbent. The eluate was evaporated under reduced pressure. The residue containing a small amount of alumina and sodium hydroxide was taken up in 50 ml of ether. It was filtered through Celite 545, and the filtrate after drying was evaporated to give 17 mg of a colorless oil. A solution of the product in ether–pentane on refrigeration deposited 4.5 mg of colorless crystals, mp 50°, $[\alpha]^{27}D$ +2.95 ± 0.5°, $[\alpha]^{27}_{578}$ +11.38 ± 0.3° (*c* 0.41, ethanol). The mixture melting point with that of the authentic sample of (*S*)(+)-**20** prepared from (*S*)(−)-α methylphenylalanine as described below showed no depression, and the infrared spectra were superimposable.

The crystalline solid (4 mg) dissolved in methyl iodide (0.2 ml) was allowed to stand at 30° for 48 hr. A white precipitate was formed. The excess methyl iodide was removed *in vacuo*, and the white solid residue was crystallized from ethanol–ether to give 3.5 mg of colorless crystals, mp 188°, undepressed on admixture with the authentic sample of the methiodide of (*S*)-**20** which had $[\alpha]^{27}D$ −20.4 ± 0.3° (*c* 0.235, ethanol). The infrared spectra (KBr) of the two samples were indistinguishable.

(*S*)(+)-N,N-Dimethyl-α-methylphenylalanine (Chart V). To a solution of (*S*)(−)-α-methylphenylalanine[17,18] (179 mg, 1 mmol) ($[\alpha]^{25}D$ −19.74° (*c* 1.16, water)) in water (15 ml) was added formaldehyde (0.5 ml, 37% solution; *ca.* 6 mmol). The mixture was hydrogenated in a Parr hydrogenation apparatus for 48 hr using 180 mg of 10% palladium-on-carbon catalyst. After the usual isolation, the product was obtained as a colorless glass. The nmr spectrum in D_2O (TMS as external reference) showed peaks at (ppm) 1.1 (3 H, singlet, protons of the methyl group on the α-carbon), 2.6 (6 H, singlet, protons of the two methyl groups on nitrogen), 2.82 (2 H, singlet, benzylic protons), and 7.06 (5 H, singlet, aromatic protons). It was converted to the crystalline hydrochloride for analysis; the analytical sample was prepared by one recrystallization from ethanol–ether, mp 260°, $[\alpha]^{27}D$ +59.9° (*c* 0.65, ethanol). The molecular weight determined mass spectrometrically was 243.1024 (calcd for $C_{12}H_{18}ClNO_2$: 243.1026).

Anal. Calcd for $C_{12}H_{18}ClNO_2$: C, 59.13; H, 7.39; N, 5.74. Found: C, 58.48; H, 7.37; N, 5.53.

(*S*)(+)-2-Dimethylamino-2-methyl-3-phenylpropanol (20) (from (*S*)(−)-α-Methylphenylalanine). To a well-stirred suspension of (*S*)(+)-N,N-dimethyl-α-methylphenylalanine (0.1025 g, 0.5 mmol) in dioxane was added lithium aluminum hydride (0.114 g, 3 mmol), and the mixture was held at gentle reflux for 48 hr. Saturated aqueous sodium sulfate (1 ml) was added after cooling the reaction mixture in an ice bath. The mixture was stirred for 30 min and filtered through Celite 545. The filtrate was first dried over potassium hydroxide and then over anhydrous magnesium sulfate solution. It was purified by preparative tlc on basic alumina to give 0.072 g (75%) of a colorless oil which crystallized on keeping at 0° for 2 days, mp 50°. It was recrystallized to give **20** as colorless crystals, mp 50°, $[\alpha]^{27}D$ +3.1 ± 0.5°, $[\alpha]^{27}_{578}$ +11.6 ± 0.3° (*c* 0.609, ethanol). The nmr spectrum in $CDCl_3$ showed peaks at (ppm) 0.9 (3 H, singlet, protons of α-methyl group), 2.32 (6 H, singlet, protons of the geminal methyl groups), 2.72 (2 H, singlet, benzylic protons), 3.2 (1 H, singlet, proton of the hydroxyl group), 3.15 and 4.2 (2 H, a pair of doublets, J = 11 cps; protons of the methylene group on the carbon bearing the hydroxyl), and 7.2 (5 H, singlet, aromatic protons). The infrared spectrum had $\lambda_{max}^{CHCl_3}$ 2.95 (medium, OH), 6.26 (weak, C=C), 6.71 (medium), 6.9 (strong), 7.15 (medium), 7.3 (weak), 9.6 (strong), 10.13 (medium), and 10.38 μ (medium). The molecular weight determined mass spectrometrically was 193.1464 (calcd for $C_{12}H_{19}NO$: 193.1467).

Methiodide of 20 (from (*S*)(−)-α-Methylphenylalanine). A solution of (*S*)(+)-**20** (10 mg, 0.05 mmol) in methyl iodide (0.5 ml) was kept at 30° for 48 hr in a well-stoppered flask. A white precipitate was formed. The excess methyl iodide was evaporated, and the solid residue was recrystallized from ethanol–ether to give 9 mg (54%) of colorless needles, mp 188°, $[\alpha]D$ −21.17 ± 0.3° (*c* 0.347, ethanol). The infrared spectrum (KBr) had λ_{max} 2.85 (weak), 6.7 (strong), 6.82 (strong), and 9.46 μ (strong).

Anal. Calcd for $C_{13}H_{22}INO$: C, 46.56; H, 6.56; I, 37.91. Found: C, 46.57; H, 6.70; I, 37.75.

(±)-1-Nitroso-2-indolinecarboxylic Acid (Chart VI). A solution of racemic (±)-ethyl 1-nitroso-2-indolinecarboxylate (0.44 g, 2 mmol) in ethanol (5 ml) and 1 N sodium hydroxide (5 ml) was heated to reflux for 3 hr. It was evaporated *in vacuo* to one-fourth of its original volume. This solution was then acidified to pH 4–5 with 0.5 N hydrochloric acid, and the light brown solid which separated was collected by suction filtration to give 317 mg of light brown crystals, mp 128–130°. Extraction of the filtrate with three 15-ml portions of ether followed by drying and evaporation furnished another 20 mg of the solid, mp 128–130°. This carboxylic acid was used without further purification for the next step. An analytical sample was prepared by recrystallization from ethanol–pentane, mp 130.5°. The infrared spectrum had $\lambda_{max}^{CHCl_3}$ 5.8 (strong, CO), 6.81 (weak), 6.95 (weak), 7.09 (strong, NO), and 7.75 μ (medium).

