

The Absolute Configuration of (+)-1-Methyl-2,6-diphenyl-4-piperidone Oxime¹

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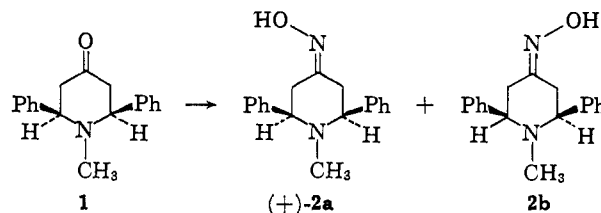
Abstract: The absolute configuration of the molecularly asymmetric compound, (+)-1-methyl-2,6-diphenyl-4-piperidone oxime (**2**), has been determined by its stereospecific degradation. The Beckmann rearrangement of the dextrorotatory oxime **2** produced (–)-1-methyl-2,7-diphenyl-1,4-diaza-5-cycloheptanone (**3**) which on acid hydrolysis gave cinnamic acid and the diamine **6a**. The synthesis of **6a** from (*R*)-(–)- α -aminophenylacetic acid gave the levorotatory isomer identical with that obtained from the acid hydrolysis of the Beckmann product. The migration of the substituent *anti* to the hydroxyl group of the oxime permits the assignment of the absolute configuration of the oxime as **2a**, *i.e.*, the hydroxyl group is *syn* to the asymmetric carbon having the *R* configuration. This is the first example of the establishment of the absolute configuration of a molecularly asymmetric compound described as a “geometrical enantiomer” in which an unsymmetrically substituted double bond (the oximido function) is interposed between two enantiomeric centers, thus converting a *meso* compound **1** into an optically active compound **2** by addition of the elements of geometrical isomerism.

The determination of the absolute configuration of compounds possessing one or more chiral (asymmetric) centers has been accomplished in many different types of systems. When the molecule has no asymmetric carbon atom, the configurational assignment requires interconversion of the molecularly asymmetric or dissymmetric molecule by a known reaction path with a molecule which possesses *C*₁ asymmetry, *i.e.*, a compound which is optically active because of the presence of a chiral center.

Relatively few examples of axially or molecularly dissymmetric molecules have been examined in this context, the first structure subjected to such an analysis being the conversion of a thebaine derivative to an optically active biphenyl by Berson.² The determination of the absolute configuration of some molecularly dissymmetric arylidenecyclohexanes has been recently reported.³ Several methods for the assignment of absolute configuration to allenes have been devised including that based on circular dichroism and electronic absorption.⁴ A summary of the correlation of configuration of allenes with chiral centers of asymmetric molecules by interconversions using established mechanistic pathways has been discussed by Eliel,^{5a} and more recently methods have been announced for assignment of configuration to allenes by asymmetric induction^{5b} and by the use of polarizability concepts.^{5c}

The optically active oxime **2** of 1-methyl-2,6-diphenyl-4-piperidone (**1**) represents a class of compounds in which molecular asymmetry results from the interposition of an unsymmetrical geometrical unit,

the oximido function, between two enantiomeric centers.⁶ The piperidone **1** possesses *C*_s symmetry, but when it is converted to the oxime, the hydroxyl group of the unsymmetrically substituted double bond may be on the same side of the ring as the carbon having the *R* configuration,^{7a} *i.e.*, *syn-R*, or on the opposite side of the ring, *i.e.*, *syn-S* or *anti-R*, and these two substances are mirror images of each other and are not superimposable.^{7b} Proof of this was obtained by the isolation of the dextrorotatory form of **2** and its hydrolysis to the *meso* ketone **1**.⁸ Optically active isomers of **2** may be described as “geometrical enantiomers,” and the phenomenon has been cited as “geometrical enantiomorphous isomerism.” The evidence for the assignment of the absolute configuration to the enantiomers of **2** is the subject of this paper.



The oxime **2** was synthesized and resolved as described previously,⁸ and the racemic and optically active forms of **2** were subjected to the Beckmann rearrangement. Since the oxime was shown to undergo racemization on heating in alcohol, the selection of acid conditions to effect the rearrangement was avoided. The use of benzenesulfonyl chloride in an aqueous acetone solution of sodium hydroxide⁹ gave only partial

(1) (a) Abstracted from the M. S. (1963) and Ph.D. (1965) theses of E. J. Tyminski, submitted to the Graduate School of the University of New Hampshire; (b) supported in part by grants (G-9489) from the National Science Foundation and (GM-07239) from the National Institutes of Health; (c) a portion of this work was presented before the Organic Division of the 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, p 46N.

