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%), $[\alpha]^{23}D$ −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.

Acknowledgment. This research was supported by the National Institutes of Health.

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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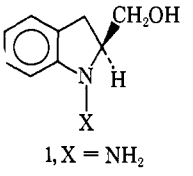
Abstract: The new approach for the asymmetric synthesis of α-amino acids from α-keto acids which is described in the foregoing paper has been extended with the development of a highly selective stereochemical system. The levorotatory chiral reagent **14** has been prepared by stereospecific synthesis 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.

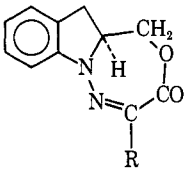
The preceding article[1] describes a new approach to the asymmetric synthesis of α-amino acids from α-keto acids by indirect reductive amination. The chiral reagent **1** was used to convert an α-keto acid to the corresponding hydrazono lactone **2**, a chiral substance containing the prochiral α-carbon 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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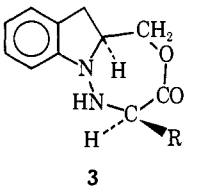

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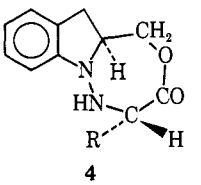

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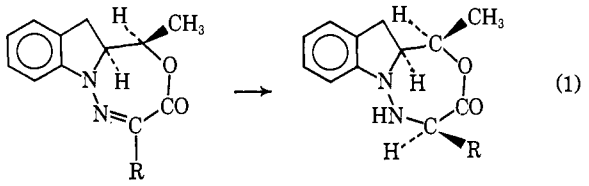
For a number of reasons it appeared possible that the replacement of one of the methylene protons of the hydrazono lactone ring in **2** by a sterically bulkier group would increase the stereoselectivity of the crucial reduction to the hydrazino lactone system. Specifically, substitution of a methyl 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

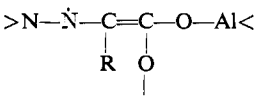
(1) E. J. Corey, R. J. McCaully, and H. S. Sachdev, *J. Am. Chem. Soc.*, **92**, 2476 (1970).

in the reduction step is to be realized. The desired course of the reduction with this methyl-substituted system is shown in eq 1. The expectation that the reduction process (1) would be more stereoselective



(1)

than the analogous reduction of **2** to **3** rests on the following assumptions: (a) that the addition of hydrogen to the prochiral center is subject to steric screening, (b) that the conformation of the lactone ring in the transition state for reduction can be approximated by the stable conformation of the ring in the hydrazono lactone itself, and (c) that in the most favorable geometry of the lactone ring, the methyl substituent exerts a screening influence on the prochiral α-carbon atom. Since there is no solid evidence regarding the mechanism of the reduction process (1) using the reagent aluminum amalgam, the validity of assumptions a and b is unclear. However, it would appear that these assumptions are at least reasonable for two likely types of mechanisms, one in which the reduction involves a hydride-like attack by a reagent containing a reactive Al-H unit, and one in which an electron is transferred to conjugated carbonyl unit to form a structure such as



which is protonated at the α-carbon atom by water. Some indication of the preferred conformation of the hydrazono lactone ring of **2** is provided by the carbonyl stretching absorption ($CHCl_3$ solution) at 5.89 μ, considerably longer in wavelength than that for the hydrazino lactone **3** (5.81 μ). The long wavelength carbonyl absorption of **2** indicates substantial electronic displacement from the γ nitrogen to the carbonyl oxygen and therefore the likelihood that the C(C)NN=CCO unit in **2** is approximately planar. The conformation which allows this condition is shown in Figure 1. In this conformation there is also a high degree of π overlap in the –OC(=O)– unit of the lactone, and there is some angle strain due to the spreading of several of the internal angles. The carbon bearing R_1 (Figure 1) is situated above the mean plane of the six other atoms of the seven-membered ring with the group R_1 projecting toward the space above the prochiral carbon–nitrogen double bond. Considerable shielding of the prochiral carbon would be expected for $R_1 = CH_3$.

The investigation of the scheme of asymmetric synthesis using eq 1 as a key step was undertaken on the basis of these considerations. The stereochemistry of the hydrazono lactone in eq 1 is designated for convenience in this paper as S_NR_O, the absolute configuration of the nitrogen-bearing chiral carbon being S and that of the oxygen-bearing center being R.

In addition to studying the S_NR_O system of eq 1, we have also been concerned with the diastereomeric

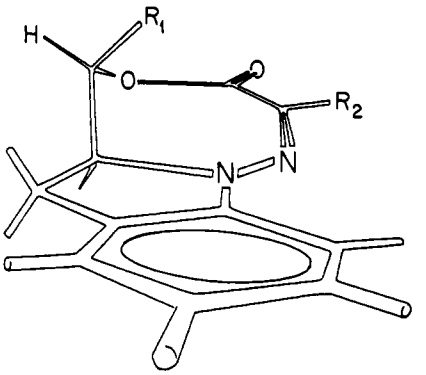
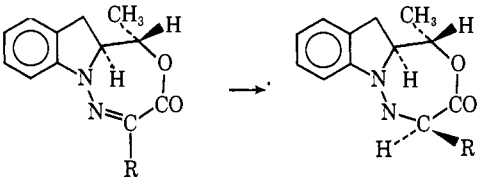


Figure 1. A representation of the conformation of hydrazono lactones with maximum π-conjugation.

series, which can be designated S_NS_O and which includes the step shown in eq 2 as a critical part.

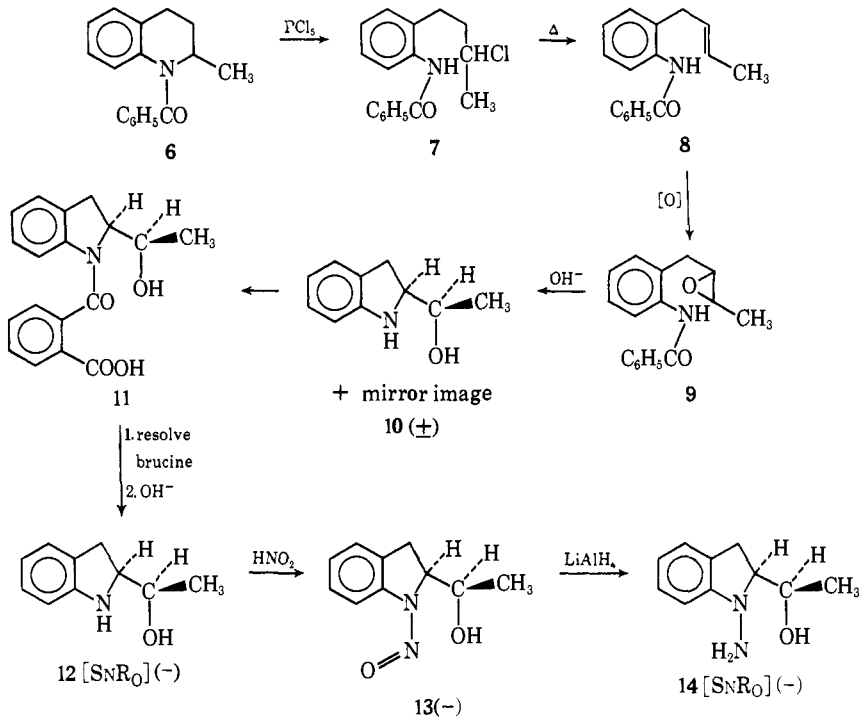


(2)

Synthesis and Absolute Configuration of Chiral Reagents. The synthesis of 1-amino-(*S*)-2-[(*R*)-1-hydroxyethyl]indoline (**14**), the reagent for asymmetric synthesis in the S_NR_O series, will be described first. The synthesis, which is outlined in Chart I, was designed so as to generate unambiguously and stereospecifically the desired relative stereochemistry in the key racemic intermediate **10**. Starting from the readily available N-benzoyl-1,2,3,4-tetrahydroquinaldine (**6**), the chloro amide **7** was prepared by von Braun cleavage using phosphorus pentachloride. Thermolysis of **7** under reduced pressure afforded stereoselectively the *trans*-unsaturated amide **8**, mp 117–118°, the configuration about the double bond being indicated both by strong infrared absorption at 10.3 μ characteristic of *trans*-CH=CH and the stability of **8** under *cis* → *trans* isomerizing conditions. Epoxidation of the double bond in **8** produced the oxide **9** which upon treatment with base underwent intramolecular nucleophilic displacement of O by N and amide hydrolysis to form the desired indoline **10** stereospecifically. The stereochemistry of **10** is clear from the *trans* geometry of the precursor **9** and the expectation of an inversion pathway for the nucleophilic displacement process. Ring closure to form a five-membered ring rather than a six-membered structure is supported by chemical correlation with the authentic indoline **21**, as shown in Chart III, and also by X-ray studies (see later section). Resolution of the hydroxyindoline (±)-**10** was accomplished readily by recrystallization of the brucine salt of the N-*o*-carboxybenzoyl derivative **11**. Alkaline hydrolysis of the resolved form of **11** afforded the optically active hydroxy indoline **12** which was converted to the N-nitroso and N-amino derivatives (**13** and **14**) in the standard way.[1]

Starting from **14** (levorotatory), a pure crystalline hydrazino lactone (**30**) was prepared by condensation with *p*-nitrophenyl pyruvate and subsequent reduction as outlined in Chart IV by the sequence **14** → **24** →

Chart I. Synthesis of 1-Amino-(*S*)-2-[(*R*)-1-hydroxyethyl]indoline

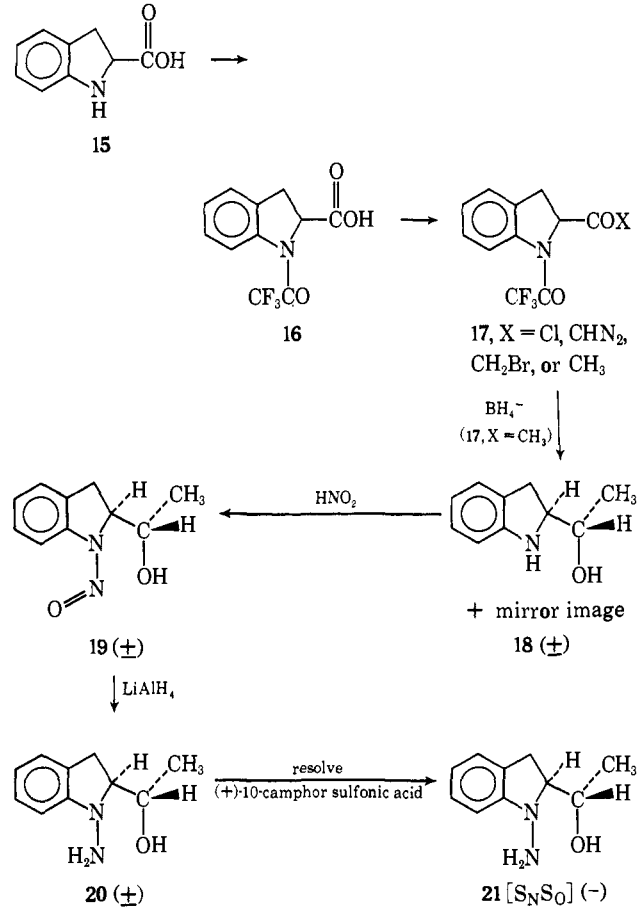


30. Acid-catalyzed hydrolysis of this hydrazino lactone followed by N–N hydrogenolysis (H_2–Pd) produced D(−)-alanine which indicated that the absolute configuration of the chiral center α to the carbonyl group in the hydrazino lactone is as shown in expression **30**. The relative configurations of the three asymmetric centers in the hydrazino lactone were found also to be as shown in formula **30** by an X-ray crystallographic analysis. This study, which is described in the last part of this discussion, was actually performed using the racemic form of **30**, obtained in a parallel fashion from the racemic form of **14**. Together this information established the absolute stereochemistry of **30** and, hence, also of the reagent **14**.

The synthesis of 1-amino-(*S*)-2-[(*S*)-1-hydroxyethyl]-indoline (**21**) is outlined in Chart II. N-Trifluoroacetyl-2-indolinecarboxylic acid was converted *via* the acid chloride to the diazo ketone **17**, X = CHN_2, and thence with hydrogen bromide to the bromo ketone **17**, X = CH_2Br. Reaction of the bromo ketone with zinc–acetic acid afforded the N-trifluoroacetyl-2-acetylindoline **17**, X = CH_3, reduction of which with sodium borohydride in ethanol gave mainly the secondary alcohol **18** along with minor amounts of the diastereomeric alcohol (**10**) (ratio *ca.* 5:1). The predominating alcohol **18** was readily obtained *via* the crystalline hydrochloride which was easily purified by recrystallization. The racemic N-aminoindoline derivative **20** was prepared from the indoline **18** by nitrosation to form the N-nitroso derivative **19** followed by hydride reduction. The resolution of the racemic N-aminoindoline **20** was effected by recrystallization of the salt with (+)-10-camphorsulfonic acid. The purified camphorsulfonate salt afforded a levorotatory base which was shown to be the S_NS_O isomer (**21**) by chemical correlation with the N-nitrosoindoline **13** (Chart I) as shown in Chart III.

