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Stereochemical Studies. X.[1] Effects of Neighboring Functional Groups on 1,2-Asymmetric Induction in the Reduction of Propiophenone Derivatives with Sodium Borohydride[2]

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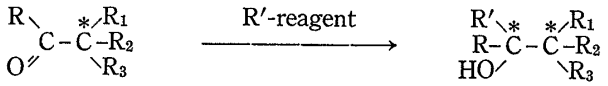
Effects of neighboring functional groups on 1,2-asymmetric induction in sodium borohydride reduction were examined with eight kinds of ketones (I—VIII) having functional groups, such as $-NH_2HCl$, -OH, and $-OCH_3$, at α- and/or β-positions to the carbonyl group. It was recognized that the stereochemical course of the reduction was highly dependent on the position of these functional groups, *i.e. erythro*-rich products were obtained in reduction of ketones having a functional group at α-position to the carbonyl group, while *threo*-rich products were obtained in reduction of ketones having a functional group at β-position to the carbonyl group. A six-membered empirical model (XXXVII) was proposed for predicting the stereochemical course in the reduction of ketones having a functional group at β-position to the carbonyl group.

Determinations of the relative configurations of the diastereomers (X, XI, XII, XIV, XV, and XVI) were also performed.

Numerous investigations[4,5] have been done on kinetically controlled 1,2-asymmetric induction in acylic ketones having one asymmetric center adjacent to the carbonyl group. To account for the stereochemical outcomes of these studies, three general explanations evaluating the transition states of the lowest energy have been advanced.[4c] In the first, three empirical models of reactant-like transition states were proposed, depending upon the substituents attached to the adjacent asymmetric center. Thus, an open chain model is



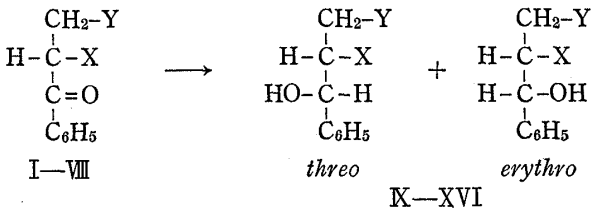
applied when the three substituents are all alkyl, aryl, or hydrogen,[5a] a cyclic model is applied when one of the substituents is hydroxy, methoxy, or amino group,[5d,e,g] and a dipolar model is applied when one of the substituents is a halogen.[5c,g] In the second explanation,[5h,i] models of reactant-like transition states, in which one of the substituents attached to the asymmetric center eclipses the carbonyl oxygen, are considered. Approaches to semi-quantitative prediction of product stereospecificities have also been made by the energetic evaluation of the

1) Part IX: K. Hiroi, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 246 (1972).
2) For a preliminary communication on this work, see S. Yamada and K. Koga, *Tetrahedron Letters*, **1967**, 1711.
3) Location: *Hongo, Bunkyo-ku, Tokyo.*
4) *a*) J.I. Klabunowski, "Asymmetrische Synthese," Deutscher Verlag der Wissenschaften, Berlin, 1963; *b*) D.R. Boyd and M.A. McKervey, *Quart. Rev.* (London), **22**, 95 (1968); *c*) S. Yamada and K. Koga, "Selective Organic Transformations," Vol. 1, ed. by B.S. Thyagarajan, Wiley-Interscience, New York, 1970, p. 1.
5) *a*) D.J. Cram and F.A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); *b*) J. Sicher, M. Svoboda, M. Hrdá, J. Rudinger, and F. Šorm, *Collection Czech. Chem. Commun.*, **18**, 487 (1953); *c*) J.W. Cornforth, R.H. Cornforth, and K.K. Mathew, *J. Chem. Soc.*, **1959**, 112; *d*) D.J. Cram and K.R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959); *e*) J.H. Stocker, P. Sidithunthorn, B.M. Benjamin, and C.J. Collins, *ibid.*, **82**, 3913 (1960); *f*) T. Matsumoto, T. Nishida, and H. Shirahama, *J. Org. Chem.*, **27**, 79 (1962); *g*) D.J. Cram and D.R. Wilson, *J. Am. Chem. Soc.*, **85**, 1245 (1963); *h*) G.J. Karabatsos, *ibid.*, **89**, 1367 (1967); *i*) G.J. Karabatsos and T.H. Althuis, *Tetrahedron Letters*, **1967**, 4991; *j*) M. Cherest, H. Felkin, and N. Prudent, *ibid.*, **1968**, 2199.

models when the substituents attached to the asymmetric center are all alkyl, aryl, or hydrogen. In the third explanation,[5j] the direction and the degree of 1,2-asymmetric induction are considered to be determined by the relative stabilities of the reactant-like transition states of the staggered conformations in which tortional strains and steric strains are evaluated to be most important.