Anal. Calcd for $C_9H_8N_2O_3$: C, 56.25; H, 4.16; N, 14.58. Found: C, 56.35; H, 4.42; N, 14.55.

(±)-2-Carbomethoxy-1-nitrosoindoline (21). A solution of the racemic nitroso acid (192 mg, 1 mmol) in ether (80 ml) was treated with a 0.2 M solution of diazomethane in ether (6 ml). Evaporation furnished 0.209 g of a light yellow crystalline solid which was recrystallized from ethyl acetate–pentane to give 177 mg (86%) of the methyl ester (±)-**21** as light yellow crystals, mp 105–106°. The infrared spectrum had $\lambda_{max}^{CHCl_3}$ 5.71 (strong, CO), 6.78 (weak), 6.85 (medium), 7.08 (strong, NO), and 7.75 μ (strong, C—O—C).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.33; H, 5.10; N, 13.22.

Chymotrypsin-Catalyzed Hydrolysis of (±)-21. Racemic methyl ester **21** (0.08 g, 0.37 mmol) and 0.08 g of α-chymotrypsin in 80 ml of 0.1 N sodium chloride were allowed to react under nitrogen using a "pH-stat" setting at pH 7.0, 0.1 N sodium hydroxide being added from an automatic buret. After 30 hr, 1.862 ml of the base had been added, corresponding to 93% hydrolysis of one enantiomorph. The rate of reaction then became much slower. The reaction mixture was extracted with four 30-ml portions of ether. The extract (neutral fraction) was dried and evaporated to give a light yellow crystalline solid which was recrystallized to give 34 mg of a light yellow, neutral solid, mp 105–106°, $[\alpha]^{27}D$ −26.5° (*c* 0.40, ethanol), which on the basis of its infrared spectrum was identified to be methyl ester **21** (levo form).

The aqueous solution left after the extraction was acidified to pH 5 with 0.1 N hydrochloric acid and extracted with four 25-ml portions of ether. The extract (acid fraction) was washed with water (10 ml) and treated with an ethereal solution of diazomethane till a faint yellow color persisted. Concentration under reduced pressure furnished a light yellow crystalline solid which was recrystallized from ethyl acetate–pentane to give 30 mg of *d*-**21**, mp 104°, $[\alpha]^{27}D$ +43.95° (*c* 0.48, ethanol). The identity of the product was confirmed by comparison of the infrared spectrum with authentic methyl ester **21**.

Transformation of (+)-2-Carbomethoxy-1-nitrosoindoline 21 (Acid Fraction) into (*R*)(+)-1-Nitroso-2-hydroxymethylindoline (Chart VI). A solution of the (+)-2-carbomethoxy-1-nitrosoindoline (obtained from the above-described acid fraction) (20 mg, 0.1 mmol) in anhydrous ether (2.5 ml) was dropped slowly into a slurry of lithium aluminum hydride (50 mg) in 20 ml of the same solvent. The mixture was stirred overnight at 28° and then held at gentle reflux for 1 hr. The excess hydride was destroyed

by the addition of 0.5 ml of saturated sodium sulfate solution. The inorganic salts were filtered through Celite 545, and the filtrate was dried and evaporated to give an amber colored oil (18 mg). The infrared spectrum of this product was identical with that of an authentic sample of 2-hydroxymethyl-N-aminoindoline.

The 2-hydroxymethyl-N-aminoindoline (18 mg), without any purification, was dissolved in a mixture of dimethoxyethane (2 ml) and 0.1 *N* hydrochloric acid (1 ml). Palladium-on-carbon catalyst (10%, 20 mg) was then added to the solution, and the mixture was hydrogenated at ordinary pressure for 2 hr. The usual workup after basification furnished 2-hydroxymethylindoline (12 mg) as an oil, the identity of which was confirmed by comparison of the infrared spectrum with that of an authentic sample of this compound.

The 2-hydroxymethylindoline (12 mg) was nitrosated at ice bath temperature in the usual manner. The product was purified by preparative thin layer chromatography (silica gel PF_{254}, ether–benzene 1:1, R_f 0.6) to give 8 mg (45% for three steps) of (*R*)(+)-1-nitroso-2-hydroxymethylindoline, mp 131–133°, $[\alpha]^{27}D$ +313° (*c* 0.51, ethanol). The infrared spectrum in chloroform was superimposable with that of a sample of (*S*)(−)-**8** (Chart II).

Transformation of (−)-2-Carbomethoxy-1-nitrosoindoline (Neutral Fraction) into (*S*)(−)-1-Nitroso-2-hydroxymethylindoline. (−)-2-Carbomethoxy-1-nitrosoindoline (35 mg) (chymotrypsin neutral fraction) upon hydride reduction followed by hydrogenolysis and nitrosation as usual gave 15 mg (44% for three steps) of (*S*)(−)-2-hydroxymethyl-N-nitrosoindoline, mp 130–133°, $[\alpha]D$ −184.1° (*c* 0.5, ethanol), identified by its infrared and nmr spectra.

Hydrolysis of (±)-2-Carbomethoxy-2-methyl-1-nitrosoindoline ((±)-22) with α-Chymotrypsin (Chart VII). A solution of the ester (±)-**22** (22 mg, 0.1 mmol) was injected into a stirred solution of α-chymotrypsin (22 mg) in 22 ml of 0.1 *N* sodium chloride using a "pH-stat" setting at pH 7.2, maintained at 30°. The reaction was stopped after 97 hr, 0.4677 ml of 0.1 *N* sodium hydroxide having been consumed corresponding to 93.5% hydrolysis of an enantiomorph. The neutral material was extracted with four 20-ml portions of ether which after evaporation of the solvent yielded 11 mg of light brown oil which was purified by thin layer chromatography (silica gel PF_{254}, ether–benzene 1:1, R_f 0.7) to give 8.1 mg of a pale colored oil which crystallized on keeping, mp 72–74°, $[\alpha]^{26}D$ +10.1° (*c* 0.5, ethanol). The infrared spectrum in chloroform solution was identical with that of the starting material.