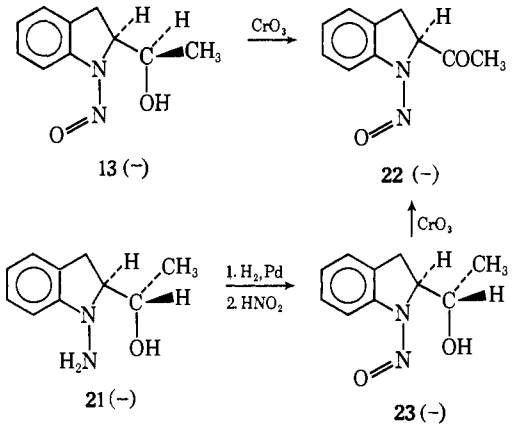
Oxidation of N-nitrosohydroxyindoline in the S_NR_O series (**13**) using the Jones chromic acid reagent afforded

Chart II. Synthesis of 1-Amino-(*S*)-2-[(*S*)-1-hydroxyethyl]indoline



the levorotatory methyl ketone **22** (Chart III). The same substance was obtained from the N-aminohydroxyindoline of the S_NS_O series (**21**) by the sequence N–N hydrogenolysis, N-nitrosation, and Jones oxidation. This correlation establishes the absolute con-

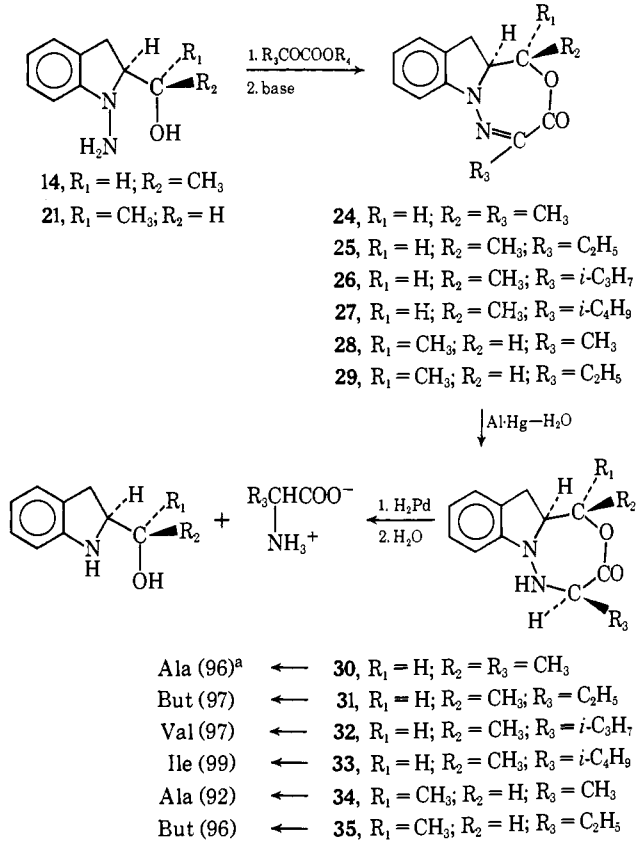
Chart III. Correlation of the (*S*)-2-[(*R*)-1-Hydroxyethyl]indoline and (*S*)-2-[(*S*)-1-Hydroxyethyl]indoline Series



figuration of **21** and also verifies the indoline formulation for the cyclization product **10** derived from the epoxide **9** (Chart I).

Asymmetric Synthesis of α-Amino Acids from the S_NR_O and S_NS_O N-Amino-2-hydroxyethylindolines 14 and 21. The N-aminohydroxyindolines **14** and **21** were utilized for the asymmetric synthesis in the general way described in the preceding paper,[1] the route being outlined in Chart IV and described in detail in the

Chart IV. Asymmetric Synthesis of α-Amino Acids



Experimental Section. Starting from the S_NR_O reagent **14** and *p*-nitrophenyl pyruvate, the crystalline hydrazono lactone **24** was prepared in the usual way.[1] Reduction of **24** yielded the hydrazino lactone **30** which without purification or fractionation of any sort was converted to alanine by ester hydrolysis followed by N–N hydrogenolysis. The amino acid so obtained was D(−)-alanine of optical purity 96 ± 1%. Similarly from the reagent **14** and esters of α-ketobutyric, isovaleric, and isocaproic acids were obtained, respectively, D-butyrine, D-valine, and D-isoleucine in optical purities of 97, 97, and 99%, respectively (all ± a maximum of 1%).

By similar processes starting from the S_NS_O reagent **21**, D-alanine and D-butyrine were obtained in optical purities of 92 and 96%, respectively (±1%).

In each of these experiments the optical purity of the amino acid which was obtained indicates the stereochemical efficiency of the asymmetric synthesis, since any procedures which might cause stereochemical fractionation during the course of the synthesis were rigorously avoided. Additionally, the chiral 2-hydroxyethylindoline reagent could be recovered for reuse in each instance, the separation from α-amino acid being accomplished simply by extraction of a mildly alkaline aqueous solution with ether.

As anticipated, the stereochemical course of reduction of the hydrazono lactones **24–27** in the S_NR_O series involves the addition of hydrogen to the prochiral α-carbon from a direction which is *cis* to the hydrogen at C-2 of the indoline ring. Further, the stereochemical efficiency of the asymmetric synthesis in this series (96–99%) is substantially greater than that observed with the first reagent studied,[1] (*S*)-1-amino-2-hydroxymethylindoline (**1**) (80–90%). From a practical viewpoint these levels of stereochemical efficiency make possible the facile and economical synthesis of 100% optically pure α-amino acids, since the pure diastereomeric hydrazino lactones **30–33** are readily obtained with very high recovery simply by recrystallization. Since the unwanted diastereomer which is to be removed constitutes only 1–4% of the unpurified hydrazino lactone obtained directly from the reduction, very little material is sacrificed in the process of total asymmetric synthesis.

It was somewhat surprising to find that the efficiency of asymmetric synthesis for the S_NS_O series based on the diastereomeric reagent **21** was also considerably greater than with the unmethylated analog **1**, though less than with **14**. This unpredicted result may be due to a repulsive interaction between the methyl substituent on the lactone ring and the 3-methylene group of the indoline ring of the hydrazono lactones **28** and **29** which serves to change the geometry of the lactone ring so as to increase the shielding of the prochiral α-carbon by the methine hydrogen of the $CHCH_3$ group. Regardless of whether this is the correct explanation, it is clear that fairly simple changes in the structure of the chiral basic hydroxyindoline reagent **1** can considerably enhance the specificity of the asymmetric synthesis. Indeed, there are a number of fairly accessible analogs of **1** which would appear to be deserving of investigation as promising reagents for ultraspecific asymmetric synthesis of α-amino acids, and it would seem probable that further improvements in the new process can be made.

It is clear from the present results that a major improvement has been made in the methodology of asymmetric synthesis (*cf.* the methods which are reviewed in ref 1), with regard to both stereochemical control and preservation of the chiral reagent. A number of significant applications of the new process can be foreseen, for example, in the synthesis of chiral

α-amino acids labeled isotopically, chiral α-amino acids of unusual structure which are not readily available from natural sources, or chiral α-amino acids of unnatural configuration.

X-Ray Diffraction Studies and Stereochemistry of Racemic 30. As indicated in the earlier part of this discussion, the assignment of absolute configuration to the chiral reagents **14** and **21** rests partly on chemical correlations and partly on the determination of relative configurations at the three chiral centers in the hydrazino lactone **30** by X-ray crystallographic analysis of the racemic form. The details of the X-ray study are described in this section.

Monoclinic needles of racemic **30**, obtained from ethanol–pentane solvent mixtures, were cut to approximately cubic shape of average dimension 0.15 mm for the analysis. The following data were derived for these crystals ($C_{18}H_{16}N_2O_2$): mol wt 232; a = 9.19 ± 0.01; b = 10.20 ± 0.01; c = 14.47 ± 0.01; β = 117° 10′ ± 15′; Z = 4; $P2_1/c$; D_{calcd} = 1.280 g/cm³; D_{measd} = 1.275 g/cm³; intensity data (Cu Kα; λ = 1.542 Å) from reciprocal lattice layers $h0l$–$h7l$ and $0kl$–$4kl$ were measured on a Supper-Pace diffractometer using two crystals mounted along the b and a axes, respectively. After correction for the Lorentz polarization factors, the data were correlated to produce a set of 2153 independent reflections[2] which were converted to normalized structure factors $|E|$. The statistical distribution of $|E|$ values, $\langle|E|\rangle$ = 0.785, $\langle|E^2 - 1|\rangle$ = 0.954, and $\langle E^2\rangle$ = 0.962, is consistent with the centric space group.

The structure was solved through the direct determination of phase angles using a local modification of Long's iterative computer program (REL)[3] which examines the consistency of trial phase angles through application of Sayre's equation[4]

$$s(E_A) = s(\sum_{A=B+C} E_B \cdot E_C)$$

The origin-defining positive E values for reflections (136), (159), and (746) were combined with four other strong reflections to produce 16 sign permutation groups. Two hundred and fifty-two additional reflections with $|E| \geq 1.5$ were examined for consistency within each of the sign groups. The correct solution converged after three cycles of iteration and led to a consistency index

$$C = \langle|E_A \sum_{A=B+C} E_B E_C|\rangle / \langle|E_A| \sum_{A=B+C} |E_B||E_C|\rangle$$

of 0.812. The next most probable distribution required six cycles of iteration and had C = 0.612. The structure **30** was clearly evident in a Fourier synthesis using the 259 above-determined coefficients. A structure factor calculation using all 2153 reflections showed the discrepancy index to be R = 0.28 and indicated no changes in the assignment of the 259 trial phase angles.

Full-matrix least squares refinements of atomic coordinates, anisotropic temperature factors, and scale factors, using the 1331 reflections of intensity greater than three times the minimum observed value, converged to R = 0.08 (Table V). All nonmethyl hydrogen atoms were located in a difference synthesis and included, though not refined, in final least squares cycles.

The fractional atomic coordinates relative to an inversion center at the origin of axes are given in Table I, while Table II presents the thermal parameters. Internal comparisons of the molecular bond distances and angles (Table III) suggest that the average errors in the latter are 0.015 Å and 1°, rather than the least squares estimated standard deviations which, on the average, are half as large.

Table I. Fractional Atomic Coordinates[a]

Atom	x	y	z
C(1)	0.1343 (7)	0.3673 (5)	0.0913 (3)
C(2)	0.0617 (8)	0.2537 (6)	0.0426 (4)
C(3)	0.1265 (9)	0.1842 (6)	−0.0131 (4)
C(4)	0.2607 (9)	0.2313 (6)	−0.0210 (4)
C(5)	0.3371 (8)	0.3455 (6)	0.0257 (4)
C(6)	0.2695 (7)	0.4136 (5)	0.0812 (3)
N(7)	0.3162 (7)	0.5346 (5)	0.1298 (4)
C(8)	0.2198 (7)	0.5739 (6)	0.1827 (4)
C(9)	0.1000 (7)	0.4587 (6)	0.1598 (4)
N(10)	0.4679 (6)	0.5922 (4)	0.1494 (3)
C(11)	0.6063 (7)	0.5705 (5)	0.2545 (4)
C(12)	0.5633 (8)	0.4706 (5)	0.3161 (4)
O(13)	0.4403 (5)	0.4944 (3)	0.3419 (3)
C(14)	0.3306 (7)	0.6053 (5)	0.2945 (4)
C(15)	0.2457 (9)	0.6326 (6)	0.3599 (5)
O(16)	0.6415 (5)	0.3709 (4)	0.3497 (3)
C(17)	0.7574 (9)	0.5275 (7)	0.2426 (5)
H(8)	0.162	0.658	0.144
H(9)	0.115	0.422	0.231
H(9′)	−0.021	0.487	0.120
H(10)	0.440	0.694	0.140
H(11)	0.632	0.670	0.285
H(14)	0.400	0.686	0.296

[a] Esd's × 10⁴ are given in parentheses.

Table II. Thermal Parameters[a]

Atom	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	108	109	45	−17	−23	−11
C(2)	170	147	64	−30	−38	−9
C(3)	210	126	82	−39	59	−18
C(4)	254	113	66	1	53	−15
C(5)	168	110	48	−3	38	−2
C(6)	116	101	35	−3	22	5
N(7)	152	144	80	−47	79	−40
C(8)	138	119	52	10	46	14
C(9)	101	166	68	−4	48	0
N(10)	143	92	53	−18	43	−2
C(11)	135	69	60	−8	47	4
C(12)	152	79	59	16	44	8
O(13)	183	96	65	36	61	27
C(14)	164	83	58	28	59	7
C(15)	235	144	91	11	119	−9
O(16)	205	85	106	45	66	32
C(17)	138	158	106	39	86	6

[a] Of the form $\exp(-\sum_i \sum_j h_i h_j \beta_{ij})$ (values have been multiplied by 10⁴).

Substituents C(6), C(9), C(15), and C(17) of the lactone ring are clearly in the *cis* relationship (Figure 2), while the tertiary hydrogen atoms H(8), H(14), and H(11) as well as the hydrogen H(10) attached to nitrogen all were located on the opposite side of the ring. The molecular conformation is best described by two least squares planes, P and Q (Table IV) which together approximately define the positions of all atoms in the

(2) Not corrected for absorption.
(3) R. E. Long, Ph.D. Dissertation, University of California, Los Angeles, Calif., 1965.
(4) D. Sayre, *Acta Cryst.*, 5, 60 (1952).