A previous paper from our laboratory reported[6] that sodium borohydride reduction of N(α-methylphenacyl)benzamide in ethanol at room temperature gave a mixture of diastereomers, in which *erythro*-isomer (N-benzoylnorephedrine) predominated over *threo*-isomer (N-benzoyl-nor-pseudo-ephedrine). Using the above explanations, the stereochemical course of this reduction was considered to be influenced by the neighboring amide group attached to the asymmetric center.[6] As we are interested in the influences of neighboring functional groups on the direction and the degree of 1,2-aysmmetric induction, eight kinds of ketones (I—VIII) with oxygen- and nitrogen-functional groups at α- and/or β-positions to the carbonyl group were selected as substrates (see Table I) and their stereochemical outcomes in sodium borohydride reduction were examined.[7]

Table I. Starting Materials and Diastereomeric Products



Compound	X	Y	Compound	X	Y
I	NH_2HCl	H	IX	NH_2	H
II	CH_3	NH_2HCl	X	CH_3	NH_2
III	OCH_3	H	XI	OCH_3	H
IV	CH_3	OH	XII	CH_3	OH
V	NH_2HCl	OH	XIII	NH_2	OH
VI	NH_2HCl	NH_2HCl	XIV	NH_2	NH_2
VII	OCH_3	OH	XV	OCH_3	OH
VIII	OCH_3	NH_2HCl	XVI	OCH_3	NH_2

Result and Discussion

Preparation of Starting Materials

Of the eight kinds of ketones (I—VIII), I,[8] III,[9] IV,[10] and V[11] were prepared according to the methods in the literature. The syntheses of II, VI, VII, and VIII are formulated in Chart 1. Thus, II was obtained from IV by chlorination of the hydroxy group with thionyl chloride followed by Gabriel synthesis, VI was obtained from the corresponding di-phthalimide derivative (XVIII) by hydrolysis, and VII was prepared from 2-methoxyacetophenone (XIX) by hydroxymethylation with formalin. Ketone (VIII) was prepared from XX, which was ob-

6) K. Koga, H. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 243 (1966).
7) *a*) Although Fischer formulae and flying-wedge formulae are used to clarify stereochemical structures, all experiments in this paper were carried out with racemic compounds; *b*) To avoid confusion in stereochemical nomenclature, all diastereomeric compounds in this paper are named *threo* or *erythro*, based on their representations in Table I.
8) Chr. Schmidt, *Ber.*, **22**, 3249 (1899).
9) G.L. Stevens, W. Malik, and R. Platt, *J. Am. Chem. Soc.*, **72**, 4758 (1950).
10) H.E. Zimmermann and J. English, Jr., *J. Am. Chem. Soc.*, **76**, 2294 (1954).
11) S. Ikuma, *Yakugaku Zasshi*, **72**, 947 (1952).