(2) J. A. Berson and M. A. Greenbaum, *J. Am. Chem. Soc.*, **80**, 445 (1958).

(3) J. H. Brewster and J. E. Privett, *ibid.*, **88**, 1419 (1966).

(4) S. F. Mason and G. W. Vane, *Tetrahedron Letters*, 1593 (1965).

(5) (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 314–316; (b) R. J. D. Evans, S. R. Landor, and J. P. Regan, *Chem. Commun.*, 397 (1965); G. Lowe, *ibid.*, 411 (1965).

(6) The dissymmetry shown by the oxime **2** differs from that described in ref 3 in that the oxime **2** does not possess axial chirality.^{7b}

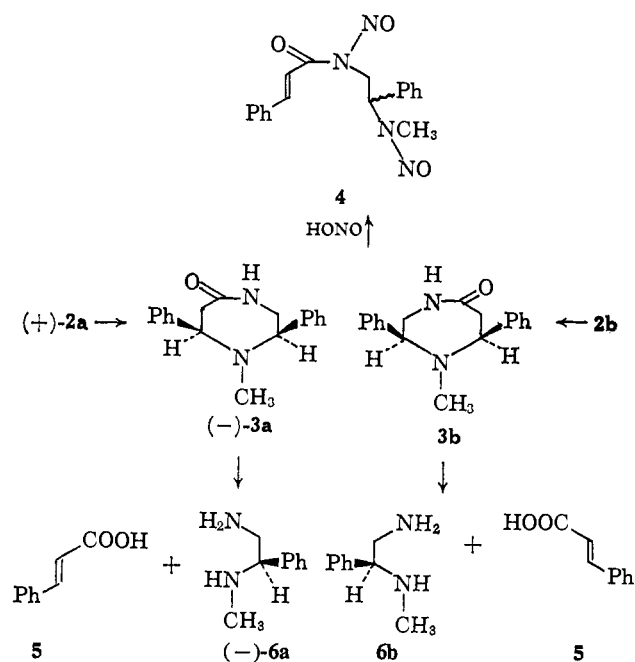
(7) (a) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956). (b) An alternative description of the absolute configuration applying the sequence rules of R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem. Intern. Ed. Engl.*, **5**, 385 (1966), would substitute the term *seqcis* for the *syn-R* isomer **2a** and *seqtrans* for the enantiomeric *syn-S* (or *anti-R*) **2b** compound. Nomenclature using a geometrical relationship and applying the sequence rule that *R* precedes *S* would describe the enantiomers as *syn-R* and *anti-R*, while the configuration which is being proved in this instance is that of the *anti* (migrating) group and thus one could use *anti-S* or *anti-R* as suggested by one of the referees.

(8) R. E. Lyle and G. G. Lyle, *J. Org. Chem.*, **24**, 1679 (1959).

(9) G. G. Lyle and R. M. Barrera, *ibid.*, **29**, 3311 (1964).

racemization (*vide infra*). The oxime **2**, $[\alpha]^{24D} +28.9^\circ$, was converted to the lactam **3**, $[\alpha]^{23D} -6.36^\circ$, in 45% yield. Based on the highest rotation ($+37.0^\circ$) obtained for the oxime **2**, this sample was at most 78.1% optically pure.

Attempts to convert the lactam **3** to the methiodide or N-oxide failed, apparently because of the steric crowding of the nitrogen function by the adjacent aromatic groups. Degradation of the lactam was attempted *via* nitrosation of **3**, but ring cleavage occurred¹⁰ producing a dinitroso product whose structure is postulated on the basis of analytical data and nmr evidence as **4** (see Experimental Section). Hydrolysis of the lactam in basic medium gave unreacted starting material even under vigorous conditions. Successful degradation was effected with 20% hydrochloric acid which produced ring cleavage at both nitrogen functions. The major product isolated was cinnamic acid (**5**), but on basification a second product was obtained as a yellow oil which formed a phenylthiourea derivative. The oil and the derivative from (+)-**2** were both optically active. Since the cinnamic acid portion of the lactam **3** was removed, leaving an optically active fragment, the base was assigned the structure **6**.