Table III. Bond Distances and Angles[a]

Bond	Distance, A	Atoms	Angle (deg)
C(1)–C(2)	1.362 (8)	1–2–3	119.5 (6)
C(2)–C(3)	1.395 (10)	2–3–4	120.4 (6)
C(3)–C(4)	1.375 (9)	3–4–5	122.3 (6)
C(4)–C(5)	1.368 (8)	4–5–6	116.2 (6)
C(5)–C(6)	1.404 (8)	5–6–1	122.7 (5)
C(6)–C(1)	1.397 (8)	5–6–7	127.9 (6)
C(6)–N(7)	1.387 (7)	6–1–2	118.9 (5)
N(7)–C(8)	1.466 (7)	6–1–9	109.0 (5)
C(8)–C(9)	1.540 (8)	2–1–9	132.1 (6)
C(9)–C(1)	1.496 (8)	1–6–7	109.4 (5)
N(7)–N(10)	1.417 (6)	6–7–8	112.7 (5)
N(10)–C(11)	1.488 (6)	6–7–10	121.2 (5)
C(11)–C(12)	1.520 (8)	7–10–11	116.5 (4)
C(11)–C(17)	1.539 (8)	10–11–12	111.7 (4)
C(12)–O(16)	1.212 (7)	10–11–17	108.8 (4)
C(12)–O(13)	1.364 (8)	17–11–12	111.3 (5)
C(14)–O(13)	1.461 (6)	11–12–13	120.7 (5)
C(14)–C(15)	1.502 (8)	11–12–16	122.2 (6)
C(14)–C(8)	1.502 (7)	16–12–13	117.0 (5)
C(8)–H(8)	1.03	12–13–14	119.3 (4)
C(9)–H(9′)	1.04	13–14–8	108.9 (4)
C(9)–H(9)	1.03	13–14–15	107.1 (4)
N(10)–H(10)	1.06	15–14–8	115.2 (5)
C(11)–H(11)	1.09	14–8–7	110.3 (5)
C(14)–H(14)	1.04	8–7–10	123.8 (5)
		7–8–9	102.8 (4)
		14–8–9	117.4 (5)
		1–9–8	105.8 (5)

[a] Esd's $\times 10^3$ for distance and $\times 10$ for angles are given in parentheses.

tricyclic skeleton. Plane *P* through the indoline moiety, atoms 1–9, defines a dihedral angle of 59° with the plane *Q* through atoms C(11), C(12), O(13), C(14), and O(16). Atom N(10) is 0.24 and −1.14 Å from planes *P* and *Q*, respectively, while the C(6)–C(12) distance is 3.29 Å. The torsional angles which define the conformation of the seven-membered ring are included in Table VI.

Table IV. Least Squares Planes[a]

Atom	Deviation, Å	Atom	Deviation, Å
	Plane *P*		
	$+0.278X - 0.491Y + 0.826Z = -0.699$		
C(1)[b]	0.01	N(7)[b]	−0.03
C(2)[b]	−0.04	C(8)[b]	−0.01
C(3)[b]	−0.02	C(9)[b]	0.06
C(4)[b]	0.02	N(10)	0.24
C(5)[b]	0.05	C(14)	1.10
C(6)[b]	−0.06		
	Plane *Q*		
	$+0.241X + 0.493Y + 0.836Z = 6.524$		
C(8)	−1.48	O(13)[b]	0.07
N(10)	−1.14	C(14)[b]	−0.05
C(11)[b]	0.02	O(16)[b]	−0.03
C(12)[b]	−0.01		

[a] Planes are defined in terms of the orthonormal axes *X*, *Y*, *Z*, which are directed along the crystallographic axes *a*, *b*, and *c**, respectively. [b] These atoms were used to calculate the planes.

Intermolecular hydrogen bonds between the nitrogen H(10) and the carbonyl oxygen O(16) define the molecular associations along the crystallographic screw axes (Figure 3). The O---H and N–H distances are 1.99 and 1.06 Å, respectively, with an N–H---O angle of approximately 165°. All other intermolecular distances suggest van der Waals contacts.

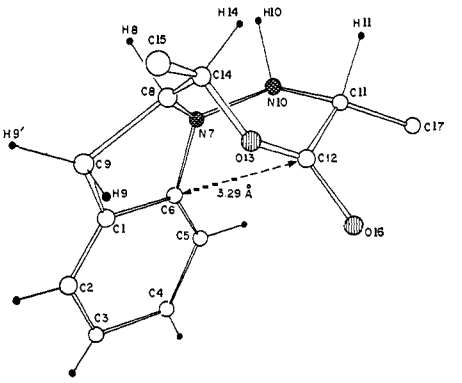


Figure 2. The molecular conformation of **30** in the crystal lattice.

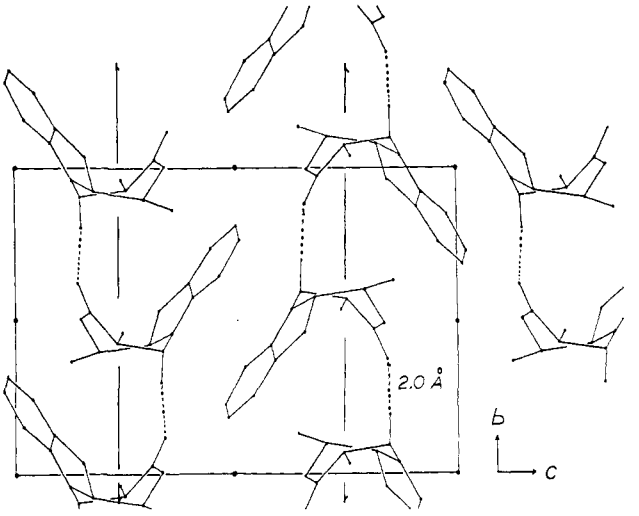


Figure 3. The hydrogen bonding of crystalline **30** along the screw axes.

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 for which shifts are given in parts per million downfield from internal tetramethylsilane. 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.

N-Benzoyl-1,2,3,4-tetrahydroquinaldine (6).[5] A vigorously stirred mixture of commercial 1,2,3,4-tetrahydroquinaldine (29.4 g, 0.2 mol) and 10% sodium hydroxide solution (100 ml) cooled in ice was treated with benzoyl chloride (29.4 g, 0.21 mol). Within a few minutes the benzoyl derivative started separating as a colorless solid. Ether (50 ml) was added to cause loosening of any lumps formed, and stirring was continued for 2 hr. Nitrogen was bubbled through the mixture to evaporate ether, and the solid was collected by filtration and washed with water. Crystallization from ethanol–pentane mixture afforded 45 g (90%) of the product **6**, mp 118–119°. The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 3.3 (medium), 6.13 (strong, CO), 6.34 (weak, C=C), 6.72, 7.22 (medium), 7.4 (medium), 7.46

(5) W. J. Pope and S. J. Peachy, *J. Chem. Soc.*, **75**, 1073 (1899).

Table V. The Observed and Calculated Structure Factors on the Absolute Scale for the Racemic Hydrazino Lactone **30**

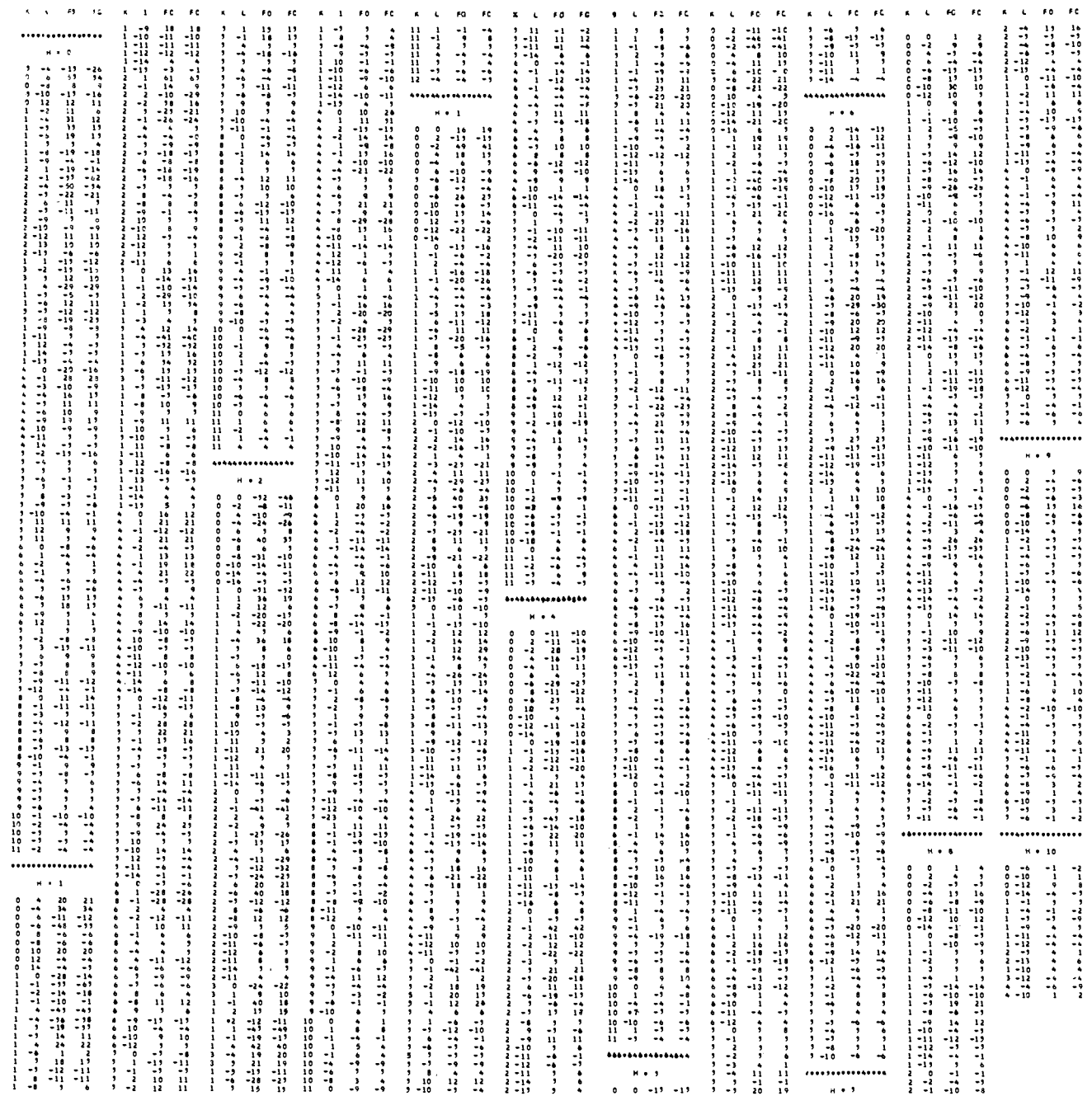


Table VI. Selected Torsional Angles[a]

Group	Angle, deg	Group	Angle, deg
7-6-1-9	−6	7-10-11-12	−9
8-9-1-6	5	10-11-12-13	63
7-8-9-1	−3	11-12-13-14	−11
9-8-7-6	0	12-13-14-8	−72
8-7-6-5	−179	13-14-8-7	53
11-10-7-6	96	14-8-7-10	38
6-7-8-14	−125	8-7-10-11	−66
9-8-7-10	164	7-10-11-17	−132
9-8-14-13	−64	10-11-12-16	−122
9-8-14-15	56	17-11-12-16	0
7-8-14-15	−174	16-12-13-14	173
2-1-9-8	176	12-13-14-15	163
8-7-6-1	4	15-14-8-9	56

[a] In sighting down the central bond, the angle is positive when the terminal atom nearest the observer must be rotated *clockwise* to eclipse the other terminal atom.

μ (medium). The nmr spectrum ($CDCl_3$) showed bands at (ppm) 1.25 (2 H, doublet, J = 6 cps), 1.62 (1 H, multiplet), 2.33 (1 H, multiplet), 2.75 (2 H, multiplet, benzylic protons), 4.86 (1 H, multiplet), 6.4–7.14 (4 H, aromatic protons), and 7.26 (5 H, aromatic, benzoyl group).

N-Benzoyl-2-(3-chloro-*n*-butyl)aniline (7). A mechanically stirred mixture of N-benzoyltetrahydroquinaldine (50 g, 0.211 mol) and phosphorus pentachloride (67.5 g, 0.3232 mol) in a flask provided with reflux condenser was heated for 2.5 hr in an oil bath maintained at 155°. The reaction mixture changed to a dark red-brown liquid. After allowing it to cool to room temperature, it was poured into a beaker containing *ca.* 500 g of ice, and the mixture was extracted with three 200-ml portions of benzene. The extract was washed four times with 50 ml of water, dried (magnesium sulfate), and evaporated under reduced pressure to give a low-melting solid which was crystallized from an ethanol–ether–pentane mixture to give 30 g (58%) of the chloro amide **7**, mp 119°. The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 2.9 (weak, NH), 3.31 (medium, CH), 5.98 (strong, CO), 6.25 (weak, C=C), 6.32 (medium), 6.63, 6.71, 6.9 (strong), 6.92 (strong), 7.22 (strong), and 8.0 μ (medium).

The nmr spectrum of **7** showed absorption at (ppm) 1.46 (3 H, doublet, J = 5.5 cps), 1.93 (2 H, quartet, methylene protons), 2.81 (2 H, triplet, benzylic protons), 4.05 (1 H, septet, tertiary proton), 7.15–7.95 (9 H, aromatic protons), and 8.16 (1 H, singlet, proton on nitrogen). The molecular weight of **7** determined mass spectrometrically was 287.1074 (calcd for $C_{17}H_{18}ClNO$: 287.1077).

Concentration of the mother liquor deposited 5 g of the starting material, mp 118–119°.

1-(2′-Benzoylaminophenyl-*trans*-2-butene (8).[6] The chloro amide **7** (2.86 g, 10 mmol) was heated at 260° and 100 mm for 15 min with stirring in a distillation flask connected to a short-path distillation apparatus. It was then distilled at 250° (1 mm). The colorless distillate which crystallized on cooling was recrystallized from dilute ethanol to furnish 2.1 g (83.5%) of **8** as a colorless solid, mp 117–118°. The infrared spectrum of **8** showed $\lambda_{max}^{CHCl_3}$ 2.9 (weak, NH), 5.98 (strong, CO), 6.24 (C=C), 6.31 (medium), 6.61 (strong), 6.91 (strong), 7.72 (medium), 7.99 (medium), and 10.3 μ (medium, *trans* olefin). The nmr spectrum ($CDCl_3$) showed peaks at (ppm) 1.72 (3 H, multiplet, methyl protons), 3.6 (2 H, broad, benzylic protons), 5.58 (2 H, unresolved broad), and 7.17–8.16 (10 H, aromatic protons and proton on nitrogen).

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 80.80; H, 6.74; N, 5.41.