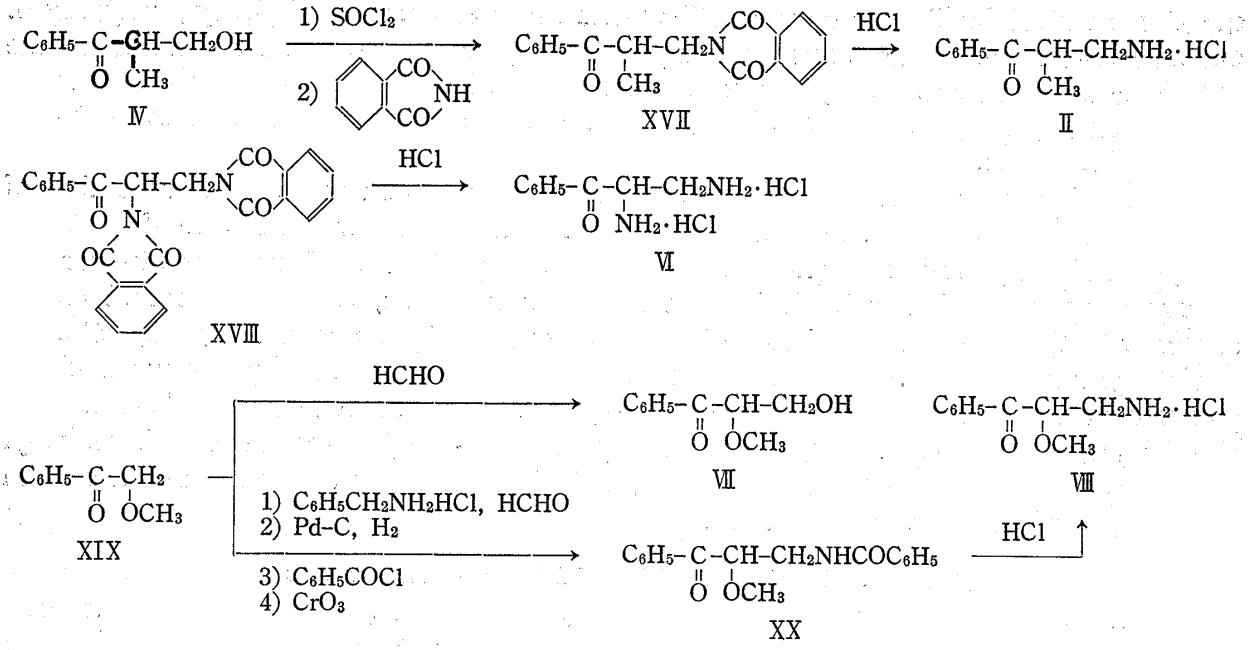
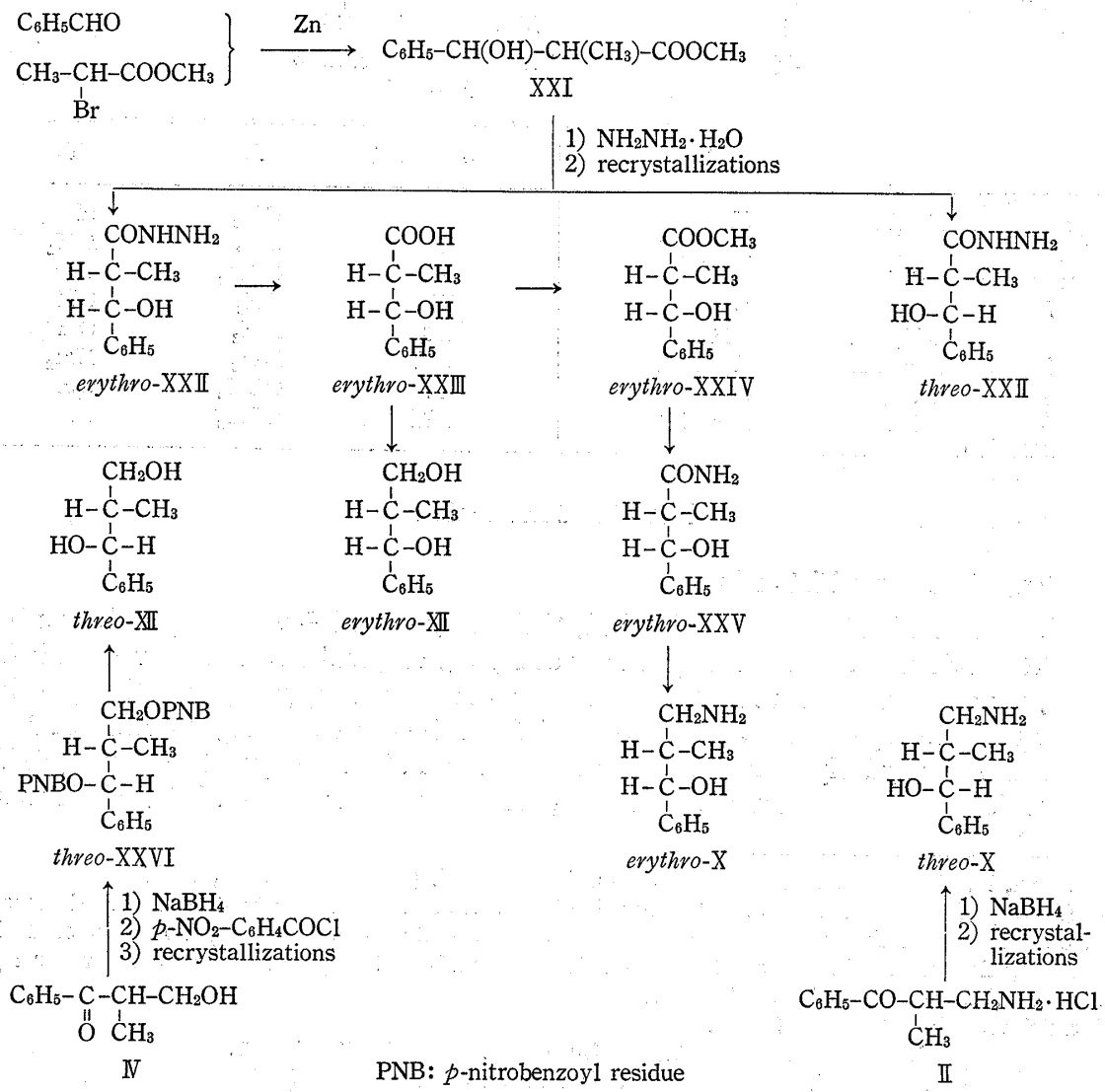