The aqueous layer was acidified to pH 4–5 with 0.1 *N* hydrochloric acid. It was immediately extracted by gentle shaking with four 15-ml portions of ether. The combined ether extracts were washed with water (10 ml), and the ether solution was treated with 1 ml of 0.2 *M* ethereal solution of diazomethane at 0°. Evaporation under reduced pressure gave a light brown oil which was purified by preparative tlc (silica gel PF_{254}, ether–benzene 1:1, R_f 0.7) to furnish 5.1 mg of pale thick oil which crystallized on keeping, mp 73–74°, $[\alpha]^{26}D$ −21.5° (*c* 0.4, ethanol). The infrared spectrum was indistinguishable from that of the authentic sample of (−)-2-carbomethoxy-2-methyl-1-nitrosoindoline, $[\alpha]^{27}D$ −25.9° (*c* 1.1, ethanol) (obtained by treatment of the corresponding levo acid (**14**) (Chart IV) with diazomethane). The mixture melting point of the two samples was undepressed.

(−)-2-Carbomethoxy-2-methyl-1-nitrosoindoline from 14. A solution of the levo acid **14** (Chart IV), $[\alpha]D$ −12° (*c* 2, ethanol) (resolved with brucine) (0.041 g, 0.2 mmol) in 20 ml of ether was treated with 2 ml of 0.2 *M* diazomethane in ether. The solvent and the excess diazomethane were evaporated to give a crystalline residue which was recrystallized from ethanol–pentane to give 32 mg (73%) of light yellow crystals, mp 74°, $[\alpha]^{27}D$ −25.9° (*c* 1.1, ethanol). The infrared spectrum was identical with that of the racemic material. The infrared spectrum had $\lambda_{max}^{CHCl_3}$ 5.68 (strong, C=O), 6.23 (weak, C=C), 6.7 (weak), 6.76 (medium), 7.0 (strong, NO), and 7.68 μ (strong, C—O—C).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.04; H, 5.66; N, 12.40.

Hydrazono Lactone 26 from (*S*)-1-Amino-2-hydroxymethylindoline and Methyl Pyruvate (Chart IX). (*S*)-1-Amino-2-hydroxymethylindoline (2.00 g, 12.2 mmol) dissolved in 22 ml of methanol was treated with 2.2 ml of methyl pyruvate, and the resulting yellow solution was stirred for 18 hr at room temperature. After the methanol was evaporated, the residue was taken up three times in toluene and evaporated. The residual oil was then dissolved in 80 ml of chloroform and washed twice with cold 10% hydrochloric acid and twice with saturated salt solution. The chloroform solution was filtered through cotton, dried over magnesium sulfate, and evaporated to 3.12 g of the hydrazone **23** as an orange oil which resisted all attempts at crystallization.

The oily hydrazono ester **23** dissolved in 680 ml of dry benzene was treated with 0.626 g (0.0116 mol) of sodium methoxide, and the mixture was stirred at reflux for 24 hr in a flask fitted with a Soxhlet extractor containing molecular sieve type 4A. The yellow solution was decanted from the undissolved sodium methoxide, washed with 100 ml of cold water and saturated salt solution, filtered through cotton, and dried over magnesium sulfate. The benzene solution was evaporated, leaving 1.94 g of yellow crystalline material which could be purified by recrystallization from methylene chloride–hexane, giving 1.85 g (70%) of hydrazono lactone **26** as yellow prisms, mp 128.0–130.0°. The analytical sample was recrystallized from ether–hexane to constant melting point, 128.7–129.1°, $[\alpha]^{27}D$ −487° (*c* 0.6, $CHCl_3$). The infrared spectrum ($CHCl_3$) of **26** manifested carbonyl absorption at 5.89 μ. The nmr spectrum ($CDCl_3$) showed a sharp methyl singlet at 2.32 ppm.

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.62; H, 5.63; N, 12.89.

Aluminum Amalgam Reductions. Aluminum foil (300 mg, 11.1 mmol) cut into four 40-mm strips was immersed with agitation for 10 sec successively in ether, ethanol, 2% aqueous mercuric chloride, ethanol, and ether. The strips were immediately cut into the reaction mixture. The reactivity of the amalgam is dependent upon the duration of submersion in the mercuric chloride solution. Extended submersion results in agglomeration of the aluminum amalgam particles and results in a decreased reaction rate. In inert solvents the reaction does not proceed until a hydroxylic solvent is added.

(−)-Hydrazino Lactone 29. To an ice-cooled magnetically stirred solution of 450 mg of the hydrazono lactone **26**, $[\alpha]^{25}D$ −517° (*c* 1.3, ethanol), in 30 ml of dimethoxyethane (freshly distilled from sodium) was added aluminum amalgam prepared from 450 mg of aluminum foil. The mixture was treated with 4.2 ml of distilled water, and the stirring was continued for 10 hr at 0° under nitrogen atmosphere. After slurrying with 100 mg of Celite 545, the mixture was filtered under suction, and the residue was washed with 30 ml of dimethoxyethane. Evaporation of the solvent *in vacuo* gave 450 mg (99%) of a colorless solid. A 100-mg portion of this product was set aside for direct conversion to D-alanine and (*S*)(+)-2-hydroxymethylindoline.

The nmr spectrum ($CDCl_3$) of the unpurified solid showed two sets of doublets at (ppm) 1.51 and 1.33 (J = 7 cps) with area ratio of 8:1 due to the protons of the methyl group on the carbon bearing the tertiary proton. The upfield doublet belonged to the methyl group of the unwanted diastereomer.