1-(2′-Benzoylaminophenyl-*trans*-2,3-oxidobutene (9). To a solution of **8** (10.04 g, 0.04 mol) in 300 ml of methylene chloride–benzene mixture (1:2) cooled in ice was added *m*-chloroperbenzoic acid (8.24 g, 0.048 mol). The mixture was stirred at 0–2° for 16 hr (some colorless solid separated). The precipitate was removed by filtration and identified as *m*-chlorobenzoic acid. The solution was washed with four 25-ml portions of a 5% cold sodium bicarbonate solution and finally with water. The organic solution on evaporation under reduced pressure furnished 10 g of a thick, light brown, transparent syrup which could not be induced to crystallize. Its infrared spectrum showed λ_{max}^{neat} 2.95 (medium, NH), 3.35 (medium, CH), 6.01 (strong, C=O), 6.2 (weak, C=C), 6.3 (medium), 6.58 (strong), 6.7 (strong), 6.92 (strong), 7.28 (weak), 7.68 (strong), 7.95 (medium), and 11.7 μ (medium, epoxide). This material was employed in the next step without further purification.

(±)-2-(1-Hydroxyethyl)indoline (10). The epoxide **9** obtained as described above was taken up in a mixture of 50 ml of methanol and 50 ml of 2 N potassium hydroxide solution. The reaction mixture immediately developed a dark brown color. It was heated under reflux for 10 hr in an atmosphere of nitrogen. Methanol was removed under reduced pressure, and the remaining aqueous portion was extracted with three 70-ml portions of ether. The extract was first dried over potassium hydroxide pellets and then over anhydrous magnesium sulfate. Evaporation of ether gave 5.1 g of crude indoline as a thick syrup. It was dissolved in 75 ml of ether and treated with dry hydrochloric acid gas until the supernatant solution did not deposit any solid. The colorless crystalline hydrochloride was collected on filter and washed with ether. One recrystallization from ethanol–ether mixture furnished 4.15 g (64% for three steps) of the hydrochloride of **10** as colorless crystals, mp 175–176°.

Anal. Calcd for $C_{10}H_{14}ClNO$: C, 60.20; H, 7.17; N, 7.17; Cl, 17.80. Found: C, 60.06; H, 7.21; N, 6.98; Cl, 17.76.

An ice-cooled solution of the hydrochloride (3.98 g, 0.02 mol) in 10 ml of water was treated with 20 ml of 5 N potassium hydroxide, and the liberated base was extracted with three 30-ml portions of ether. The ether extract was dried as before. Evaporation of the solvent gave 3.1 g (95%) of the racemic indoline **10** as a colorless oil which crystallized on keeping, mp 47–48°. The infrared spectrum had $\lambda_{max}^{CHCl_3}$ 2.91 (strong, NH, OH), 6.22 (medium), 6.75 (strong), 6.86 (medium), 8.05 (medium), and 13.4 μ (strong). The nmr spectrum ($CDCl_3$) showed peaks at (ppm) 1.05 (3 H, doublet, J = 6 cps, methyl protons), 2.82 (2 H, doublet, J = 10 cps, benzylic protons), 3.7 (2 H, multiplet, tertiary protons), 4.0 (2 H, singlet, exchangeable protons), and 6.3–6.95 (4 H, multiplet, aromatic protons).

Resolution of (±)-10. A. 2-(1-Hydroxyethyl)-1-*o*-carboxybenzoylindoline (11). To a solution of the (±)-indoline **10** (0.815 g, 5 mmol) in 50 ml of benzene was added phthalic anhydride (0.74 g, 5 mmol), and the mixture was heated under gentle reflux for 6 hr with stirring. The reaction mixture was cooled, and the crystalline product was collected on filter. Recrystallization of the solid from aqueous ethanol gave 1.2 g (80%) of racemic **11** as colorless crystals, mp 186–188°. The infrared spectrum had λ_{max}^{Nujol} 2.9 (weak, OH), 3.43 (strong, CH), 5.9 (strong, acid CO), 6.11 (strong, amide CO), 6.3 (weak, C=C), 6.75 (strong), 6.87 (medium), 7.19 (strong), and 7.86 μ (medium).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.40; H, 5.50; N, 4.50. Found: C, 68.89; H, 5.62; N, 4.34.

B. Brucine Salt of 11. To a solution of the phthaloyl derivative (6.22 g, 20 mmol) in 100 ml of ethyl acetate was added brucine (7.32 g, 20 mmol). The initially clear solution gave rise to a thick insoluble gum. The solvent was evaporated under reduced pressure, and the residue was triturated with 50 ml of ethanol, after which a colorless solid crystallized. This was collected on filter and washed with ethanol. After three recrystallizations from ethanol, it had a constant specific rotation, $[\alpha]^{27}D$ −86.89°, $[\alpha]^{27}_{546}$ −106.06° (c 0.45, methanol), the yield being 3.5 g (52%), mp 227–228°.

Anal. Calcd for $C_{41}H_{43}N_3O_8$: C, 69.77; H, 6.11; N, 5.95. Found: C, 69.16; H, 6.36; N, 5.80.

C. (−) Form of 11. A solution of the brucine salt of **11** (7.4 g) in methylene chloride (100 ml) was extracted with four 25-ml portions of 0.2 N potassium carbonate solution. The basic aqueous solution after cooling in ice was acidified with 21 ml of 1 N hydrochloric acid and extracted with three 60-ml portions of methylene chloride. The extract was dried (anhydrous magnesium sulfate) and evaporated to give 3.3 g of resolved **11** as a colorless solid. Recrystallization of this solid from dilute ethanol furnished 2.9 g (85%) of (−)-**11**, mp 173–174°, $[\alpha]^{27}D$ −120.1°, $[\alpha]^{27}_{546}$ −144.3° (c 0.442, methanol).

The infrared spectrum in chloroform solution was identical with that of the racemic material.

D. (−)-(*S*)-2-[(*R*)-1-Hydroxyethyl]indoline (12). A mixture of (−)-**11** (2.9 g) in 20 ml of methanol and 30 ml of 10% potassium hydroxide was refluxed for 10 hr under nitrogen atmosphere. Most of the organic solvent was removed under reduced pressure, and the residue was extracted with four 50-ml portions of ether. The extract was first dried over potassium hydroxide and then over anhydrous magnesium sulfate. Evaporation of ether furnished 1.23 g (86%) of (−)-**12** as a colorless oil which crystallized on keeping, mp 64–65°, $[\alpha]^{28}D$ −21.1°, $[\alpha]_{546}$ −26.8° (c 0.556, methanol).

The infrared and nmr spectra of the resolved material were identical with those of the racemic hydroxyindoline **10**.

1-Nitroso-(*S*)-2-[(*R*)-1-hydroxyethyl]indoline (13). To an ice-cooled stirred solution of (−)-indoline **12** (1.141 g, 7 mmol) in 0.1 N hydrochloric acid (70 ml) was added dropwise a solution of sodium nitrite (0.483 g, 7 mmol) in 10 ml of water. The nitroso derivative separated immediately as a dirty yellow solid. After 15 min the reaction mixture was extracted with three 50-ml portions of ether, washed with water, and dried over anhydrous magnesium sulfate. Removal of the organic solvent under reduced pressure gave 1.3 g of the product **13** as a crystalline yellow solid which was recrystallized from ethanol–pentane mixture as shining pale crystals (1.13 g, 85%), mp 112–113°, $[\alpha]^{27}D$ −368.65° (c 0.67, methanol), $[\alpha]^{27}_{578}$ −409.04° (c 0.6). The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 2.9 (weak, OH), 6.25 (weak, C=C), 6.75, 6.84 (medium), 7.18, 7.74 (strong), and 8.5 μ (medium). The nmr spectrum ($CDCl_3$) showed peaks at (ppm) 1.02, 1.27 (3 H, pair of doublets, ratio 4:1, J = 6.5 cps, methyl protons), 3.07 (1 H, doublet, J = 11 cps), 3.25 (1 H, doublet, J = 11 cps, benzylic protons as AB quartet), 4.23 (1 H, doublet of quartets, J = 6.5 cps, spacing = 1.75 cps, tertiary proton on carbon bearing hydroxyl), 4.79 (1 H, doublet of triplets, J = 7 cps, spacing = 1.5 cps, tertiary proton on five-membered ring), and 7.12–7.87 (4 H, multiplet, aromatic protons).

The racemic material had mp 103–104° and identical spectra.

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.27; H, 6.38; N, 14.36.

1-Amino-(*S*)-2-[(*R*)-1-hydroxyethyl]indoline (14). To a slurry of lithium aluminum hydride (0.627 g, 16.5 mmol) in 50 ml of ether was added slowly a solution of the *l*-N-nitrosoindoline **13** (1.05 g, 5.5 mmol) in 50 ml of the same solvent. After stirring the reaction mixture for 8 hr at 25°, it was refluxed for 30 min, then cooled in an ice bath. The excess hydride was destroyed by the addition of 4.5 ml of saturated solution of sodium sulfate under nitrogen atmosphere. The mixture of inorganic salts was filtered and washed with ether (25 ml). After drying the ether solution over anhydrous magnesium sulfate, the solvent was evaporated to give 0.91 g (93%) of **14** as a colorless syrup which crystallized on keeping, mp 105°, $[\alpha]^{26}D$ −24.3°, $[\alpha]^{26}_{578}$ −25.7° (c 1, ethanol). The nmr spectrum ($CDCl_3$) showed peaks at (ppm) 1.22 (3 H, doublet, J = 6.5 cps), 2.75–3.5 (6 H, multiplet), 4.3 (1 H, doublet of quartets, tertiary proton on carbon bearing hydroxyl group), and 6.72–7.33 (4 H, multiplet, aromatic protons).

(6) *Cf.* J. v. Braun and A. Steindorff, *Ber.*, **37**, 4723 (1904).

The racemic amino indoline, mp 100°, obtained in the same manner had identical nmr spectrum.

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.22; H, 7.89; N, 15.63.

1-Trifluoroacetyl-2-carboxyindoline (16). To a solution of 3.26 g (2 mmol) of 2-carboxyindoline prepared by saponification of the ethyl ester[1] in trifluoroacetic acid (15 ml) cooled to −10° was slowly added 5.04 g (2.4 mmol) of trifluoroacetic anhydride over a period of 15 min.[7] After stirring for an additional 15 min at this temperature, the reaction mixture was allowed to attain room temperature (*ca.* 0.5 hr). The excess anhydride and the solvent were removed under reduced pressure to give a light brown solid residue. It was taken up in *ca.* 150 ml of ether when a small amount (70 mg) of a high melting solid was left undissolved which was filtered and discarded. The ether solution was evaporated, and the residue was crystallized once from carbon tetrachloride after clarifying with Norit to give **16**, mp 147°, 4.6 g (89%); $\lambda_{max}^{CHCl_3}$ 5.75 (strong, CO, acid), 5.86 (strong, CO, amide), 6.26 (weak, C=C), 6.75 (medium), 7.06 (medium), 7.97 (medium), 8.7 (strong), and 9.2 μ (strong).

Anal. Calcd for $C_{11}H_8F_3NO_3$: C, 50.96; H, 3.09; N, 5.40. Found: C, 51.42; H, 3.33; N, 5.20.

1-Trifluoroacetyl-2-diazoacetylindoline (17, X = CHN_2). To a solution of N-trifluoroacetylindoline acid **16** (2.59 g, 10 mmol) in 25 ml of dry dioxane was added thionyl chloride (2.38 g, 20 mmol), and the mixture was heated under gentle reflux for 0.5 hr with exclusion of moisture. The solvent and the excess thionyl chloride were removed under vacuum with complete exclusion of moisture. The semisolid acid chloride was taken up in 20 ml of dry dioxane and injected slowly into a well stirred ice-cooled solution of dry diazomethane (25 mmol in 100 ml of ether, distilled from barium oxide and kept over sodium wire for 2 hr). The reaction mixture was allowed to stand at ice bath temperature for 1 hr and then at 25–26° for 1 hr. The excess diazomethane was removed under vacuum, and the solution was filtered through Celite 545. The filtrate on evaporation gave a pale solid which was crystallized from carbon tetrachloride to give 2.4 g (85.6%) of the diazo ketone **17**, X = CHN_2, as off-white crystals, mp 124.7–125.7°. The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 4.7 (strong, diazo), 5.89 (strong, >NCOCF$_3$), 6.1 (medium, ketone), 6.78 (weak), 7.36 (medium), 8.0 (medium), and 8.7 μ (strong). The nmr spectrum ($CDCl_3$) exhibited peaks at (ppm) 2.95–3.82 (2 H, broad multiplet, benzylic protons), 5.04 (1 H, broad doublet, tertiary proton), 5.25 (1 H, singlet, diazo methine proton), 7.2 (3 H, broad multiplet, aromatic protons), and 8.13 (1 H, broad multiplet, aromatic proton nearest to the ring nitrogen). The molecular weight determined mass spectrometrically was 283.0564 (calcd for $C_{12}H_8F_3N_3O_2$: 283.0568).

Anal. Calcd for $C_{12}H_8F_3N_3O_2$: C, 50.88; H, 2.82; N, 14.82. Found: C, 50.96; H, 2.99; N, 14.45.

1-Trifluoroacetyl-2-bromoacetylindoline (17, X = CH_2Br). A slow stream of hydrogen bromide was passed through a solution of 2.83 g (10 mmol) of the diazo ketone **17**, X = CHN_2, in 100 ml of ether at 20° until no more effervescence due to the evolution of nitrogen was perceptible. The excess hydrogen bromide was removed by simply evaporating with excess carbon tetrachloride. The solid residue thus obtained was dissolved in methylene chloride (100 ml) and washed with 1% sodium bicarbonate solution. After drying the organic solution (magnesium sulfate), the solvent was evaporated to give 3.3 g of a highly crystalline colorless solid, mp 121.5–123°, which was once recrystallized from dry ethanol to give 3 g (90%) of the bromo ketone **17**, X = CH_2Br, as colorless crystals, mp 122.3–123.3°. The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 5.75 (medium, ketone), 5.85 (strong, >NCOCF$_3$), 6.25 (weak, C=C), 6.75 (medium), 6.84 (weak), 7.0 (medium), 7.95 (medium), and 8.72 μ (strong). The nmr spectrum ($CDCl_3$) had peaks at (ppm) 3.3–3.72 (2 H, multiplet, benzylic protons), 4.25 (2 H, singlet, methylene protons), 5.65 (1 H, broad doublet, J = 11.5 cps, tertiary proton), 8.2 (1 H, broad multiplet, aromatic proton nearest to nitrogen), and 7.22 (3 H, broad multiplet, aromatic protons).