Chart 1. Synthetic Routes of II, VI, VII, and VIII



PNB: *p*-nitrobenzoyl residue

Chart 2. Syntheses and Relative Configurations of X and XII

tained from XIX by the Mannich reaction with benzylamine hydrochloride and formalin, followed by catalytic hydrogenolysis of the product with palladium-charcoal, N-benzoylation, and oxidation with chromic anhydride.

Relative Configurations of Diastereomeric Reduction Products

Of the eight pairs of diastereomeric products (IX—XVI), *threo*-IX,[12] *erythro*-IX,[6,12] *threo*-XIII,[13] and *erythro*-XIII[13] are known. Preparations of *threo*-X, *erythro*-X, *threo*-XII, and *erythro*-XII were performed from known samples as shown in Chart 2. Thus, the Reformatsky reaction of benzaldehyde with methyl 2-bromopropionate afforded a diastereomeric mixture of methyl 2-methyl-3-phenylhydracrylate (XXI). The reaction of XXI with hydrazine hydrate followed by fractional recrystallizations gave a high-melting isomer (*erythro*-XXII) and a low-melting isomer (*threo*-XXII), whose relative configurations had been demonstrated.[14] Hydrolysis of *erythro*-XXII afforded the corresponding carboxylic acid (*erythro*-XXIII); lithium aluminum hydride reduction of which gave *erythro*-XII. Esterification of *erythro*-XXIII followed by a reaction with ammonia in methanol afforded the *erythro*-amide (*erythro*-XXV). Lithium aluminum hydride reduction of *erythro*-XXV afforded *erythro*-X. On the other hand, *threo*-X and *threo*-XII were conveniently obtained from II and IV, respectively. Thus, sodium borohydride reduction of II followed by repeated recrystallizations afforded *threo*-X. Sodium borohydride reduction of IV followed by a reaction with *p*-nitrobenzoyl chloride in pyridine, then by repeated recrystallizations of the product gave one isomer (*threo*-XXVI) of mp 156—157°. Hydrolysis of this afforded *threo*-XII.

threo-XIV was obtained by lithium aluminum hydride reduction of *threo*-phenylserine amide.[15]