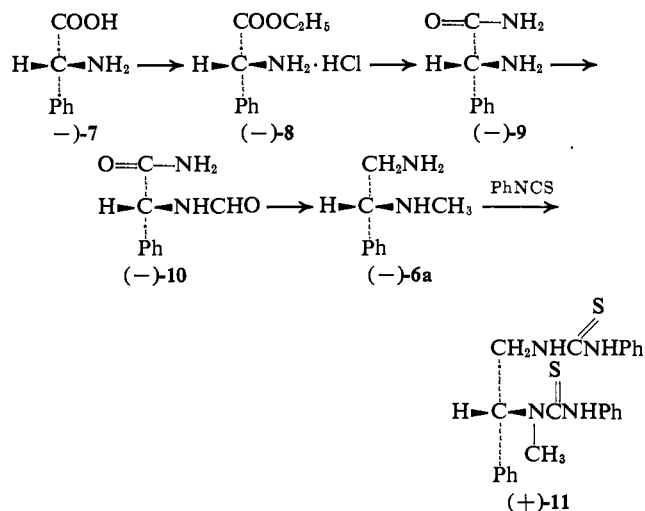


The proof of the structure and absolute configuration of the diamine **6** were obtained by an alternate synthesis from (*R*)-(-)- α -aminophenylacetic acid (**7**).¹¹ Esterification of **7** was accomplished by ethyl alcohol and hydrogen chloride to give **8** which was converted to the free base and saturated with ammonia to produce the amide **9**. The formyl derivative **10** was prepared from **9** with formamide, and the amido groups were reduced to the primary and the secondary amine functions with lithium aluminum hydride. The oily diamine obtained from this synthesis was identical

(10) Smith and co-workers have shown the susceptibility of tertiary amines to cleavage by nitrous acid in a number of systems, *e.g.*: P. A. S. Smith and H. G. Pars, *J. Org. Chem.*, **24**, 1325 (1959).

(11) For discussion and leading references to configuration of **7**, see B. C. Hibbin, E. D. Hughes, and C. K. Ingold, *Chem. Ind. (London)*, 933 (1954).

in physical properties with the oil **6** obtained from the cleavage reaction of the lactam **3**. Both of the diamines **6** were levorotatory and both were converted to dextrorotatory bisphenylthiourea derivatives **11**.



The synthesis of the phenylthiourea derivative **11** starting with pure (*R*)-(-)- α -aminophenylacetic acid (**7**) should yield **11** with a reasonable degree of optical purity. The reaction procedures were selected to maintain mild conditions, and they had been used with similar compounds and gave little or no racemization. The Beckmann rearrangement of (+)-**2a** and degradation of the lactam (-)-**3a**, however, may have proceeded with some racemization. In fact, one conversion of **2** to **3** produced a racemic product, but in three other cases the (+)-oxime **2** yielded (-)-lactam **3**.

In view of the synthetic procedures, the configuration of the asymmetric carbon of the diamine **6a** must be the same as that of the amino acid (-)-**7**, namely *R*. It follows that the configuration of the right (diamine) moiety of lactam (-)-**3a** is also *R*. Since the Beckmann rearrangement proceeds by migration of the substituent *anti* to the hydroxyl group of the oximido function, the absolute configuration of the oxime which led to the (-)-lactam **3a** must have the structure **2a** (in which the hydroxyl group is *anti* to the *S* center of the piperidone ring¹²).