The molecular weight of **17**, X = CH_2Br, determined mass spectrometrically was 334.9769 (calcd for $C_{12}H_9BrF_3NO_2$: 334.9771).

1-Trifluoroacetyl-2-acetylindoline (17, X = CH_3). To a stirred solution of the bromo ketone **17**, X = CH_2Br (6.72 g), in a mixture of anhydrous ether (250 ml) and glacial acetic acid (13 ml), zinc dust (13 g) was added in small portions. After 2 hr the reaction mixture was filtered through Celite 545 and the filter cake washed with ether. The filtrate was evaporated *in vacuo*, and the residue dissolved in methylene chloride (300 ml) was washed with 2% sodium bicarbonate solution and then with water. The methylene chloride solution after drying (magnesium sulfate) was evaporated to give a solid residue which was once crystallized from ethanol to furnish 4.7 g (87%) of **17**, X = CH_3, as a colorless crystalline solid, mp 108.5–109.5°. The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 5.76 (medium, CO, ketone), 5.86 (strong, CO, trifluoroacetylamide), 6.25 (weak, C=C), 6.74 (medium), 6.83 (weak), 7.02 (medium), 7.95 (medium), 8.32 (strong), and 8.7 μ (strong). The nmr spectrum ($CDCl_3$) had peaks at (ppm) 2.17 (3 H, singlet, methyl protons), 5.2–5.3 (1 H, doublet, J = 11.5 cps, tertiary proton), 7.28 (3 H, broad multiplet, aromatic protons), and 8.2 (1 H, broad multiplet, aromatic proton nearest to nitrogen).

Anal. Calcd for $C_{12}H_{10}F_3NO_2$: C, 56.40; H, 3.89; N, 5.83. Found: C, 55.98; H, 3.83; N, 5.82.

Borohydride Reduction of 1-Trifluoroacetyl-2-acetylindoline (17, X = CH_3) to 18. To a solution of sodium borohydride (0.151 g, 4 mmol) in 10 ml of ethanol cooled in ice was added dropwise a solution of the ketone **17**, X = CH_3 (0.514 g, 2 mmol) in 10 ml of dry ethanol. After 0.5 hr the mixture was warmed to 40° for 0.5 hr. A saturated solution prepared from 1.5 g of sodium potassium tartrate was added, and the mixture was evaporated under reduced pressure to remove most of the ethanol. The residue was taken up in water (10 ml) and extracted with three 25-ml portions of ether. After drying the extract (magnesium sulfate), it was evaporated to give 280 mg (87%) of a thick colorless oil. Thin layer chromatographic (tlc) analysis of the product (ether development, silica gel) showed two overlapping spots (R_f 0.45). The infrared spectrum of the mixture of diastereomeric alcohols showed $\lambda_{max}^{CHCl_3}$ 2.9 (medium, OH, NH), 6.23 (strong, C=C), 6.76 (strong), 6.87 (strong), and 8.5 μ (strong). The nmr spectrum of the mixture (CCl_4) exhibited peaks at (ppm) 1.1 (3 H, doublet with shoulders, J = 5 cps, methyl protons), 2.3–3.12 (2 H, multiplets, benzylic protons), 4.28 (2 H, broad singlet, OH and NH protons), and 6.35–6.97 (4 H, multiplet, aromatic protons). A solution of 4.7 g of the diastereomeric mixture in 150 ml of ether was treated with excess dry hydrochloric acid gas dissolved in ether until no more precipitation of the salt was observed on treatment of the supernatant liquid with gaseous hydrogen chloride. The precipitate was filtered and washed with ether to give 5 g of the white solid, mp 203–213°. It was recrystallized from ethanol–ether (2:1) mixture to furnish 2.8 g of the salt, mp 212–214°. A second recrystallization from the same solvent mixture furnished 2.3 g of the salt, mp 215–217°. Mother liquors on standing deposited more solid which was collected and recrystallized as before to give another 0.6 g of the salt, mp 215–217°. The total yield of the hydrochloride of (±)-**18** was 50%. The infrared spectrum had λ_{max}^{KBr} 2.95 (strong, OH, NH), 3.5–3.98 (strong, N^+H_2), 6.39 (medium, C=C), 6.79 (medium), 6.86 (medium), and 7.27 μ (medium).

Anal. Calcd for $C_{10}H_{14}ClNO$: C, 60.20; H, 7.17; N, 7.17. Found: C, 60.30; H, 7.13; N, 6.92.

To a solution of the purified hydrochloride of **18** (225 mg, 1.125 mmol) in water (3 ml) was added 5 *N* sodium hydroxide (10 ml), and the mixture was extracted with two 25-ml portions of ether. The extract was dried (magnesium sulfate) and evaporated to give 183 mg (95%) of the indoline **18** as a colorless solid, mp 44–46°. The infrared spectrum in chloroform was identical with that of the original diastereomeric mixture while in the nmr spectrum (CCl_4) the doublet due to the methyl group at 1.1 ppm was sharper and had no shoulders.

An analytical sample of the indoline **18** was obtained by one recrystallization from hexane–ether mixture, mp 49.8°.

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.47; H, 8.11; N, 8.43.

(±)-1-Nitroso-2-(1-hydroxyethyl)indoline (19). To a solution of the (±)-indoline **18** (0.163 g, 1 mmol) in ether (30 ml) cooled in an ice bath was added 0.1 *N* hydrochloric acid (10 ml). A solution of sodium nitrite (0.069 g, 1 mmol) in 2 ml of water was added dropwise with stirring which caused the aqueous layer to become light orange in color. After stirring for about 30 min, the ether layer was separated and the aqueous portion extracted with 20 ml of ether, the combined ether extracts were washed with water (10 ml), dried (magnesium sulfate), and evaporated to give 0.165 g of a light yellow oil. It was purified on a silica gel (PF_{254}) thick layer plate using a mixture of ether and benzene (1:3) for developing. The nitrosoindoline **19** (R_f 0.45) was obtained as a light pale oil (0.145 g, 78%) which crystallized on keeping, mp 76–77°. A small amount of the starting material (5 mg) which had lower R_f than the product was recovered. The infrared spectrum of the nitrosoindoline **19** showed $\lambda_{max}^{CHCl_3}$ 2.65 (shoulder), 2.85 (medium, OH), 3.3, 6.75 (medium), 6.83 (medium), 7.11 (strong, broad, NO),

(7) *Cf.* F. Weygand and R. Greiger, *Ber.*, **89**, 647 (1956).

and 7.73 μ (strong). The nmr spectrum in deuteriochloroform exhibited a pair of doublets at 1.03 and 1.26 ppm with an area ratio 6:1 (J = 6 cps) attributable to the methyl group. The benzylic protons appeared as a doublet at 3.18 ppm (J = 7 cps) with a partly overlapping peak due to the hydrolic proton at 3.04. The tertiary proton on the indoline nucleus appeared as a quartet (spacing *ca.* 6.5 cps) which appears to result from a fortuitous overlap of two triplets, as the two middle peaks had partly resolved shoulders. This assignment was verified by a double resonance experiment. Irradiation of the benzylic protons' resonance frequency caused the quartet to collapse to a doublet (J = 6.5 cps). The tertiary proton attached to the carbon bearing the hydroxyl group appeared as a sextet which dould have resulted from a partial overlap of a pair of quartets (the two middle peaks were of greater intensity than the rest). A decoupling experiment supported this assignment. The sextet collapsed to a doublet (J = 6.5 cps) upon irradiation at the methyl resonance frequency. Out of the four aromatic protons three appeared as a doublet (J = 3.5 cps) and one as a multiplet at 7.8 ppm. An analytical sample of **19** was prepared by recrystallization from ethanol–pentane solution, mp 78–78.5°.

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.40; H, 6.30; N, 14.27.

(±)-1-Amino-2-(1-hydroxyethyl)indoline (20). To a stirred suspension of lithium aluminum hydride (95 mg, 2.5 mmol) in ether (25 ml) was added dropwise a solution of the nitroso compound **19** (144 mg, 0.75 mmol) in 30 ml of the same solvent. The reaction mixture was stirred at room temperature for 2 hr, then heated under gentle reflux for 0.5 hr and worked up in the usual way to give a colorless syrup which crystallized on storage at 0–2° overnight and was once recrystallized from hexane to furnish 105 mg (80%) of colorless solid, mp 54–56°. The infrared spectrum showed $\lambda_{max}^{CCl_4}$ 2.94 (strong, OH and NH_2), 3.3 (medium, CH), 6.2 (weak, C=C), 6.75 (medium), 6.96 (medium), and 8μ (medium). The nmr spectrum (CCl_4) exhibited peaks at (ppm) 1.07 (3 H, doublet, J = 6 cps, methyl protons), 2.4–4.1 (4 H, multiplet, benzylic and tertiary protons), 4.31 (3 H, singlet, exchangeable protons), and 6.48–7.15 (4 H, multiplet, aromatic protons).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.90; N, 15.72. Found: C, 67.33; H, 8.00; N, 15.53.

(−)-1-Amino-(*S*)-[(*S*)-2-hydroxyethyl]indoline (21). To a solution of (+)-10-camphorsulfonic acid (1.16 g, 5 mmol) in dry ethanol (15 ml) was added a solution of the racemic indoline **20** (0.89 g, 5 mmol) in 50 ml of ether which caused a white solid to separate immediately. More ether was added until no further precipitation was observed. The colorless solid was collected on filter and washed with ether. Four recrystallizations at 20–21° from dry ethanol furnished 300 mg (30%) of the salt, mp 167–168°, $[\alpha]^{27}D$ +11.6° (*c* 2.6, methanol).

Anal. Calcd for $C_{20}H_3N_2O_5S$: C, 58.52; H, 7.37; N, 6.82. Found: C, 57.88; H, 7.37; N, 6.42.

In order to obtain the free resolved base, the salt (300 mg) was treated with 10 ml of 10% potassium hydroxide, and the basic solution was extracted with three 25-ml portions of ether. The ether extract was first dried over potassium hydroxide pellets and then over anhydrous magnesium sulfate. Evaporation of the solvent gave 122 mg (94%) of the free resolved base **21** as a colorless oil which crystallized on keeping, mp 72–73.5°, $[\alpha]^{27}D$ −28.06° (*c* 0.588, methanol). Its infrared and nmr spectra were identical with those of the racemic material.

Jones Oxidation of (−)-1-Nitroso-(*S*)-2-[(*R*)-1-hydroxyethyl]-indoline (13). To a solution of (−)-nitrosoindoline **13**, $[\alpha]^{27}D$ −368.65° (*c* 0.67, methanol) (9.6 mg, 0.05 mmol), in acetone (1 ml) cooled in ice was added 2.25 *M* Jones reagent (0.075 ml). The mixture was allowed to stir for 15 min at ice-bath temperature, after which it was diluted with 4 ml of ice-water and extracted with three 10-ml portions of ether. The extract was washed in water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to give 6.5 mg of pale needlelike crystals, mp 96–97.5°. The product was recrystallized from ether–pentane to give colorless crystals (4.5 mg), mp 98°, $[\alpha]^{27}D$ −338.4° (*c* 0.396, ethanol). The infrared spectrum of this product was identical with that of the racemic ketone prepared in the same way from the N-nitroso derivative of (±)-**10** or from (±)-**19** (see below).

Racemic 1-Nitroso-2-acetylindoline from (±)-19. To a solution of 96 mg (0.5 mmol) of the nitroso alcohol in acetone (3 ml) cooled in ice was added dropwise (in ~5 min) Jones reagent (0.33 ml, 2.25 *M* solution). The mixture was stirred at 0° for 15 min, after which it was diluted with water (25 ml), basified (pH 8) with 2% sodium carbonate solution, and extracted with three 25-ml portions of ether. The extract after drying (magnesium sulfate) was evaporated to give a light yellow solid which was recrystallized from ethyl acetate–pentane mixture to give 70 mg (74%) of solid, mp 103–104°, $\lambda_{max}^{CHCl_3}$ 3.34 (CH), 5.8 (C=O), 6.28 (C=C), 6.77, 6.84, 7.1, 7.39, 7.75, and 8.56 μ. The nmr spectrum ($CDCl_3$) showed peaks at (ppm) 2.17 (3 H, singlet, methyl protons), 2.8–3.73 (2 H, multiplet, benzylic protons), 5.14 (1 H, doublet of doublets, J = 10 and 5 cps, tertiary proton), and 7.1–7.9 (4 H, multiplet, aromatic protons). The N-nitroso ketone obtained from (±)-**10** had mp 103–104°, undepressed upon admixture with the above product, and superimposable infrared and nmr spectra.

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.53; N, 14.73. Found: C, 63.17; H, 5.45; N, 14.90.

Conversion of (−)-21 to (−)-22 by Jones Oxidation. A solution of the 1-aminoindoline (−)-**21**, $[\alpha]^{27}D$ −28.06° (*c* 0.87, ethanol) (17.8 mg, 0.1 mmol), in a mixture of 0.1 *N* hydrochloric acid (0.1 ml) and dimethoxyethane (2 ml) was hydrogenated at ordinary pressure for 2 hr after addition of 18 mg of palladium hydroxide-on-carbon catalyst. The mixture was filtered through Celite 545 and worked up in the usual way to give (*S*)-2-[(*S*)-1-hydroxyethyl]-indoline as a colorless syrup (15.5 mg, 94%) which crystallized on keeping, mp 51–52°, $[\alpha]^{27}D$ +47.1° (*c* 0.83, ethanol). The nmr spectrum was identical with that of (±)-**18**. This indoline was subjected to N-nitrosation in the usual way to give after purification by preparative thin layer chromatography (silica gel PF_{254}, R_f 0.5, ether–benzene, 1:1) 13.5 mg (70%) of **22** as light yellow crystals, mp 81–82°, $[\alpha]^{27}D$ −268.4° (*c* 1.15, ethanol). The infrared spectrum in chloroform was identical with that of a sample of the racemic nitrosoindoline **19**. Jones oxidation of the (−)-nitrosoindoline **23** according to the procedure employed above furnished the (−)-nitroso ketone **22**, mp 98°, in 60% yield, $[\alpha]D$ −340.5° (*c* 0.205, ethanol). The mixture melting point of this with the sample of the (−)-nitroso ketone **22** obtained from (−)-**13** showed no depression. Further, the infrared spectra of the nitroso ketone from the two sources were indistinguishable.