In similar reaction sequences, *threo*-XV, *erythro*-XV, and *erythro*-XVI were prepared and their relative configurations were demonstrated with the aid of nuclear magnetic resonance (NMR), as shown in Chart 3. Aldol condensation of benzaldehyde and methyl methoxyacetate was successful only when diethylaminomagnesium bromide was used[16] to give a diastereomeric mixture of methyl 2-methoxy-3-methylhydracrylate (XXVII) in 15% yield. The reaction of XXVII with ammonia in methanol followed by repeated recrystallizations of the product afforded the amide (*erythro*-XXVIII), from which the corresponding acid (*erythro*-XXIX), the alcohol (*erythro*-XV) and the amine (*erythro*-XVI) were derived. The isomeric alcohol (*threo*-XV) was obtained from VII as shown in Chart 3. Their relative configurations were demonstrated by converting diastereomeric diols (*threo*-XV and *erythro*-XV) to their corresponding 1,3-dioxane derivatives (*threo*-XXXI and *erythro*-XXXI, as well as *threo*-XXXII and *erythro*-XXXII). In their NMR spectra, signals of benzylic protons (Ha) appeared as doublets. Coupling constants were 2.3 and 2.1 Hz in the 1,3-dioxane derivatives (*threo*-XXXI and *threo*-XXXII, respectively) from one diastereomeric diol (*threo*-XV), while 9.0 and 8.1 Hz in the 1,3-dioxane derivatives (*erythro*-XXXI and *erythro*-XXXII, respectively) from the other diastereomeric diol (*erythro*-XV). It is well known that the coupling constant (J_{ab}) is decided by the dihedral angle with the adjacent proton (Hb). In six-membered cyclic compounds, values are reported to be 9.2,[17a] 5—8,[17b] 8—14,[17c] or 11.0[17d] Hz when Ha and Hb are

12) W.N. Nagai and S. Kanao, *Ann.*, **470**, 157 (1929).
13) K.N.F. Shaw and S.F. Fox, *J. Am. Chem. Soc.*, **75**, 3417 (1953).
14) *a*) H.E. Zimmermann and J. English, Jr., *J. Am. Chem. Soc.*, **76**, 2291 (1954); *b*) J. Wein, *Acta Chim. Acad. Sci. Hung.*, **17**, 181 (1958).
15) Pl. A. Plattner, A. Boller, H. Frick, A. Fürst, B. Hegedüs, H. Kirchensteiner, St. Majnoni, R. Schlapfer, and H. Spiegelberg, *Helv. Chim. Acta*, **40**, 1531 (1957).
16) *cf.* K. Sisido, K. Kumazawa, and H. Nozaki, *J. Am. Chem. Soc.*, **82**, 125 (1960).
17) *a*) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *b*) L.M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N.Y., 1959; *c*) N.S. Baccha and D.H. Williams, "Application of NMR Spectroscopy. Illustration from the Steroidal Field," Holden-Day Inc., San Francisco, London, Amsterdam, 1964; *d*) K.C. Ramey and J. Messick, *Tetrahedron Letters*, **1965**, 4423.