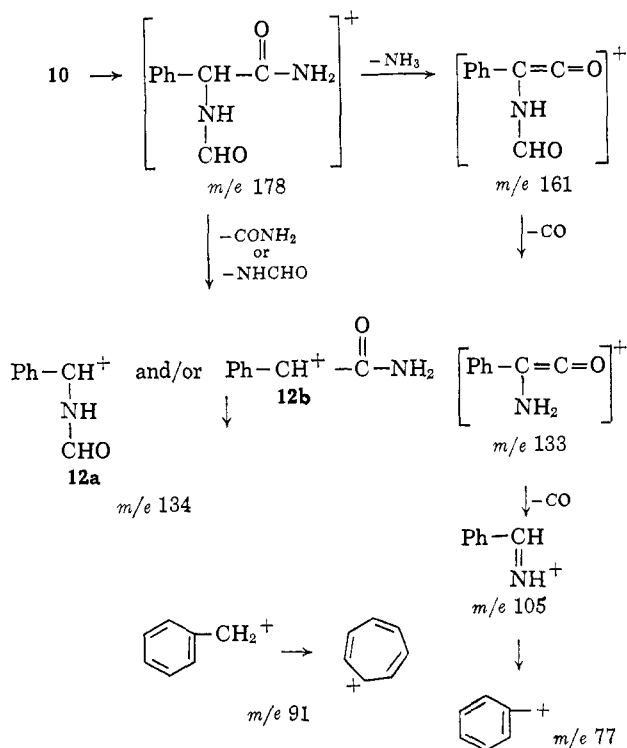
An examination of the optical rotatory dispersion curves was undertaken to see if any correlation of configuration with the shapes of the curves could be discerned. Most of the compounds had rather low optical rotatory power, and examination of their ORD curves at low wavelengths was prevented by the high absorption in the ultraviolet region. The ORD curves of phenylglycine (**7**) and its derivatives were all of negative sign and consistently decreased in rotatory power as the symmetry of the substituents on the asymmetric carbon increased. The amino acid **7** gave a plain, strongly negative curve to 270 μ , essentially identical with that of the ethyl ester hydrochloride **8**. There appeared to be a very small Cotton effect between 270 and 250 μ in the amino acid which did not appear in the ester. The amide **9** gave a weak, plain curve to 265 μ . The formamido derivative **10**, however, showed a very weak, negative curve with apparently a positive background,

(12) Although C-2 atoms (lower right) in **2a** and **3a** have the same configuration, the configurational symbol happens to be opposite: *S* in **2a**, *R* in **3a**.

but the molecular rotation at 270 $m\mu$ was only -21° . The low rotation emphasized the symmetry of the substituents in this molecule.

The oxime **2a** gave an ORD curve that had one small positive Cotton effect between 304 and 285 $m\mu$ ($a + 0.4$). The low-rotating curve of the lactam **3a** appeared to be a positive Cotton effect superimposed on a negative background. The absorption was too large, however, to measure the curve through the presumed Cotton effect, a problem also apparent in the diamine **6a** which gave a very weak, negative curve to 323 $m\mu$. The correlation of configuration and ORD curve has essentially no significance with these compounds.

The mass spectrum of the formyl derivative **10** was also interesting because of the possibility of degrading two amide functions in different directions. The peak at 178 m/e represents the molecular weight of the compound. Gilpin¹³ has studied the mass spectral patterns of a variety of amides, but the presence of a primary and a secondary amide function and the very labile formyl group complicated the interpretation of the spectrum of **10**. The base peak at 134 m/e or the only slightly smaller one at 133 m/e can be arrived at by three possible fragmentation patterns. The peak at $M - 17$ suggests the loss of a molecule of ammonia and that at $M - 29$ of loss of the formyl group. The ion of m/e 134 most probably should have structure **12a** or **12b** resulting from removal of either of the amide groups. Further fragmentation to produce the benzyl ion (m/e 91) or its tropylium isomer and the phenyl ion (m/e 77) would follow standard pathways. The pattern adds further support to the assigned structure of **10**.



The chemical evidence for the assignment of the absolute configuration to the oxime **2a** of 1-methyl-2,6-diphenyl-4-piperidone establishes that the dextrorotatory enantiomer has the *anti-S* (or *syn-R*) configuration,

(13) J. A. Gilpin, *Anal. Chem.*, **31**, 935 (1959).

as shown in the formulation. This is the first example of geometrical enantiomorphous isomerism for which the absolute configuration has been assigned. Work on analogous systems is in progress in this laboratory.

Experimental Section¹⁴

1-Methyl-2,7-diphenyl-1,4-diaza-5-cycloheptanone (3). A mixture of 5.0 g (0.018 mole) of racemic 1-methyl-2,6-diphenyl-4-piperidone oxime⁸ (**2**), 3.25 g (0.018 mole) of benzenesulfonyl chloride, 2.5 g of sodium hydroxide, 25 ml of water, and 100 ml of acetone was refluxed on a steam bath for 8 hr. Water (250 ml) was added to the reaction mixture, and most of the acetone was removed under reduced pressure. The resulting mixture was extracted three times with ether and the ethereal solution dried over potassium carbonate. Evaporation of the solvent yielded 2.7 g (54%) of 1-methyl-2,7-diphenyl-1,4-diaza-5-cycloheptanone (**3**). Recrystallization from methanol gave 1.18 g (43%) of **3**, mp 167–168°, which gave infrared absorption in chloroform at 1665 cm^{-1} indicative of the lactam carbonyl group and NH absorption at 3423 cm^{-1} . A halocarbon mull showed the carbonyl band at 1715 cm^{-1} .