***p*-Nitrophenyl Pyruvate.** To a stirred solution of *p*-nitrophenol (2.78 g, 0.02 mol) and 1-ethyl-3-(3′-dimethylamino)propyl carbodiimide[8] (5.74 g, 0.03 mol) in 100 ml of 1:2 methylene chloride–acetonitrile mixture cooled in an ice–salt bath was added pyruvic acid (2.64 g, 0.03 mol) over a period of 5 min. After 0.5 hr the reaction mixture was allowed to warm to 24° and kept at this temperature for 2 hr. The clear reaction mixture was washed with three 40-ml portions of water and the organic solution evaporated to give a light yellow oil which was suspended in 50 ml of water. After stirring for 10 min at 25°, the aqueous solution was drained out and this operation was repeated. The oil solidified on keeping and was crystallized from benzene–pentane mixture to give 1.8 g (43%, based on phenol) of the ester, mp 79–80°. The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 5.73 (strong, CO, ester), 5.8 (strong, CO, ketone), 6.24 (weak, C=C), 6.34 (medium), 6.6 (strong, NO_2), 6.78 (medium), 7.47 (strong, NO_2), and 9 μ (strong, C—O—C).

Anal. Calcd for $C_9H_7NO_5$: C, 51.61; H, 3.37; N, 6.70. Found: C, 51.45; H, 3.49; N, 6.69.

***p*-Nitrophenyl α-Ketobutyrate.** To a stirred solution of *p*-nitrophenol (1.39 g, 0.01 mol) and 1-ethyl-3-(3′-dimethylamino)propyl carbodiimide[8] (2.86 g, 0.015 mol) in a 1:2 methylene chloride–acetonitrile mixture (100 ml) cooled in ice–salt bath was added dropwise a solution of 2-ketobutyric acid (1.53 g, 0.015 mol) in 15 ml of the same solvent mixture. After 30 min the reaction mixture was allowed to attain room temperature (25°) and kept for 2 hr. It was then washed with water, and the solvent was evaporated under reduced pressure. A pale solid thus left was suspended in 30 ml of water and stirred for 5 min and collected on filter after washing with water (10 ml). Crystallization of the solid from ethyl acetate–pentane mixture gave 1 g (44%) of the ester as off-white crystals, mp 101°. The infrared spectrum had $\lambda_{max}^{CHCl_3}$ 5.7 (strong, CO, ester), 5.76 (strong, CO, ketone), 6.2 (weak, C=C), 6.3 (medium), 6.6 (strong, NO_2), 6.75 (medium), 7.49 (strong, NO_2), and 9.2 μ (strong, C—O—C).

Anal. Calcd for $C_{10}H_9NO_5$: C, 53.82; H, 4.06; N, 6.28. Found: C, 53.62; H, 4.24; N, 5.80.

Hydrazono Lactone 24 (Chart IV). To an ice-cooled solution of *p*-nitropyruvate (0.23 g, 1.1 mmol) in 30 ml of ether was added slowly with shaking a cooled solution of the S_NR_O N-aminoindoline **14** (0.196 g, 1.1 mmol) in 30 ml of the same solvent. The clear reaction mixture was stored at 0–2° for 12 hr, after which it was allowed to warm to 25° and kept for 2 hr. Evaporation of the solvent afforded the hydrazono-*p*-nitrophenyl ester as a deep yellow semisolid (0.405

(8) J. C. Sheehan and P. A. Cruickshank, *Org. Syn.*, **48**, 83 (1968).

g) which was used in the next step without further purification. The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 2.8 (weak, OH), 3.33 (weak, CH), 5.8 (strong, CO), 6.25 (weak, C=C), 6.67 (C=N), 6.75, 6.87, 7.43 (strong), 8.0–8.3 (broad), 8.89, and 9.12 μ (strong). A sample of the racemic material obtained in a similar manner had an identical infrared spectrum. A solution of the hydrazono ester (0.405 g) in 100 ml of dry benzene was heated at reflux for 6 hr after addition of triethylamine (0.166 g, 1.65 mmol) under a nitrogen atmosphere. The reaction mixture was diluted with 50 ml of *n*-pentane and washed sequentially with three 20-ml portions of cold water, three 25-ml portions of 1% sodium bicarbonate solution, and two 20-ml portions of cold water. After drying the organic solution over anhydrous magnesium sulfate, it was evaporated under reduced pressure to give the hydrazono lactone **24** as a solid. Recrystallization from an ethanol–pentane mixture furnished 0.18 g (70% for two steps) of **24** as pale yellow crystals, mp 175–176°, $[\alpha]^{27}D$ −759.0° (*c* 0.46, methanol).

The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 3.3 (weak, CH), 5.98 (strong, CO), 6.22 (weak, C=C), 6.3 (weak), 6.48 (strong, C=N), 6.78 (strong), 6.88 (medium), 7.25 (medium), 8.31 (strong), 8.89 (medium), and 10.78 μ (medium). The nmr spectrum ($CDCl_3$) exhibited peaks at (ppm) 1.28 (3 H, doublet, J = 7 cps, methyl group on carbon carrying oxygen), 2.35 (3 H, methyl group on carbon on double bond), 2.67–3.75 (2 H, multiplet, benzylic protons), 4.28–4.34 (2 H, multiplet, tertiary protons), and 6.8–7.3 (4 H, multiplet, aromatic protons). The racemic lactone obtained in a similar manner had mp 146–147° and identical spectral properties.

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.42; H, 6.37; N, 11.94.

Hydrazino Lactone 30. To an ice-cooled solution of the *l*-hydrazono lactone **24** (99 mg, 0.426 mmol) in dimethoxyethane (6 ml) was added aluminum amalgam prepared from 99 mg of aluminum foil. The mixture was treated with water (0.6 ml) and stirred for 14 hr at 0°. It was then filtered through Celite 545 and the filter cake washed with 1:1 benzene–ethyl acetate mixture (15 ml). The filtrate on evaporation *in vacuo* gave 94.8 mg (95%) of a colorless crystalline solid, mp 137–138°. An analytical sample was prepared by recrystallization of 22 mg of the material from ethanol–pentane to give 17 mg of needlelike crystals, mp 144°, $[\alpha]D$ −50.0° (*c* 0.38, ethanol), $\lambda_{max}^{CHCl_3}$ 5.75 and 5.83 (shoulder) (C=O), 6.23 and 6.27 (shoulder) (C=C), 6.75, 6.92, 8.5, 8.7, 9.03, and 9.33 μ.

The nmr spectrum of **24** ($CDCl_3$) at 100 MHz had peaks at (ppm) 1.4 and 1.6 (6 H, doublets, J = 7 cps, due to the protons of the two methyl groups), 2.7 (1 H, doublet, J = 3.5 cps) and 2.88 (1 H, singlet) (due to benzylic protons), 3.46 (1 H, broad peak, due to the proton on nitrogen overlapping the multiplet at 3.63 (1 H) due to the teritary proton on the indoline nucleus), 4.3 (1 H, quartet, J = 7.0 cps, due to the tertiary proton on the carbon flanked by nitrogen and the carbonyl group), 4.83 (1 H, multiplet, due to the tertiary proton on the carbon bearing oxygen), and 6–7.25 (4 H, multiplet, due to the aromatic protons). These assignments were confirmed by double and triple resonance experiments. Upon simultaneous irradiation at the methyl and benzylic resonances, the multiplets at 4.83 and 3.63 collapsed into doublets with J = 3.7 cps in each case.

The racemic lactone prepared in the same manner had identical spectra and had mp 170–171°. This material was employed for the X-ray crystallographic study described earlier.

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.97; N, 12.06. Found: C, 67.08; H, 6.97; N, 12.04.

Hydrolysis and Hydrogenolysis of Hydrazino Lactone 30. Synthesis of D-Alanine. A magnetically stirred solution of 69.6 mg (0.3 mmol) of the *unpurified* hydrazino lactone **30** in a mixture of dimethoxyethane (3 ml) and 0.1 *N* hydrochloric acid (3 ml) was heated at 70° for 1.25 hr under nitrogen atmosphere. After allowing the solution to cool to 26°, it was injected into a hydrogenation flask containing 72 mg of palladium hydroxide-on-carbon catalyst prehydrogenated in a mixture of 0.1 *N* hydrochloric acid (0.1 ml) and dimethoxyethane (1 ml). The required amount of hydrogen was taken up in *ca.* 40 min, after which the mixture was filtered. The filtrate was treated with 3.5 ml of 0.1 *N* ammonium hydroxide and reduced *in vacuo* to half of its volume. It was extracted with three 15-ml portions of ether. The extract was dried over anhydrous magnesium sulfate and evaporated to give 40 mg of the indoline **12** which was purified by preparative thin layer chromatography on silica gel (PF_{254}) containing sodium phosphate buffer, pH 7.00. The indoline **12** had R_f 0.3 when 3:2 ether–benzene mixture was employed for developing. The recovered indoline **12**, mp 64°, 37.5 mg (77%), exhibited ir and nmr spectra identical with those of the authentic sample and had $[\alpha]^{27}D$ −21.3° (*c* 1.2, ethanol).

The aqueous solution was acidified with 1 ml of 0.1 *N* hydrochloric acid and the solution deposited on an ion exchange column (Dowex 50W-X8) (15 ml, acid form). After removal of chloride ions with *ca.* 40 ml of water, the amino acid was eluted with 1 *N* ammonium hydroxide (50 ml). The eluate on evaporation *in vacuo* at 0–2° furnished a colorless crystalline solid residue which was sublimed at 220° (0.01 mm) to give 21 mg (78%) of colorless crystals of D-alanine, $[\alpha]^{27}D$ −31.03 ± 0.2° (*c* 0.4672, acetic acid), the calculated optical purity being 95.9 ± 1% (an authentic sample of D-alanine sublimed under the same conditions had $[\alpha]^{27}D$ −32.30 ± 0.2° (*c* 0.5811, acetic acid)). The infrared spectrum of the synthesized sample was superimposable on that of the authentic sample.

Similarly from recrystallized hydrazino lactone **30** optically pure D-alanine, $[\alpha]^{27}D$ −32.35 ± 0.2°, was obtained.

Hydrazono Lactone 25. An ice-cooled solution of N-aminoindoline reagent **14** (0.016 g, 0.6 mmol) in ether (30 ml) was added slowly with stirring to a cooled solution of *p*-nitrophenyl α-ketobutyrate (0.1338 g, 0.6 mmol) in 50 ml of ether. The mixture was stored at 0–2° for 12 hr and then at 25–26° for 2 hr, when it became yellow in color. Removal of the solvent *in vacuo* gave a thick yellow oil, $\lambda_{max}^{CHCl_3}$ 2.7–2.9 (OH), 3.31 (CH), 5.8 (C=O), 6.25 (C=C), 6.7 (C=N), 6.77, 6.9, 7.45, 8–8.3, and 8.9 μ. It was then dissolved in dry benzene (100 ml) and triethylamine (0.151 g, 1.5 mmol) was added. The solution was refluxed for 7 hr under exclusion of moisture. After the usual workup (see above) the product **25** was obtained as a pale crystalline solid (98 mg, 70.5%), mp 151°, $[\alpha]^{27}D$ −658.2°, $[\alpha]^{27}_{578}$ −706.7° (*c* 0.28, methanol), $\lambda_{max}^{CHCl_3}$ 3.36 (CH), 5.95 (C=O), 6.2 (C=C), 6.45 (C=N), 6.76, 6.85, 7.22, 7.3, and 8.95 μ. The nmr spectrum ($CDCl_3$) of **25** showed peaks at (ppm) 1.2 (3 H, triplet, J = 7.1 cps, methyl protons on carbon next to methylene), 1.257 (2 H, doublet, J = 7 cps, methyl protons on carbon bearing tertiary proton), 2.73 (2 H, quartet, J = 7.1 cps, methylene protons of the ethyl group), 3.05–3.72 (2 H, multiplet, benzylic protons), 4.38–4.74 (2 H, multiplet, tertiary protons), and 6.79–7.28 (4 H, multiplet, aromatic protons).

A sample of the racemic form of **25** prepared in the same manner after recrystallization from ethanol–pentane had mp 150° and identical spectra.

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.79; H, 6.71; N, 11.35.

Hydrazino Lactone 31. To a solution of the hydrazono lactone **25** (95 mg) in dimethoxyethane (4.5 ml) cooled in ice was added aluminum amalgam prepared from 95 mg of aluminum foil. The mixture was then treated with water (0.45 ml) and stirred for 12 hr at 0°. Filtration through Celite 545 and evaporation of the filtrate under reduced pressure gave 91 mg (92.7%) of a colorless solid, mp 96–98°. A small amount of the sample recrystallized from ethanol–pentane had mp 103°, $[\alpha]^{27}D$ −20.6° (*c* 0.2032, ethanol), $\lambda_{max}^{CHCl_3}$ 3.4 (CH), 5.75 and 5.8 (shoulder) (C=O), 6.22 (C=C), 6.75, 6.89, 7.3, 8.49, 8.68, 8.94, and 9.32 μ. The nmr spectrum of the unpurified lactone ($CDCl_3$) showed peaks at (ppm) 1.03 (3 H, triplet, J = 7.25 cps, protons of methyl next to methylene), 1.39 (3 H, doublet, J = 6.9 cps, methyl protons), 1.79 (2 H, quartet, J = 7.25 cps, methylene protons), 2.79 (2 H, doublet, J = 10 cps, benzylic protons), 3.1–3.76 (2 H, multiplet, proton on the indoline ring and proton on nitrogen), 3.99 (1 H, quartet, J = 6.9 cps, proton on carbon flanked by nitrogen and carbonyl), 4.84 (1 H, doublet of quartets), and 6.6–7.38 (4 H, multiplet, aromatic protons). A sample of the racemic lactone prepared in the same manner had mp 104° and identical spectra.