The rest of the product (350 mg) was once crystallized from ethanol–petroleum ether to give 206 mg of colorless crystals, mp 101.5–103°; a second crop (22 mg), mp 150–155°, was obtained on keeping the mother liquor at 3–4° for 10 hr. The lower melting solid was then recrystallized once from ethanol–carbon tetrachloride–pentane to give 190 mg (55%) of colorless crystals, mp 102.5–103.5°, $[\alpha]^{23}D$ −111.6 ± 0.5° (*c* 1, ethanol). The nmr spectrum ($CDCl_3$) of this product showed a doublet centered at (ppm) 1.51 and was devoid of any resonance at 1.33, while the nmr spectrum ($CDCl_3$) of the higher melting solid (150–155°) showed two sets of doublets at (ppm) 1.51 and 1.33 with area ratio 2:3 indicating an enrichment of the minor diastereomer in this sample. The infrared spectrum of this product, mp 102.5–103.5°, showed $\lambda_{max}^{CHCl_3}$ 5.81 (strong, C=O), 6.2 (medium, C=C) 6.7 (medium), 6.8 (shoulder, medium), 6.87 (medium), 8.3 (strong, C—O—C), and 9.33 μ (strong).

A sample of the racemic lactone prepared by this procedure melted at 124–127°.

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.06; H, 6.62; N, 12.83.

Hydrolysis and Hydrogenolysis of the Purified (−)-Hydrazino Lactone 29. Formation of D-Alanine and (*S*)(+)-2-Hydroxymethylindoline. A. Acid Hydrolysis. A solution of the (−)-lactone **29** (mp 102.5–103.5°, $[\alpha]^{25}D$ −111.6 ± 0.5° (*c* 1, ethanol)) in dimethoxyethane (4 ml) and 0.1 *N* hydrochloric acid (4 ml) was heated at 69° for 1.25 hr. It was cooled to *ca.* 25° and injected into a prehydrogenated suspension of 65 mg of palladium hydroxide-on-carbon catalyst in 1 ml of 0.01 *N* hydrochloric acid. The required amount of hydrogen (*ca.* 6.5 ml) was taken up in 40 min after which the hydrogenation was stopped. The catalyst was filtered and washed with water and dimethoxyethane. The combined filtrates were evaporated *in vacuo* after basifying to pH 8–9 with 1 *N* ammonium hydroxide. The residue dissolved in *ca.* 20 ml of water was extracted with two 20-ml portions of ether. The organic solution was dried (magnesium sulfate) and evaporated *in vacuo* to furnish 38 mg

(85%) of (*S*)(+)-2-hydroxymethylindoline (**7**) as a colorless syrup which solidified (mp 66–68°) on refrigeration. Its infrared spectrum was identical with that of the authentic sample, and it had $[\alpha]^{25}D$ +59.5° (*c* 1, ethanol).

The aqueous solution left after extraction of the indoline was acidified with 0.1 *N* hydrochloric acid (0.2 ml). The solution was desalted by passage through an ion exchange column carrying *ca.* 12 ml of Dowex 50W-X8 (acid form). The column was washed with *ca.* 40 ml of water until no chloride ions could be detected in the washing (silver nitrate). The amino acid was then eluted with *ca.* 35 ml of 1 *N* ammonium hydroxide at 0–5°. The basic solution was evaporated at 0–5° *in vacuo* and sublimed *in vacuo* to give 23.5 mg (88%) of D-alanine of 99.06 ± 0.8% optical purity, $[\alpha]^{25}D$ −31.9 ± 0.25° (*c* 0.75, acetic acid); an authentic sample of D-alanine had $[\alpha]^{25}D$ −32.21 ± 0.25° (*c* 0.8, acetic acid). The two samples had superimposable infrared spectra in potassium bromide.

B. Base Hydrolysis. To a stirred solution of the purified (−)-lactone **29** (65.5 mg, 0.3 mmol) in 3 ml of dimethoxyethane cooled in ice was added 0.1 *N* sodium hydroxide solution (3 ml) from a microburet (with the tip dipped in the solution) during 4 hr. The mixture was stirred for an additional 0.5 hr at ice bath temperature, after which it was acidified with 6 ml of 0.1 *N* hydrochloric acid. It was then hydrogenated over palladium hydroxide-on-carbon catalyst (65 mg, prehydrogenated in 1 ml of 0.01 *N* hydrochloric acid) as above. The workup as before furnished 37.0 mg (83%) of the (+)-indoline **7**, mp 65–67.5°, $[\alpha]^{25}D$ +59° (*c* 1.1, ethanol), and 22 mg (82.8%) of D-alanine, $[\alpha]^{25}D$ −31.0 ± 0.25° (*c* 0.81, acetic acid) of 96.25% optical purity. An authentic sample of D-alanine had $[\alpha]^{25}D$ −32.21 ± 0.25° (*c* 0.8, acetic acid).

In another similar run D-alanine of 98% optical purity was obtained.

Control Experiment for the Final Isolation of Alanine. It was the purpose of this experiment to see if any resolution of the amino acid occurred during the final precipitation process. Authentic L-alanine (99.7 mg, 1.12 mmol), $[\alpha]^{27}D$ +32.7 ± 1.1° (*c* 1.5, acetic acid) (lit.[30] $[\alpha]^{24-26}D$ +33.0°, acetic acid), together with authentic (±)-alanine (100.1 mg, 1.13 mmol) were dissolved in 10.0 ml of water. A 2.0-ml aliquot was evaporated to dryness, and the residue was taken up in a small amount of water. The aqueous solution was subjected to the isolation procedure described above. The observed rotation for alanine obtained (94%) in this manner was $[\alpha]^{27}D$ +15.4 ± 0.5°. The rotation observed for the isolated alanine was $[\alpha]^{27}D$ +16.0 ± 0.4°.

A 2.0-ml aliquot of a solution of 83.9 mg (0.941 mmol) of L-alanine and 15.8 mg (0.177 mmol) of (±)-alanine dissolved in 10.0 ml of water was processed in exactly the same way as reported above to give 35.9 mg (90%) of alanine. The calculated rotation for this sample was $[\alpha]^{27}D$ +27.5 ± 0.9°; the observed rotation for this sample was $[\alpha]^{27}D$ +28.0 ± 0.7°.