The nmr spectrum in chloroform gave a single peak (3 H) at 1.76 ppm indicative of the N-methyl group and a broadened triplet at 3.49 ppm for the two benzylic protons which are split by slightly different methylene groups at C-3 and C-6.

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19. Found: C, 77.11; H, 7.27.

(-)-1-Methyl-2,7-diphenyl-1,4-diaza-5-cycloheptanone (3a). A mixture of 3.6 g of (+)-1-methyl-2,6-diphenyl-4-piperidone oxime⁸ (**2a**), $[\alpha]_D^{25} + 28.9^\circ$ (c 2.0, 95% ethanol), 2.34 g of benzenesulfonyl chloride, 1.8 g of sodium hydroxide, 18 ml of water, and 72 ml of acetone was heated under reflux on a steam bath for 6 hr and the reaction mixture worked up as described for the racemic compound to give 1.25 g (44.7%) of (-)-1-methyl-2,7-diphenyl-1,4-diaza-5-cycloheptanone (**3a**), mp 169.5–170°, $[\alpha]_D^{25} - 6.63^\circ$ (c 1.07, methanol). The infrared spectrum of the optically active lactam was identical with that of racemic **3**.

Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19. Found: C, 76.83; H, 7.07.

ORD in methanol (c 0.765): $[\phi]_{589} - 73.3^\circ$, $[\phi]_{650} - 91.6^\circ$, $[\phi]_{589} - 88.0^\circ$, $[\phi]_{575} - 176^\circ$, $[\phi]_{505} \pm 0.0^\circ$.

Nitrosation of 1-Methyl-2,7-diphenyl-1,4-diaza-5-cycloheptanone (3). A solution of 1.64 g (0.0059 mole) of 1-methyl-2,7-diphenyl-1,4-diaza-5-cycloheptanone (**3**) in 6 ml of glacial acetic acid and 30 ml of acetic anhydride was cooled to 0° and treated with 10 g (0.145 mole) of sodium nitrite for 24 hr. Water (approximately 100 ml) was added and the organic material isolated by extraction with ether. Evaporation of the ethereal solution gave a yellow solid which after recrystallization from 95% ethanol gave 0.85 g (42.4%) of the nitrosated product, mp 139–140°. The nuclear magnetic resonance spectrum of the product showed the N-methyl protons shifted downfield to 2.76 ppm and the benzylic proton (triplet) at 3.49 ppm. The vinyl protons appeared as a quartet centered at 5.89 ppm. The methylene group appeared as two doublets at 4.6 and 4.75 ppm. The downfield shift of the methylene group indicates that it is adjacent to the N-nitroso group rather than adjacent to the carbonyl, suggesting structure **4** for the bisnitroso product.

Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 63.90; H, 5.33; N, 16.57. Found: C, 63.94; H, 5.31; N, 16.70.

The nitrosation reaction was carried out in identical fashion on 0.256 g of (-)-1-methyl-2,7-diphenyl-1,4-diaza-5-cycloheptanone (**3a**) and gave 69 mg (22%) of a dextrorotatory product whose infrared absorption spectrum was identical with that obtained from

(14) Melting points were obtained using a Kofler hot-stage melting point apparatus equipped with a polarizing microscope and are uncorrected. Optical rotatory dispersion curves were determined on a Rudolph recording spectropolarimeter Model 260/658/850/810-609 with a 1-cm path length. The solvent and concentration (g/100 ml) are given for each curve. The mass spectrum was determined by Applied Physics Corp. on an Atlas CH-4 mass spectrometer equipped with a T04 ion source and a vacuum lock. Microanalyses were determined by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y., or by Klaus Weinhardt of our laboratories using an F & M Model 180 carbon, hydrogen, and nitrogen analyzer. Infrared absorption spectra were obtained on a Perkin-Elmer Model 337 spectrophotometer. Solids were examined as mulls in halocarbon oil from 4000 to 1300 cm^{-1} and in Nujol from 1300 to 650 cm^{-1} .

the racemic lactam. The (+)-dinitroso product melted at 139–142°, $[\alpha]_D^{25} +11.50^\circ$ (c 1.17, chloroform), after recrystallization from ethanol.