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.18; H, 7.32; N, 11.22.

Hydrolysis and Hydrogenolysis of Hydrazino Lactone 31. Synthesis of D-Butyrine. A solution of the *unrecrystallized* hydrazino lactone **31** (74 mg, 0.3 mmol) in a mixture of dimethoxyethane (3 ml) and 0.1 *N* hydrochloric acid (3 ml) was heated under argon atmosphere for 75 min at 70–74° with magnetic stirring. The colorless reaction mixture was injected into a hydrogenation flask containing a prehydrogenated suspension of palladium hydroxide-on-carbon catalyst (74 mg) in a mixture of 0.1 *N* hydrochloric acid (0.1 ml) and dimethoxyethane (1 ml). The required amount of hydrogen was taken up in about 40 min. The reaction mixture was then filtered and washed with 3 ml of a 1:1 mixture of dimethoxyethane and water. The clear filtrate was evaporated to about one-fourth of its original volume under reduced pressure. It was extracted with three 15-ml portions of ether after diluting with 8 ml of water. The ether extract, after drying over magnesium sulfate, was evaporated to give 41 mg (84%) of colorless oil, which crystal-

lized on keeping, mp 64–65°, $[\alpha]^{27}D$ −21.2° (*c* 1.11, ethanol). Its infrared spectrum was superimposable with that of an authentic sample of indoline **12**.

The aqueous solution (left after the extraction of indoline) was acidified with 1 ml of 0.1 *N* hydrochloric acid. It was deposited on an ion exchange column of Dowex 50W-X8 (15 ml, acid form) until the washings were free of chloride ion. The amino acid was eluted with 1 *N* ammonium hydroxide (45 ml) at 0°. Evaporation of the eluate at 0–2° *in vacuo* gave 22.82 mg of a colorless solid which was sublimed at 220° (0.005 mm) to give 22.0 mg (70%) of D-butyrine, $[\alpha]^{27}D$ −41.43 ± 0.2°, $[\alpha]^{27}_{578}$ −43.8 ± 0.2° (*c* 0.4405, acetic acid), the calculated optical purity being 97.2 ± 1% (an authentic sample of D-butyrine sublimed under identical conditions had $[\alpha]^{27}D$ −42.61 ± 0.2°, $[\alpha]^{27}_{578}$ −44.95° (*c* 0.436, acetic acid)). The infrared spectra of the synthesized and the authentic sample were completely superimposable.

Hydrazono Lactone 26. To an ice-cooled magnetically stirred solution of methyl α-ketoisovalerate (0.104 g, 0.8 mmol) in ether (60 ml) was slowly added a cooled solution of the N-aminoindoline **14** (0.1428 g, 0.8 mmol) in ether. The mixture was stored at 0–2° for 72 hr and then at 26–27° for 2 hr. Evaporation of the solvent followed by removal of traces of water *in vacuo* gave hydrazono ester as a thick oil, $\lambda_{max}^{CHCl_3}$ 2.85 (OH), 3.9 (CH), 5.78 (C=O), 6.22, 6.73, 6.86, 7, 7.32, and 7.7–8.1 μ (C—O—C).

To a solution of the oil in dry benzene (120 ml) was added sodium methoxide (15 mg), and the solution, protected from moisture, was heated under reflux in a Soxhlet apparatus carrying Linde Molecular Sieves, Type 4A. The reaction mixture was washed with three 25-ml portions of cold water and dried (magnesium sulfate). Evaporation of the organic solvent *in vacuo* gave a pale crystalline solid which was recrystallized from ethanol–pentane to give 134 mg (65%) of shining needlelike crystals, mp 93°, $[\alpha]^{27}D$ −550.3° (*c* 0.157, ethanol), $\lambda_{max}^{CHCl_3}$ 3.9 (CH), 5.95 (C=O), 6.2 (C=C), 6.42 (C=N), 6.75, 7.21, 7.3, 7.7, 8.6, 9.25, 9.76, and 10.2 μ. The nmr spectrum ($CDCl_3$) showed peaks at (ppm) 1.25–1.325 (9 H, multiplet, protons of three methyl groups), 2.635–3.715 (3 H, multiplet, benzylic protons and tertiary proton of the isopropyl group), 4.32–4.73 (2 H, multiplet, tertiary protons), and 6.78–7.3 (4 H, multiplet, aromatic protons). A sample of the racemic lactone prepared in this manner had identical spectra and had mp 94°.

Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.62; H, 7.15; N, 10.95.

Hydrazino Lactone 32. To a cooled solution of the hydrazono lactone **26** in dimethoxyethane (4 ml) was added aluminum amalgam prepared from 80 mg of aluminum foil. The mixture was then treated with 0.4 ml of water and stirred at 0° for 6.5 hr. It was filtered through Celite 545, and the filter cake was washed with 1:1 ethyl acetate–benzene solution (15 ml). Evaporation of the filtrate *in vacuo* furnished 79 mg of **32** as a colorless solid, mp 106–107°. A small amount was recrystallized from ethanol–pentane mixture, mp 108°, $[\alpha]^{27}D$ +24.2° (*c* 0.43, ethanol), $\lambda_{max}^{CHCl_3}$ 2.9 (NH), 3.88 (CH), 5.74 and 5.8 (shoulder) (C=O), 6.21 (C=C), 6.75, 6.89, 7.3, 8.5, 8.71, 8.90, 9.07, and 9.25 μ. The nmr spectrum of the unrecrystallized sample of **32** ($CDCl_3$) showed peaks at (ppm) 1.2 (6 H, triplet, J = 7 cps, protons of methyls of isopropyl), 1.4 (3 H, doublet, J = 6.8 cps, methyl protons), 2.19 (1 H, multiplet, tertiary proton of isopropyl), 2.75 (2 H, doublet, J = 10 cps, benzylic protons), 3.19–4.09 (3 H, multiplet, proton on nitrogen, tertiary proton on carbon attached to carbonyl and nitrogen, and tertiary proton on indoline ring), 4.87 (1 H, multiplet, tertiary proton on carbon bearing oxygen), and 6.95–7.23 (4 H, multiplet, aromatic protons).

A sample of the racemic lactone obtained in this manner had identical spectra and had mp 106.5–108°. The molecular weight determined mass spectrometrically was 260.1527 (calcd for $C_{15}H_{20}N_2O_2$: 260.1525).

Hydrolysis and Hydrogenolysis of the Hydrazino Lactone 32. Synthesis of D-Valine. To a solution of the unrecrystallized (+)-hydrazino lactone **32** (0.052 g, 0.2 mmol) in dimethoxyethane (12 ml) was added 0.1 *N* hydrochloric acid (16 ml, 8 equiv), and the reaction mixture was stirred under nitrogen for 20 hr at 70° and for 3 hr at 90°. The reaction mixture turned pink in color during this time. After hydrogenation as described above and the usual workup, 15 mg (40%) of the indoline **12**, mp 64°, $[\alpha]D$ −21.1° (*c* 1, ethanol), was recovered. The infrared spectrum of this material was superimposable on that of the authentic **12**. The water soluble amino acid was isolated as usual from an ion exchange column (Dowex 50W-X8, acid form) to give 13.14 mg of a colorless solid. This was sublimed at 210–220° (0.005 mm) to give 12.5 mg (53.5%) of D-valine, $[\alpha]^{27}D$ −50.35°, $[\alpha]^{27}_{578}$ −52.51° (*c* 0.4766, acetic acid). An authentic sample of D-valine sublimed under the same conditions had superimposable infrared spectrum and had $[\alpha]^{27}D$ −51.95°, $[\alpha]^{27}_{578}$ −54.3° (*c* 0.5062, acetic acid). The calculated optical purity of the synthetic sample is 96.7 ± 1%.

Hydrazono Lactone 27. To a solution of methyl α-ketoisocaproate (0.1296 g, 0.9 mmol) in 30 ml of ether cooled in ice was added dropwise a solution of the amino indoline **14** (0.1602 g, 0.9 mmol) in 30 ml of the same solvent. The colorless mixture was stored at 0–2° for 48 hr and then at 26° for 3 hr, and the solvent was removed *in vacuo*. The infrared spectrum of the hydrazono ester obtained as yellow colored oil had $\lambda_{max}^{CHCl_3}$ 2.9, 3.34, 5.78, 5.85 (shoulder), 6.21, 6.5, 6.76, 6.86, 6.97, 7.31, 8.15, 8.66, and 9.44 μ. To a solution of the ester in 100 ml of benzene was added 14 mg of sodium methoxide. The magnetically stirred mixture was refluxed for 10 hr in a Soxhlet apparatus carrying Linde Molecular Sieve, Type 4A. The light yellow reaction mixture was washed with cold water, and the organic solution was dried (magnesium sulfate) and evaporated *in vacuo* to give a thick light yellow oil which was chromatographed on a buffered (pH 7.0 ± 0.02) silica gel PF_{254} thick layer plate. A benzene and ether mixture (3:2) was used for developing, and the product **27** (R_f 0.55) was obtained as a pale thick oil (0.171 g, 70%) which crystallized on keeping overnight at 0–2°. It was recrystallized from pentane to give a solid, mp 70°, $[\alpha]^{27}D$ −615.8°, $[\alpha]^{27}_{578}$ −658.5° (*c* 0.227, ethanol). The infrared spectrum had $\lambda_{max}^{CHCl_3}$ 5.94, 6.2, 6.25 (shoulder), 6.48, 6.76, 6.85, 6.98 (shoulder), 7.23, 7.32, 7.71, 8.9, 9.2, 9.5, and 10.65 μ. The nmr spectrum of **27** ($CDCl_3$) exhibited peaks at (ppm) 0.965 (6 H, doublet, J = 6 cps, protons of methyl groups of the isopropyl group), 1.275 (3 H, doublet, J = 6.5 cps, methyl protons), 1.52–3.715 (5 H, multiplet, tertiary proton of the isopropyl group, methylene protons and benzylic protons), 4.5 (2 H, multiplet, tertiary proton on carbon bearing nitrogen and tertiary proton on carbon bearing oxygen), and 7.02 (4 H, multiplet, aromatic protons).

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.35; H, 7.47; N, 10.05.

Hydrazino Lactone 33. To a solution of the (−)-hydrazono lactone **27** (100 mg) in dimethoxyethane (5 ml) cooled in ice was added aluminum amalgam prepared from 100 mg of aluminum foil. After addition of water (0.5 ml) the mixture was magnetically stirred for 7 hr at 0°. The unreacted aluminum and the alumina formed were filtered through Celite 545 and the filter cake was washed with an ethyl acetate–benzene mixture (1:1). The colorless clear filtrate thus obtained was evaporated *in vacuo* to give 96 mg (95%) of a colorless oil which crystallized on keeping, mp 95–96°. This material was used as such for the synthesis of D-leucine. A small portion was recrystallized from ethanol–pentane mixture to give colorless crystals, mp 96°, $[\alpha]^{27}D$ −19.4° (*c* 0.02325, ethanol). The infrared spectrum had $\lambda_{max}^{CHCl_3}$ 2.9 (weak and broad), 3.39, 5.8 (shoulder), 5.84, 6.15, 6.28 (shoulder), 6.75, 6.83, 6.9, 7.25, 7.33, 7.95, 8.5, 8.92, and 9.31 μ. The nmr spectrum ($CDCl_3$) showed peaks at (ppm) 0.975 (6 H, doublet, J = 5.5 cps, protons of the methyls of isopropyl group), 1.46 (3 H, doublet, J = 7 cps, methyl protons and tertiary proton of the isopropyl group), 2.83 (2 H, multiplet, benzylic protons), 3.175–3.875 (2 H, multiplet, proton on nitrogen and tertiary proton on carbon joined to the carbonyl and NH group), 4.125 (1 H, multiplet, unresolved, tertiary proton on the indoline ring), 4.8 (1 H, septet, tertiary proton on carbon bearing methyl group and oxygen), and 6.98 (4 H, multiplet, aromatic protons).

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.48; H, 7.45; N, 10.22.

Hydrolysis and Hydrogenolysis of (−)-Hydrazino Lactone 33. Synthesis of D-Leucine. A solution of (−)-lactone **27** (75 mg, 0.275 mmol) in freshly distilled dimethoxyethane (6 ml) was treated with 0.05 *N* hydrochloric acid (6.32 ml, 1.15 equiv) and heated under a nitrogen atmosphere at 72–73° for 2.5 hr. The colorless solution was hydrogenated over palladium-on-carbon catalyst (75 mg) in 0.01 *N* hydrochloric acid (1 ml) and dimethoxyethane (1 ml). The required amount of hydrogen was taken up in *ca.* 40 min. The reaction mixture was filtered and evaporated *in vacuo* to near dryness. The residue was dissolved in water (10 ml), cooled in ice, and extracted with three 20-ml portions of ether after basification to pH 8–9 with 1 *N* ammonium hydroxide. The ether extract after drying (magnesium sulfate) was evaporated to give indoline which crystallized on keeping. It was purified on thick layer basic alumina PF_{254} plate to give 36 mg (81%) of the (−)-indoline **12**, mp 63–64° $[\alpha]D$ −21.2° (*c* 1.1, ethanol).

The aqueous solution was evaporated to dryness *in vacuo* at 0–5° and the amino acid isolated as above. D-Leucine was ob-

tained as a colorless solid (29 mg) which was sublimed at 220° (0.01 mm) to furnish 28 mg (78%) of the amino acid, $[\alpha]^{27}D$ −23.44 ± 0.2°, $[\alpha]^{27}_{578}$ −24.74 ± 0.2° (*c* 0.4647, acetic acid). An authentic sample of L-leucine sublimed under similar conditions had $[\alpha]^{27}D$ +23.73 ± 0.2°, $[\alpha]^{27}_{578}$ +25.28 ± 0.2° (*c* 0.455, acetic acid), the optical purity of the synthetic amino acid being 98.9 ± 0.8%. The infrared spectrum of the synthetic D-leucine was identical with that of an authentic sample of L-leucine.