Hydrolysis and Hydrogenolysis of the Unpurified (−)-Hydrazino Lactone 29. Formation of D-Alanine and (*S*)(+)-2-Hydroxymethylindoline. From 65.5 mg (0.3 mmol) of the unpurified (−)-lactone **29** obtained above, following the procedure used for the acid hydrolysis of purified **32**, 37.5 mg (84%) of the (+)-indoline, $[\alpha]^{25}D$ +59.8° (*c* 0.95, ethanol), mp 66–68°, was recovered, and 23 mg (86%) of D-alanine (indistinguishable infrared spectrum (KBr) from that of an authentic sample), $[\alpha]^{25}D$ −25.1 ± 0.3° (*c* 0.74, acetic acid) of 78% optical purity was obtained. (A measurement with an authentic sample of D-alanine gave $[\alpha]^{25}D$ −32.21 ± 0.2° (*c* 0.8, acetic acid) under the same conditions.) In another experimental sequence using the same procedures, D-alanine of 82% optical purity was isolated.

(−)-Hydrazono Lactone 27. To a stirred solution of methyl α-ketobutyrate (prepared from 0.714 g (7 mmol) of α-ketobutyric acid and diazomethane) in 50 ml of ether was added over a period of 10 min a solution of 0.984 g (6 mmol) of optically active (*S*)-1-amino-2-hydroxymethylindoline (obtained from (*S*)(+)-2-hydroxymethylindoline), $[\alpha]^{25}D$ +60° (*c* 0.9, ethanol) in 50 ml of the same solvent. The reaction mixture was stored at 22–23° for 10 hr, which caused it to become deep yellow in color. Evaporation of the solvent *in vacuo* gave the hydrazono ester **24** as a thick oil (1.5 g), $\lambda_{max}^{CHCl_3}$ 2.85 (medium, OH), 5.75 (strong, C=O), 6.2 (weak, C=C), 6.35 (weak, C=N), 6.74 (medium), 6.81 (medium), 6.93 (medium), and 8.1 μ (broad, strong, C—O—C). This intermediate ester was not purified. A stirred deep yellow solution of the ester in 450 ml of benzene was allowed to reflux for 1.5 hr in a Soxhlet apparatus carrying molecular sieves (Linde type 4A). The solution was cooled to 50° and treated with 270 mg (5 mmol) of sodium methoxide and then heated under reflux for 5 hr using a fresh batch of the molecular sieves. The reaction mixture became light yellow in color. It was filtered through Celite 545, and the clear filtrate was washed with three 20-ml portions of water. After drying (magnesium sulfate), evaporation of the organic solution furnished a thick oil which solidified on refrigeration. It was crystallized from cyclohexane to give 0.83 g (60%) of light yellow solid, mp 118–119°, [α] −423° (*c* 0.590, chloroform). The infrared spectrum of the product showed $\lambda_{max}^{CHCl_3}$ 5.9 (shoulder), 5.95 (strong, C=O), 6.21 (weak, C=C), 6.4 (shoulder, strong), 6.48 (strong, C=N), 6.76 (strong), 6.85 (medium), 6.95 (weak), 7.3 (medium), 7.67 (medium), and 8.2 μ (broad, strong, C—O—C).

The corresponding racemic lactone prepared according to the above procedure in a scaled up run was obtained in 88% yield, mp 117–118°. The infrared and nmr spectra of this material were identical with those of the optically active product.

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.89; H, 6.38; N, 12.16.

(−)-Hydrazino Lactone 30. To an ice-cooled solution of 350 mg of the (−)-lactone **27** ($[\alpha]^{27}D$ −423° (*c* 0.59, chloroform), source (*S*)(+)-2-hydroxymethylindoline) in 25 ml of dimethoxyethane was added aluminum amalgam prepared from 350 mg of aluminum foil. The rection mixture was treated with water (3.5 ml) and allowed to stir at 0° for 8 hr. The excess aluminum and alumina were filtered through Celite 545, and the filter cake was washed with ether–dimethoxyethane (1:1) (25 ml). The colorless clear filtrate was dried over magnesium sulfate and evaporated *in vacuo* to give 346 mg (98%) of a colorless solid. Out of this, 100 mg of the material (without purification) was set aside for conversion to D-butyrine. The rest of the product (246 mg) on three crystallizations from ethanol–carbon tetrachloride–pentane furnished 146 mg (59%) of **30** as colorless crystals, mp 119–120°, $[\alpha]^{23}D$ −132.6° (*c* 0.7, ethanol). It showed only one spot on tlc analysis (silica gel) (R_f 0.5, benzene–ether, 3:1). The infrared spectrum in chloroform showed $\lambda_{max}^{CHCl_3}$ 2.8 (broad, weak, NH), 6.22 (medium, C=C), 6.75 (medium), 6.88 (strong), 7.98 (strong), 8–8.5 (broad, strong, C—O—C), and 9.52 μ (strong). The nmr spectrum ($CDCl_3$) exhibited a triplet centered at (ppm) 1 (3 H, *J* = 7 cps) due to the methyl group and a multiplet at 1.5–4.25 (8 H) due to the rest of the nonaromatic protons. The aromatic protons were shown as a multiplet at 6.65 (4 H).

The corresponding racemic lactone prepared in a similar manner melted at 142–143.5° and had identical infrared and nmr spectra.

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.24; H, 6.98; N, 12.15.

Hydrolysis and Hydrogenolysis of the Purified (−)-Hydrazino Lactone 30. Formation of D-Butyrine and (*S*)(+)-2-Hydroxymethylindoline. Base Hydrolysis. To a solution of the recrystallized (−)-hydrazino lactone **30** (mp 119–120°), [α]D −132.6° (*c* 0.7, ethanol, source (*S*)(+)-**9**) (81.2 mg, 0.35 mmol) in dimethoxyethane (3.5 ml) cooled in an ice bath was added with stirring 0.1 *N* aqueous sodium hydroxide (0.35 ml) from a microburet over a period of 4 hr. The reaction mixture was stirred for an additional 0.5 hr at 0° and then acidified with 0.6 ml of 1 *N* hydrochloric acid. The acidic reaction mixture was allowed to attain room temperature and was injected into a prehydrogenated suspension of palladium hydroxide-on-carbon catalyst (81 mg) in 0.1 *N* hydrochloric acid (1 ml). The hydrogenation was carried out at *ca.* 25° at atmospheric pressure. The required amount of hydrogen was taken up in *ca.* 40 min. The catalyst was washed with water (2 ml), and the ice-cooled filtrate was basified with 1 *N* ammonium hydroxide to pH 8–9. The basic solution on evaporation at 0–5° *in vacuo* gave a colorless solid residue which was extracted with three 10-ml portions of chloroform after suspending in 12 ml of water. The organic solution after drying (magnesium sulfate) on evaporation furnished 39 mg (75%) of (*S*)(+)-2-hydroxymethylindoline as a colorless oil which was nitrosated in the usual manner to give 37 mg (60% for 2 steps) of (−)-1-nitroso-2-hydroxymethylindoline, mp 133–135°, $[\alpha]^{25}D$ −344° (*c* 1, ethanol) (identity confirmed by comparison of the infrared spectrum with that of the authentic sample).