Acid Hydrolysis of 1-Methyl-2,7-diphenyl-1,4-diaza-5-cycloheptanone (3). A solution of 1.3 g (0.0047 mole) of **3** in 50 ml of 20% hydrochloric acid was heated on a steam bath for 2 hr. After cooling, the solid which was deposited was separated by filtration and subsequently identified as cinnamic acid, mp 131–132°, mmp 131–133°. The filtrate was made basic with potassium carbonate and extracted with ether. The extracts were dried and removed leaving a yellow oil having infrared NH absorption at 3263 cm^{-1} , N-methyl at 1370 cm^{-1} , and aromatic CH absorption at 757 and 697 cm^{-1} . The amine failed to give a crystalline hydrochloride, acetyl, or benzoyl derivatives but formed a bisphenylthiourea derivative, mp 158.5–160°. The infrared absorption spectrum showed bands at 3312 (NH), 1542 (amide II), and 1340 and 1215 cm^{-1} (thiourea bands), as well as aromatic absorption at 758, 749, 703, and 685 cm^{-1} . The structure was postulated for the basic hydrolysis product as β -(N'-methylamino)- β -phenylethylamine (**6**) forming the derivative **11**.

Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{S}_2$: C, 65.71; H, 5.71; N, 13.33. Found: C, 65.95; H, 5.81; N, 13.45.

The hydrolysis of 1.2 g of (–)-1-methyl-2,7-diphenyl-1,4-diaza-5-cycloheptanone (**3a**), $[\alpha]_D^{24} -6.36^\circ$, was carried out as described above for the racemic material yielding 0.61 g (95%) of cinnamic acid, mmp 131–132°, and 0.0422 g of the diamine **6**, $[\alpha]_D^{24} -6.77^\circ$ (c 3.35, ethanol); phenylthiourea derivative, mp 160–161°, $[\alpha]_D^{24} +5.0^\circ$ (c 0.685, 95% ethanol). The infrared spectra of the diamine (–)-**6** and the derivative (+)-**11** were identical with those of racemic **6** and **11**, respectively. ORD of diamine **6** in ethanol (c 3.35): $[\phi]_{695} -6.26^\circ$, $[\phi]_{589} -6.26^\circ$, $[\phi]_{525} -21.0^\circ$.

(–)-Ethyl α -Aminophenylacetate Hydrochloride (**8**). A suspension of 10 g of α -aminophenylacetic acid (**7**), $[\alpha]_D^{24} -157.7^\circ$ (c 1.03, 5% HCl), in 200 ml of absolute ethanol was treated with anhydrous hydrogen chloride until the amino acid dissolved and the solution was saturated (about 10 min more). The solution was concentrated to one-third of the original volume and cooled to room temperature. Addition of 125 ml of anhydrous ether followed by cooling in ice gave 5.5 g (39%) of the hydrochloride (**8**) of ethyl α -aminophenylacetate, mp 198°, $[\alpha]_D^{24} -115^\circ$ (c 0.814, 5% HCl). No attempt was made to free the ester of unreacted acid, and the rotation of **8** is higher than reported in water (lit.¹⁵ mp 203°, $[\alpha]_D -89.3^\circ$ (c 5.07, H_2O)). ORD in ethanol (c 1.004): $[\phi]_{695} -207^\circ$, $[\phi]_{589} -250^\circ$, $[\phi]_{400} -651^\circ$, $[\phi]_{295} -1950^\circ$.

(–)- α -Aminophenylacetamide (**9**). The ester hydrochloride **8** was converted to the free base by neutralizing an aqueous solution with sodium hydroxide and extracting with ether. Removal of the solvent gave the oily ester. Absolute ethanol (40 ml) was saturated with anhydrous ammonia, the ester (4.6 g) freed from the hydrochloride was added, and the solution was allowed to stand at room temperature for 2 weeks. Removal of the solvent under reduced pressure and treatment of the residue with anhydrous ether gave 3.2 g (92%) of α -aminophenylacetamide (**9**), mp 128°, $[\alpha]_D^{24} -41.98^\circ$ (c 0.505, 95% ethanol). The infrared absorption spectrum was identical with that of racemic **9** prepared by the same procedure, mp 127–129° (lit.¹⁶ mp 128–129°). ORD in 95% ethanol (c 0.505): $[\phi]_{695} -68.4^\circ$, $[\phi]_{589} -37.0^\circ$, $[\phi]_{575} -51.3^\circ$, $[\phi]_{285} -482^\circ$.