Hydrazono Lactone 28. To a solution of *p*-nitrophenyl pyruvate (0.352 g, 1.68 mmol) in ether (30 ml) cooled in ice was added slowly with shaking a cooled solution of the S_NS_O 1-aminoindoline reagent **21**, $[\alpha]^{27}D$ −28.06° (*c* 0.588, methanol) (0.3 g, 1.68 mmol), in 20 ml of the same solvent. The mixture was stored for 12 hr at 0–2° and then at 25° for 2 hr. Removal of the solvent *in vacuo* afforded the hydrazono ester as bright yellow oil (0.625 g). The hydrazono ester dissolved in dry dioxane (150 ml) was heated to reflux for 4 hr after addition of 0.202 g (2 mmol) of triethylamine. A workup similar to that of the lactones **24–27** furnished after one recrystallization 170 mg (62%) of **28** as light yellow crystals, mp 117–118°, $[\alpha]^{27}D$ −171° (*c* 0.42, ethanol). (The (±)-lactone prepared similarly had mp 125°.) The infrared spectrum ($CHCl_3$) had bands at 5.94 (strong, C=O), 6.2 (weak, C=C), 6.44 (strong, C=N), 6.73 (strong), 6.81 (medium, shoulder), 6.98 (weak), 7.26 (medium), 7.67 (medium), 7.85 (medium), and 8.4 μ (medium). The nmr spectrum in deuteriochloroform showed a doublet at (ppm) 1.48 (3 H, J = 6.5 cps) due to the methyl group attached to the carbon bearing a tertiary proton, a singlet for the methyl group attached to the carbon of C=N moiety at 2.3 (3 H), a multiplet at 3.22 (2 H) due to the benzylic protons, a quartet at 4.28 (1 H, J = 9 cps) with broad peaks due to the tertiary proton on the indoline ring. The lowest field peak of this quartet overlapped with the highest field peak of the quintet at 4.72 (1 H, spacing = 7 cps) due to the tertiary proton on the carbon carrying methyl group and oxygen. A partial resolution (*ca.* 2.5) of the overlapping peaks of the two tertiary protons was effected by running the spectrum in acetone-d_6. The four aromatic protons appeared as a multiplet at 7.1 (4 H). The assignments of the tertiary protons were supported by double resonance experiments. Irradiation at the methyl resonance (at 1.48) caused the quintet to collapse to a doublet with J = 6 cps. Furthermore, the irradiation at the center of the quartet (tertiary proton on the indoline ring) led to the appearance of the benzylic protons' resonance as an AB quartet, J_{AB} = 19 cps.

The molecular weight determined mass spectrometrically was 230.1049 (calcd for $C_{13}H_{14}N_2O_2$: 230.1055).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.97; H, 6.35; N, 11.98.

Hydrazino Lactone 34. From the hydrazono lactone **28** (90 mg) by the usual reduction procedure using aluminum amalgam (90 mg) (reaction time 12 hr at 0°), there was obtained 88 mg (97%) of the unrecrystallized hydrazino lactone **34**, mp 124–126°, which was used in the next step without purification.

An analytical sample of **34** purified by one recrystallization from ethanol–pentane had mp 126°, $[\alpha]^{27}D$ −135.6° (*c* 0.351, ethanol). (A sample of racemic hydrazino lactone prepared similarly also had mp 126°.)

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.97; N, 12.06. Found: C, 66.92; H, 6.83; N, 12.06.

Hydrolysis and Hydrogenolysis of the Hydrazino Lactone 34. Formation of D-Alanine. A solution of the unpurified lactone **34** (88 mg, 0.4 mmol) obtained above in 4 ml of freshly distilled dimethoxyethane and 4 ml of 0.1 *N* hydrochloric acid (4.15 ml) was heated under an atmosphere of nitrogen at 68° for 1 hr. After the usual hydrogenation for 40 min over 88 mg of prereduced palladium-on-carbon catalyst in 0.2 ml of 0.1 *N* hydrochloric acid and 2 ml of (1:1) dimethoxyethane–water mixture, the mixture was filtered through Celite 545 and the residue washed with dilute dioxane. The filtrate was evaporated to near dryness *in vacuo*. The residue was taken up in 10 ml of water and basified with 0.6 ml of 1 *N* ammonium hydroxide solution after cooling in ice. The ice-cooled basic solution was extracted with two 25-ml portions of ether. The ether extract after evaporation yielded 52 mg (80%) of recovered indoline as a light brown thick oil (identical infrared and nmr spectra with those of the authentic racemic sample of this compound). This was transformed into the N-amino derivative **21** by the nitrosation and reduction sequence to give 38 mg (68% for 2 steps) of **21**, $[\alpha]^{27}D$ −27.9° (*c* 0.5, methanol).

The aqueous solution was evaporated *in vacuo* at 3–4° to give a colorless residue. It was dissolved in 10 ml of water, and the solution was acidified with 0.15 ml of 0.1 *N* hydrochloric acid and desalted in the usual manner on a Dowex 50W-X8 ion exchange column at 3–4°. The basic eluate thus obtained was evaporated *in vacuo* at 2–4° to afford 33.8 mg of a colorless solid which was sublimed at 220° (0.01 mm) to furnish 32.1 mg (90%) of D-alanine, $[\alpha]^{27}D$ −28.95 ± 0.15° (*c* 0.8376, acetic acid). An authentic sample of D-alanine sublimed under the same conditions had $[\alpha]^{28}D$ −31.49 ± 0.15° (*c* 0.8175, acetic acid), the optical purity of the synthetic sample being 92 ± 1%. The infrared spectra of the two samples of D-alanine (potassium bromide disk) were superimposable.

Hydrazono Lactone 29. A solution of the N-aminoindoline **21** (267 mg, 1.5 mmol), $[\alpha]^{27}D$ −28.0° (*c* 0.8, ethanol), in 15 ml of ether was added dropwise to a stirred solution of *p*-nitrophenyl 2-ketobutyrate (335 mg, 1.5 mmol) in 30 ml of the same solvent cooled in an ice bath. The reaction mixture was stored at 0–2° for 12 hr and then at 25° for 2 hr. Evaporation of the solvent gave the hydrazono ester as a bright yellow oil (0.57 g). The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 3.0 (medium, OH), 5.84 (medium, CO, ester), 6.05 (medium, CO, lactone), 6.2 (medium, C=C), 6.3 (strong), 6.43 (medium, C=N, lactone), 6.58 (strong, NO_2), 6.76 (strong), 6.87 (medium), 7.5 (strong, NO_2), 7.78 (medium), and 9 μ (strong, C—O—C). A solution of this ester in dry dioxane (125 ml) was heated at reflux for 3.5 hr after addition of 0.303 g (3 mmol) of triethylamine. After isolation in the usual way the product **29** was recrystallized from ethanol–pentane to give 180 mg (50%), mp 123°, $[\alpha]^{28}D$ −126.6° (*c* 0.58, ethanol). The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 5.93 (strong, CO), 6.25 (weak, C=C), 6.45 (strong, C=N), 6.76 (strong), 6.85 (medium, shoulder), 7.32 (medium), 7.7 and 7.88 μ (medium, C—O—C). The molecular weight determined mass spectrometrically was 244.1203 (calcd for $C_{14}H_{16}N_2O_2$: 244.1211).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.55; H, 6.57; N, 10.82.

Hydrazino Lactone 35. To a solution of the hydrazono lactone **29** (73.2 mg, 0.3 mmol) (prepared above) in 4 ml of dimethoxyethane cooled in ice was added aluminum amalgam prepared from 73 mg of aluminum foil. After addition of 0.4 ml of water, the reaction mixture was stirred for 14 hr at 0°. The usual isolation afforded 71 mg (96%) of **35** as colorless crystals, mp 126–128°. The infrared spectrum showed $\lambda_{max}^{CHCl_3}$ 2.9 (weak, NH), 5.83 (strong, CO), 6.19 (medium, C=C), 6.75 (medium), 6.91 (medium), 8.3 (strong, broad, C—O—C), and 9.5 μ (medium). The nmr spectrum ($CDCl_3$) exhibited peaks at (ppm) 1.06 (3 H, triplet, J = 7 cps, protons of the methyl of ethyl group), 1.38 (3 H, doublet, J = 6.5 cps, protons of the methyl group on the carbon bearing oxygen), 1.98 (2 H, multiplet, methylene protons of the ethyl group), 2.5–3.5 (4 H, multiplet, benzylic protons, tertiary proton of the indoline ring and the proton on nitrogen), 3.86 (1 H, multiplet, proton on carbon attached to NH and CO groups), 4.7 (1 H, multiplet, tertiary proton on the carbon bearing oxygen), and 6.65–7.17 (4 H, multiplet, aromatic protons).

This material was used for the following step without any purification. A small sample recrystallized from ethanol–pentane mixture had mp 128° and $[\alpha]^{27}D$ −135.5° (*c* 0.1918, ethanol).

The racemic form of the hydrazino lactone **35** prepared in this manner had mp 121° and identical infrared and nmr spectra.

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.28. Found: C, 67.89; H, 7.28.

Hydrolysis and Hydrogenolysis of Hydrazino Lactone 35. Formation of D-Butyrine. A solution of the unpurified hydrazino lactone **35** (obtained above) (70 mg, 0.29 mmol) in a mixture of dioxane (3 ml) and 0.1 *N* hydrochloric acid (3.1 ml) was heated at 68–70° for 1.25 hr under nitrogen atmosphere. After allowing it to cool to 25°, it was injected into a hydrogenation flask carrying 70 mg of palladium hydroxide-on-carbon catalyst suspended in a 1:1 mixture of dioxane and water (2 ml) containing 0.1 ml of 0.1 *N* hydrochloric acid. The hydrogenation was complete in 40 min. The ether extract obtained from the usual workup gave 38 mg of optically active indoline which was transformed into the N-amino derivative **21**, mp 72–73° (25 mg, 65% for two steps), $[\alpha]^{27}D$ −27.8° (*c* 0.56, methanol).

The basic aqueous solution was evaporated *in vacuo* at 0–3°. The residue was dissolved in 10 ml of water and acidified with 0.15 ml of 0.1 *N* hydrochloric acid. It was desalted as usual on a Dowex 50W-X8 (acid form) ion exchange column at 3–4° to give 26.2 mg of a colorless solid which was sublimed at 220° (0.01 mm) to give 25 mg (86%) of D-butyrine, $[\alpha]D$ −42.12 ± 0.2° (*c* 0.4618, acetic acid). An authentic sample of D-butyrine sublimed under the same conditions had $[\alpha]D$ −43.8 ± 0.2° (*c* 0.4656, acetic acid), the optical purity of the synthetic sample being 96.4 ± 1%. The infrared spectra of the two samples (potassium bromide disk) were indistinguishable.

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The Synthesis of Deamino-oxytocinoic Acid and Acetone-oxytocinoic Acid and Their Use in the Preparation of Deamino-oxytocinoyloxytocin and Oxytocinoyloxytocin[1,2]

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Abstract: Deamino-oxytocinoic acid and acetone-oxytocinoic acid have been synthesized. Deamino-oxytocinoic acid possessed approximately 8.6 units/mg of avian vasodepressor activity and less than 0.2 units/mg of oxytocic activity. Acetone-oxytocinoic acid possessed no detectable avian vasodepressor or oxytocic activity, whereas oxytocinoic acid possesses approximately 3.8 units/mg of oxytocic activity and no avian vasodepressor activity. Deamino-oxytocinoic acid and acetone-oxytocinoic acid were each condensed with oxytocin to give deamino-oxytocinoyloxytocin and acetone-oxytocinoyloxytocin. Heating of the latter compound with 0.25% acetic acid liberated oxytocinoyloxytocin. Deamino-oxytocinoyloxytocin and oxytocinoyloxytocin exhibited extremely low levels of oxytocic and avian vasodepressor activity.

In studies on the relationship of structure to the pharmacological activity of oxytocin, a number of peptide derivatives of oxytocin have been synthesized by addition of one or more amino acid residues to the free amino group at position 1 of the hormone.[4-9] It has also become of interest to study the pharmacological properties of compounds in which the oxytocin molecule is extended at position 9, and it occurred to us that the acetone derivative of oxytocinoic acid should prove useful as an intermediate in the synthesis of analogs of this type. In this derivative the free amino group of oxytocinoic acid[10] would be protected by acetone and, by analogy to the behavior of acetone-oxytocin,[11-13] the structure of which is shown in Figure 1, the acetone should be readily removable under the mild conditions used in the regeneration of oxytocin from its acetone derivative. For lengthening of the peptide side chain of deamino-oxytocin,[14-17] deamino-oxytocinoic acid should prove useful. Deamino-oxytocinoic acid and acetone-oxytocinoic acid were therefore synthesized and used in the preparation of deamino-oxytocinoyloxytocin and oxytocinoyloxytocin, respectively.

Deamino-oxytocinoic acid was synthesized by use of the solid phase method as described for the synthesis of deamino-oxytocin,[18] except that unnitrated chloromethylcopolystyrene–2% divinylbenzene was used and cleavage of the protected polypeptide from the resin was effected by HBr in trifluoroacetic acid.[19] The analog was purified by partition chromatography[20] and gel filtration[21] on Sephadex G-25, and was crystallized from water. Deamino-oxytocinoic acid possessed approximately 8.6 units/mg of avian vasodepressor activity[22] and less than 0.2 units/mg of oxytocic activity.[22] Crystalline deamino-oxytocin possesses approximately 975 units/mg of avian vasodepressor activity and 800 units/mg of oxytocic activity.[17]

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(2) All optically active amino acid residues are of the L variety.

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