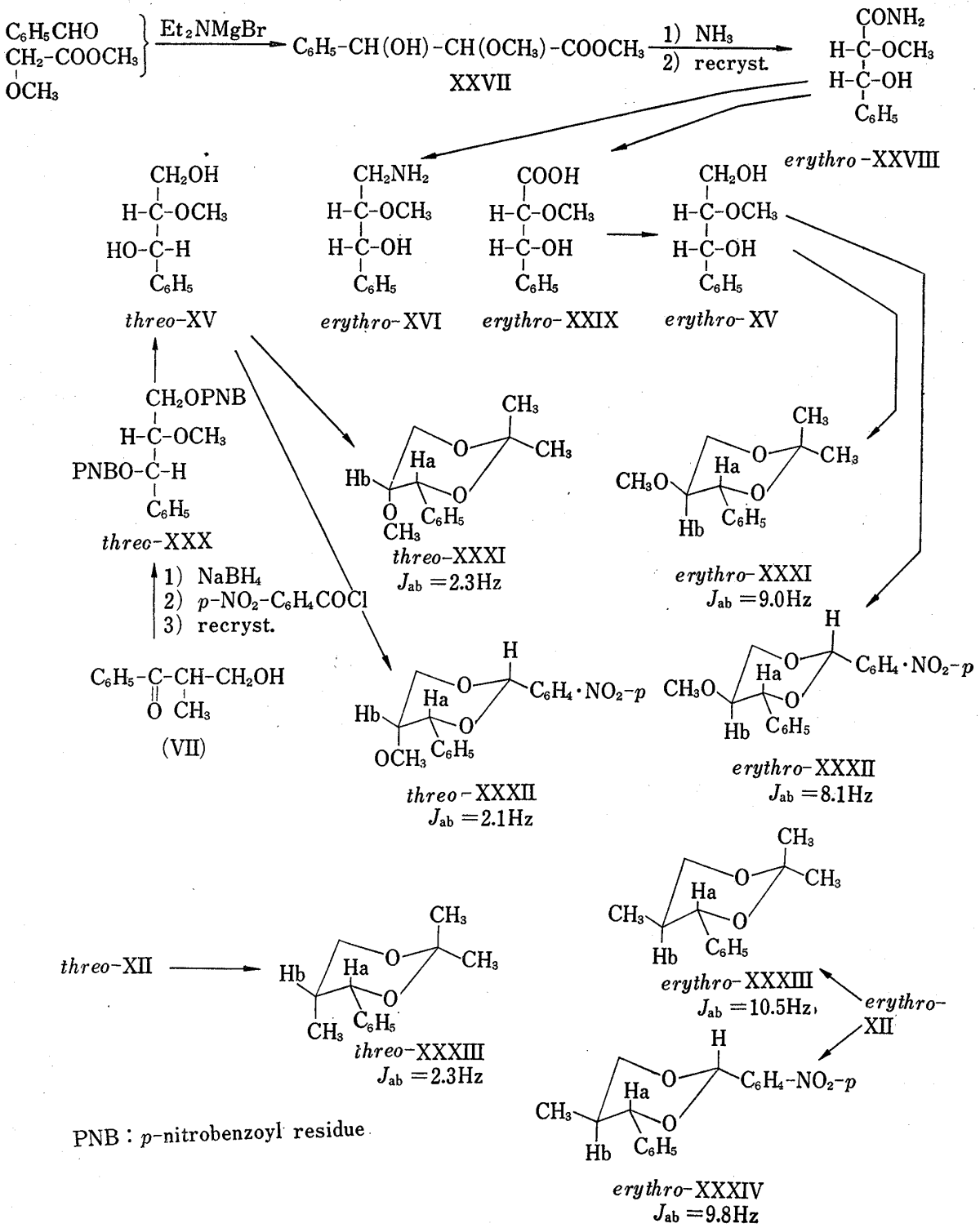


Chart 3. Syntheses and Relative Configurations of XV and XVI

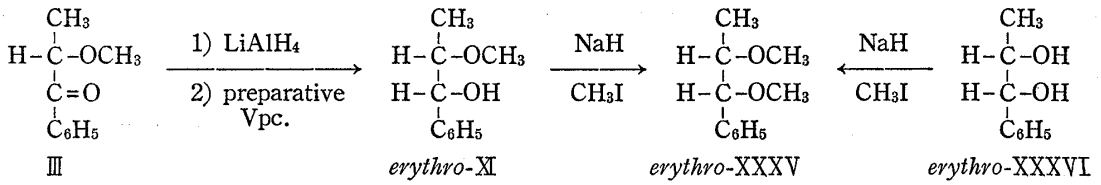


Chart 4. The Isolation and Relative Configuration of *erythro*-XI

trans-diaxial (180°), 1.7,[17a] 2—4,[17b] 1—7,[17c] or 2.8[17d] Hz when Ha and Hb are *cis* (60°). Values for reference compounds prepared from *threo*-XII and *erythro*-XII of known relative configurations, as above, are consistent with reported values. Therefore, the relative configurations of XV and XVI were determined, as shown in Chart 3.

Finally the alcohol (*erythro*-XI) was isolated from a mixture of diastereomers by preparative gas chromatography. Its relative configuration was determined by converting it to the corresponding dimethyl ether derivative (*erythro*-XXXV), which was identified with an authentic specimen derived from known *erythro*-1-phenyl-1,2-propanediol (*erythro*-XXXVI),[18] as shown in Chart 4.