(15) A. McKenzie and G. O. Wills, *J. Chem. Soc.*, 127, 283 (1925).

(16) R. G. Jones, *J. Am. Chem. Soc.*, 71, 78 (1949).

α -Formamidophenylacetamide (**10**). A mixture of 0.94 g of α -aminophenylacetamide (**9**) and 5 ml of formamide was heated in an oil bath at 150° for 15 min. After the reaction mixture was cooled to room temperature, water (30 ml) was added. The product was salted out by the addition of potassium carbonate and was collected by filtration, washed with cold water, and dried, giving 0.547 g (49.2%) of α -formamidophenylacetamide (**10**), mp 264–267°, which gave infrared bands of the formyl group at 2850 and 1700 cm^{-1} . This synthesis was modeled on that used for formulation of optically active diastereomers without racemization.^{17,18}

Optically active α -formamidophenylacetamide (**10**) was prepared by the method described above from 2.02 g of (–)- α -aminophenylacetamide (**9**), $[\alpha]_D^{24} -41.98^\circ$ (c 0.505, 95% ethanol), giving 1.07 g (45%) of **10**, mp 263–266°, $[\alpha]_D^{24} -19.25^\circ$ (c 0.405 methanol). The infrared absorption spectrum of optically active **10** was identical with that of racemic α -formamidophenylacetamide.

Anal. Calcd for $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_2$: C, 60.77; H, 5.66; N, 15.72. Found: C, 61.00; H, 5.69; N, 15.77.

ORD in methanol (c 1.34): $[\phi]_{680} -24.0^\circ$, $[\phi]_{589} -21.4^\circ$, $[\phi]_{375} -9.35^\circ$, $[\phi]_{350} -12.02^\circ$, $[\phi]_{270} -21.36^\circ$. Mass spectrum: 178 (parent peak), 161, 149, 134 (base peak), 118, 106, 91, 77, 44.

Lithium Aluminum Hydride Reduction of α -Formamidophenylacetamide (10). A solution of 0.47 g of α -formamidophenylacetamide (**10**) in tetrahydrofuran was added dropwise with stirring to a slurry of 0.5 g of lithium aluminum hydride in tetrahydrofuran heated under reflux. The resulting mixture was heated under reflux for 17 hr and cooled in an ice bath, and the excess lithium aluminum hydride was decomposed with 5 ml of wet ether and 10 ml of water. The organic layer was decanted, the inorganic salts were washed with ether, and the combined organic extracts were dried over potassium carbonate. Solvent removal by distillation under reduced pressure gave 0.328 g (82.6%) of β -(N'-methylamino)- β -phenylethylamine (**6**) as a yellow oil. The infrared spectrum of the diamine obtained from the above procedure was identical with that of β -(N'-methylamino)- β -phenylethylamine isolated from the hydrolysis of racemic **3**.

Treatment of this oil with phenyl isothiocyanate gave a solid phenylthiourea, mp 158–160°, whose infrared spectrum and melting point were identical with those obtained above. No depression of melting point was observed in a mixture melting point.

Optically active β -(N'-methylamino)- β -phenylethylamine (**6a**) was prepared, according to the method described above, from 0.465 g of (–)- α -formamidophenylacetamide (**10**), $[\alpha]_D^{24} -19.25^\circ$ (c 0.405, methanol), giving 0.328 g (84%) of (–)- β -(N'-methylamino)- β -phenylethylamine (**6a**) (levorotatory in ethanol); phenylthiourea, mp 162–163°, $[\alpha]_D^{24} +11.52^\circ$ (c 0.01, 95% ethanol). Under these reduction conditions racemization does not occur, as has been shown previously.¹⁹

Acknowledgment. The authors are grateful to the National Science Foundation for a grant (G-22,718) assisting in the purchase of a Varian A-60 nuclear magnetic resonance spectrometer. Thanks are due to Applied Physics Corporation for the determination of the mass spectrum.

(17) J. Weijlard, *et al.*, *ibid.*, 73, 1216 (1951).

(18) G. G. Lyle and W. Lacroix, *J. Org. Chem.*, 28, 900 (1963).

(19) D. E. Wolf, W. H. Jones, J. Valient, and K. Folkers, *J. Am. Chem. Soc.*, 72, 2820 (1950).