The aqueous solution obtained after extraction of the indoline was acidified with 0.1 *N* hydrochloric acid (0.25 ml) and desalted as before by passage through Dowex 50W-X8 (acid form) to give 28.5 mg (80%) of D-butyrine as a white solid, $[\alpha]^{25}D$ −40.8 ± 0.3° (*c* 0.8, acetic acid). The infrared spectrum of this sample was superimposable on that of an authentic sample of D-butyrine, $[\alpha]^{25}D$ −41.7° ± 0.3° (*c* 0.75, acetic acid). The optical purity of the synthesized sample was 97.4%.

(30) J. P. Greenstein, S. M. Birnbaum, and M. C. Otey, *J. Biol. Chem.*, 204, 307 (1953).

Hydrolysis and Hydrogenolysis of the Unpurified (−)-Hydrazino Lactone 30. Formation of D-Butyrine and (*S*)(+)-2-Hydroxymethylindoline. Base Hydrolysis. From the unpurified (−)-lactone **30** (source, (+)-2-hydroxymethylindoline) (81.2 mg, 0.35 mmol) according to the above procedure, 39 mg (75%) of (*S*)(+)-2-hydroxymethylindoline (**9**) was obtained, which on nitrosation gave 36 mg (59% for two steps) of (−)-1-nitroso-2-hydroxymethylindoline, mp 133–135°, $[\alpha]^{25}D$ −344° (*c* 1, ethanol). D-Butyrine (27 mg, 75%) of 89.56% optical purity was obtained, $[\alpha]^{25}D$ −37.35 ± 0.31° (*c* 0.83, acetic acid); an authentic sample of D-butyrine under identical conditions had $[\alpha]^{25}D$ −41.7 ± 0.3° (*c* 0.75, acetic acid). The identity of the synthetic sample of the amino acid was established through comparison of its infrared spectrum (KBr) with that of the authentic sample.

Acid Hydrolysis. A solution of the unpurified (−)-lactone **30** (94 mg, 0.4 mmol) (obtained directly on aluminum amalgam reduction of **27**, $[\alpha]^{23}D$ −423° (*c* 0.59, chloroform)) in a mixture of dimethoxyethane (4 ml) and 0.1 *N* hydrochloric acid (4 ml) was heated under nitrogen at 70° for 1.5 hr. The solution was allowed to cool to 25° and hydrogenated in the presence of prehydrogenated palladium hydroxide-on-carbon catalyst (94 mg) in a mixture of hydrochloric acid (0.25 ml) and dimethoxyethane (1 ml). The hydrogenation was complete in 40 min. The workup as before furnished 48 mg (81%) of (*S*)(+)-**9**, $[\alpha]^{25}D$ +60.5 ± 0.5° (*c* 1.66, ethanol), and 32.1 mg (80%) of D-butyrine (sublimed at 215° (0.001 mm)), $[\alpha]^{25}D$ −37.66 ± 0.3° (*c* 0.579, acetic acid) of 90% optical purity. An authentic sample of D-butyrine sublimed under identical conditions had $[\alpha]^{25}D$ −41.84 ±0.3° (*c* 0.588, acetic acid) and indistinguishable infrared spectrum (KBr) from that of the synthetic sample.

(+)-Hydrazono Ester 25 (Chart IX). A cooled solution of the 1-aminoindoline (*S*)(−)-**17** (from (*S*)(+)-**16** (0.801 g, 4.5 mmol)) in ether (50 ml) was added dropwise to a stirred ice-cooled solution of freshly distilled methyl pyruvate (0.46 g, 4.5 mmol) in 100 ml of the same solvent. The light pink solution thus obtained was kept at 0–2° for 12 hr and then at 25–26° for 6 hr, which caused it to turn deep yellow in color. The solvent and traces of water formed during the reaction were removed *in vacuo* to give 1.18 g of a deep yellow solid. One crystallization from ethanol–hexane mixture furnished 1.03 g (87%) of the hydrazono ester **25** as fluffy yellow crystals, mp 100–101°, $[\alpha]^{24}D$ +413° (*c* 0.97, ethanol). The infrared spectrum had $\lambda_{max}^{CHCl_3}$ 2.88 (medium, OH), 5.8 (strong, CO), 6.25 (medium, C=C and C=N), 6.8 (strong), 6.88 (strong), 8.1–8.4 (strong, C—O—C), and 8.7 μ (strong, C—O—C). The nmr spectrum ($CDCl_3$) exhibited a singlet at (ppm) 1.4 (3 H) due to the protons of the methyl group on the ring, a singlet at 2.15 (3 H) due to the protons of the methyl group on the double bond, a singlet at 2.94 (2 H) due to the benzylic protons, and a singlet at 3.28 (1 H) due to the proton of the hydroxy group. The protons of the carbomethoxy group were displayed as a singlet at (ppm) 3.84 (3.5 H) overlapping one peak of a doublet due to one of the methylene protons which appeared as a doublet each (J = 11.5 cps) centered at (ppm) 3.55 (1 H) and 3.91 (0.5 H). Of the aromatic protons one (presumably the one nearest to the ring nitrogen) was shown as a doublet at (ppm) 6.05 (1 H, J = 7.5 cps), and the other three protons were exhibited as a multiplet at 6.95 (3 H). The racemic hydrazono ester made in this manner had mp 131–132° and identical infrared and nmr spectra.

Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.41; H, 7.16; N, 10.58.

(−)-Hydrazono Lactone 28 (from (+)-25). A yellow solution containing 450 mg of the optically active ester **25** ([α]D +413° (*c* 0.97, ethanol)) in 650 ml of dry benzene was refluxed for *ca.* 1 hr in a Soxhlet apparatus containing molecular sieves (Linde Type 4A). It was cooled to room temperature, and sodium methoxide (Fisher Reagent) (31 mg; *ca.* 0.3 equiv) was added. The mixture was refluxed for 3.5 hr causing it to become pale in color. It was filtered through Celite 545 and washed with two 20-ml portions of cold water. The benzene solution was taken to dryness *in vacuo* to furnish 390 mg of a light yellow solid. One crystallization from cyclohexane gave 360 mg (90%) of **28** as pale crystals, mp 126°, $[\alpha]^{24}D$ −37.1° (*c* 1.1, ethanol). The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 5.89 (strong, CO), 6.2 (weak), 6.26 (shoulder, weak C=C), 6.45 (strong, C=N), 6.75 (strong), 6.86 (medium), 6.95 (shoulder, medium), 7.67 (strong), 8.5 (strong), 8.92 (strong) and 9.43 μ (strong). The nmr spectrum ($CDCl_3$) exhibited a singlet at (ppm) 1.31 (3 H) due to protons of the angular methyl group, a singlet at 2.32 (3 H) due to the protons of the methyl group on the double bond, a singlet at 3.04 (2 H) due to benzylic protons, a doublet each for the methylene protons at 4.1 (1 H, J = 11 cps) and 4.52 (1 H, J = 11 cps), and a multiplet at 7.1 (4 H) due to the aromatic protons.

A sample of the racemic material prepared in the same manner had mp 133–134° and identical infrared and nmr spectra.

Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.10; H, 6.35; N, 12.04.

(−)-Hydrazino Lactone 31. To a stirred solution of the (−)-hydrazono lactone **28** $[\alpha]^{24}D$ −37.1° (*c* 1.1, ethanol) (464 mg) in dimethoxyethane (25 ml, freshly distilled over sodium) cooled in ice was added amalgam prepared from 464 mg of aluminum foil followed by 4 ml of water. The mixture was stirred at 0° for 30 hr, after which it was diluted with 25 ml of dimethoxyethane and filtered through Celite 545. The colorless filtrate was dried (sodium sulfate) and evaporated *in vacuo* at 0–5° to furnish a colorless solid (455 mg, 97%), mp 152–154°.

A portion of the product (100 mg) was kept aside for degradation to alanine without any purification. The rest of the product was crystallized once from ethanol–pentane mixture and then from carbon tetrachloride–ethanol–pentane mixture to give 215 mg (60.5%) of **31** as a colorless solid, mp 156.5–157.5° (single spot on silica gel thin layer chromatogram), $[\alpha]^{25}D$ −165.7° (*c* 1.15, ethanol). The infrared spectrum of **31** showed $\lambda_{max}^{CHCl_3}$ 2.9 (broad, weak, NH), 5.79 (strong, C=O), 6.2 (medium, C=C) 6.73 (medium), 6.82 (shoulder, medium), 6.89 (medium), and 8.2 μ (strong, C—O—C). The nmr spectrum ($CDCl_3$) exhibited a singlet at (ppm) 1.23 (3 H) due to the protons of the angular methyl group, a doublet at 1.52 (2 H, J = 7.5 cps) due to the protons of the methyl group on the carbon carrying a tertiary proton and a singlet at 2.87 (2 H) due to the benzylic protons. Further, a doublet (J = 12.5 cps) for each of the methylene protons was exhibited at 4.15 and 4.58 ppm. These two sets of signals overlapped a multiplet due to the tertiary proton and the resonance due to the proton on the nitrogen (total area under the peaks was 4 H). A multiplet appeared at 7.0 (ppm) (4 H) due to the aromatic protons. A sample of the racemate corresponding to **31** prepared as above had mp 121° and identical spectra.

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.05; H, 7.04; N, 11.94.

D-Alanine from Unpurified (−)-Hydrazino Lactone 31. To a solution of the unpurified (−)-lactone **31** (69.6 mg, 0.3 mmol) in 3 ml of dimethoxyethane (distilled over sodium) was added 3 ml of 0.1 *N* hydrochloric acid, and the mixture was heated for 55 min in an oil bath at 68–69°. The reaction mixture was allowed to cool to room temperature and injected into a hydrogenation flask containing 69 mg of prehydrogenated palladium hydroxide-on-carbon catalyst in 1 ml of 0.05 *N* hydrochloric acid. The required amount of hydrogen was taken up in *ca.* 30 min, after which the rate slowed down considerably and the hydrogenation was stopped. The catalyst was filtered, and the filtrate cooled in ice was basified to pH 8–9 with 1 *N* ammonium hydroxide. It was evaporated at 0–5° *in vacuo* to give a white residue. The indoline formed was extracted into two 20-ml portions of ether after suspending the residue in water (10 ml). The combined ether extract after drying (sodium sulfate) and evaporation gave 40 mg (82%) of the optically active indoline **18** as a colorless oil which tends to become pink on keeping. It was immediately nitrosated with sodium nitrite in 1 equiv of 0.05 *N* hydrochloric acid at 0° to afford the *l*-nitroso derivative (35 mg, yield 75% based on the indoline), mp 97–98°, $[\alpha]^{24}D$ −98.6° (*c* 1, ethanol). The infrared and nmr spectra of this material were identical with those of the authentic sample.

The aqueous solution left after extraction of the optically active indoline **18** was acidified with 0.2 ml of 0.1 *N* hydrochloric acid. The solution was desalted by passage through an ion exchange column packed with Dowex 50W-X8 (acid form) (*ca.* 12 ml). The amino acid was eluted with 1 *N* ammonium hydroxide (*ca.* 40 ml) at 3–4°. The basic solution was taken to dryness at 0–3° to give D-alanine (22 mg, 82%), $[\alpha]^{24}D$ −23.82 ± 0.3° (*c* 0.7, acetic acid). Infrared spectrum of the synthesized amino acid was indistinguishable from that of an authentic sample which had $[\alpha]^{24}D$ −32.24 ± 0.25° (*c* 0.7, acetic acid), the optical purity of the synthetic sample being 74.5%.

D-Alanine from Purified (−)-Hydrazino Lactone 31. Acid Hydrolysis. Following the above procedure from 82.2 mg (3.5 mmol) of (−)-**31** ($[\alpha]^{24}D$ −165.7° (*c* 1.15, ethanol)), D-alanine (25 mg, 81%) of 99% purity was obtained, $[\alpha]^{24}D$ −32 ± 0.25° (*c* 0.8, acetic acid). Authentic sample under these conditions had $[\alpha]^{24}D$ −32.24 ± 0.25° (*c* 0.8, acetic acid). The (*S*)-2-hydroxymethyl-2-methylindoline (**18**) (42 mg, 83%) obtained was converted to the nitroso derivative in 75% yield; 37 mg, mp 97–98°, $[\alpha]^{23}D$ −98.6° (*c* 1, ethanol).

D-Alanine from Purified (−)-Hydrazino Lactone 31. Base Hydrolysis. To a stirred solution of 69.6 mg (3 mmol) of the (−)-lactone **31** ($[\alpha]^{24}D$ −165.7° (*c* 1.15, ethanol)), in 4.5 ml of dimethoxyethane, cooled at 0–2°, was added 3 ml of 0.1 *N* sodium hydroxide over 4 hr. After stirring for an additional 0.5 hr, the mixture was acidified with 6 ml of 0.1 *N* hydrochloric acid. Upon hydrogenolysis in the usual manner followed by the workup as before, 21.0 mg (79%) of D-alanine of 91% optical purity was obtained, $[\alpha]^{24}D$ −29.1 ± 0.3° (*c* 0.7, acetic acid). 2-Hydroxymethyl-2-methylindoline (*S*)-**18** was obtained as a colorless oil (43 mg, 85%) which was converted into the N-nitroso derivative, mp 97° (38 mg, 75%), $[\alpha]^{28}D$ −98.5° (*c* 1, ethanol). The identity of the product was confirmed in each case through comparison of the infrared spectrum with that of the authentic sample. From this result it is clear that the basic hydrolysis procedure is unsatisfactory in the conversion of **31** to D-alanine, since appreciable racemization is involved.

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Studies on the Asymmetric Synthesis of α-Amino Acids. II. New Systems for Highly Specific Asymmetric Synthesis with Conservation of the Chiral Reagent

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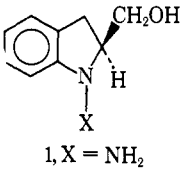
Abstract: The new approach for the asymmetric synthesis of α-amino acids from α-keto acids which is described in the foregoing paper has been extended with the development of a highly selective stereochemical system. The levorotatory chiral reagent **14** has been prepared by stereospecific synthesis and resolution (Chart I) and has been applied to the asymmetric synthesis of a number of α-amino acids (Chart IV). The D-amino acids alanine, butyrine, valine, and isoleucine were obtained directly in optical purities of 96, 97, 97, and 99%, respectively, from levorotatory **14**. Moreover, amino acids of essentially 100% optical purity are readily and efficiently obtained by interposing a recrystallization process in the scheme. The chiral reagent is not destroyed in the course of asymmetric synthesis and is therefore available for repeated use. The absolute configuration of reagent **14** follows from a three-dimensional X-ray crystallographic analysis of the racemic form of the hydrazino lactone **30** in combination with a chemical correlation of levorotatory **30** with **14** and D-alanine. The results of the X-ray analysis of (±)-**30** are summarized. The synthesis and absolute configuration of the levorotatory reagent **21**, a diastereomer of **14**, is also described together with its application to the asymmetric synthesis of D-alanine and D-butyrine.

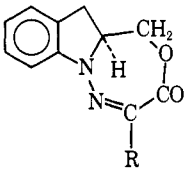
The preceding article[1] describes a new approach to the asymmetric synthesis of α-amino acids from α-keto acids by indirect reductive amination. The chiral reagent **1** was used to convert an α-keto acid to the corresponding hydrazono lactone **2**, a chiral substance containing the prochiral α-carbon atom as part of a seven-membered ring. Reduction of the hydrazono lactone **2** by means of aluminum amalgam–water proceeded stereoselectively, but not stereospecifically, to form a hydrazino lactone of stereostructure **3** as the major product (80–90%) together with the diastereomer **4** (10–20%) in lesser amount. The mixture could be converted to α-amino acid either with or without separation of diastereomers, and in the process the chiral reagent **5** was regenerated.

This method of asymmetric synthesis was designed originally with the following objectives: (1) predictable synthesis of either a D- or L-α-amino acid by choice of the chiral reagent, (2) high stereoselectivity, and (3) conservation of the chiral reagent so as to allow its repeated use in the process. The initial phase of this investigation demonstrated the feasibility of the new method with regard to the first and third of these objectives. However, the second, high stereoselectivity, was not attained. This article is concerned with the modification of the structure of the chiral reagent to allow for high stereoselectivity as well as reagent conservation and predictability.



1, X = NH_2

5, X = H



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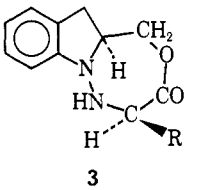

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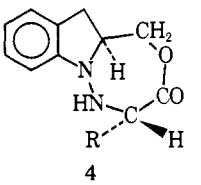

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For a number of reasons it appeared possible that the replacement of one of the methylene protons of the hydrazono lactone ring in **2** by a sterically bulkier group would increase the stereoselectivity of the crucial reduction to the hydrazino lactone system. Specifically, substitution of a methyl group for that methylene proton which is *trans* to the vicinal methine proton seemed advantageous. This change places a large group (compared with hydrogen) on the side of the lactone ring which has to be shielded against hydrogen addition if enhancement of stereoselectivity

(1) E. J. Corey, R. J. McCaully, and H. S. Sachdev, *J. Am. Chem. Soc.*, 92, 2476 (1970).