Methods for Analyzing the Ratios of Diastereomeric Products

It was desirable for the present study to be able to analyze the ratios of diastereomers (IX—XVI) produced without purifications or derivative preparations. Therefore, analyses by NMR spectroscopy were initially investigated with various solvents. As a result, acetic acid was found to be the most suitable solvent for the following three reasons; (1) signals of diastereomeric protons at the benzylic position separate well except in XV, (2) products dissolve quite well, and (3) signals of amino- and hydroxy-protons shift away to the carboxyl proton region. Chemical shifts of signals of diastereomeric benzylic protons in the reduction products in acetic acid are shown in Table II. Inspection using synthetic mixture of *threo*-IX and *erythro*-IX showed that known and calculated per cent compositions agreed within 2%, when signal areas were analyzed gravimetrically.

Table II. A List of Chemical Shifts (τ-value) of Benzylic Protons in Diastereomers[a] (in AcOH, 60 MHz)

	threo-isomer	*erythro*-isomer
IX	5.33	4.80
X	4.95	5.50
XI	5.45[b]	5.09
XII	5.05	5.50
XIII	5.16[c]	4.86[c]
XIV	5.00	4.58[b]
XV	5.08	5.08
XVI	5.05[b]	5.00

a) for nomenclature, see 7b;
b) A value obtained from the spectrum of a mixture of diastereomers;
c) A value obtained by the instrument operating at 100 MHz.

Analyses of the diastereomeric ratios of XV were performed by gas chromatography after acetylation of the reduction product.

Stereochemical Course of Sodium Borohydride Reduction

Reduction of the ketones (1 mmole) was carried out with sodium borohydride (3 mmoles for III, IV, and VII, 4 mmoles for I, II, V, and VIII, 5 mmoles for VI) in ethanol (20 ml) at reflux and ice-cooling (1—4°) temperatures. In ketones I, II, III, and IV, $-NH_2HCl$, -OH, or $-OCH_3$ groups are attached at α- or β-position to the carbonyl group. In ketones V, VI, VII, and VIII, these groups are attached both at α- and β-positions to the carbonyl group. The direction and degree of 1,2-asymmetric induction were investigated in relation to the neighboring functional groups. Results are shown in Table III, from which the following conclusions were drawn.

It is apparent that the directions of 1,2-asymmetric induction in sodium borohydride reduction of I and III agree with those predicted by a five-membered cyclic model[5d,e,g] with the

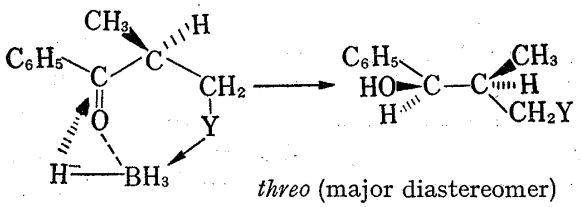
18) M. Svoboda and J. Sicher, *Collection Czech. Chem. Commun.*, **20**, 1452 (1955).

Table III. Diastereomeric Ratios in Reduction Products

Compound	C_6H_5-CO-CH(X)-CH_2Y X	Y	at 1—4° *threo*:*erythro* (%)	(%)	at 78° *threo*:*erythro* (%)	(%)	$\lvert\Delta\Delta F^{\ddagger}\rvert$[a] kcal/mole
I	NH_2HCl	H	<5	>95	8	92	1.7
II	CH_3	NH_2HCl	94	6	90	10	1.5
III	OCH_3	H	17	83	27	73	0.7
IV	CH_3	OH	77	23	71	29	0.6
V	NH_2HCl	OH	19	81	44	56	0.2
VI	NH_2HCl	NH_2HCl	50	50	36	64	0.4
VII	OCH_3	OH	34	66	41	59	0.3
XIII	OCH_3	NH_2HCl	2	1[b]	3	2[b]	0.3

a) Calculated based on data at 78°;
b) rough estimation

participation of a functional group attached at α-position to the carbonyl group. In II and IV, reduction products were rich in *threo*-isomer. This result is explainable by assuming a six-membered empirical model (XXXVII), with participation of a functional group at β-position to the carbonyl group. The six-membered model (XXXVII) is, therefore, empirically applicable for predicting the stereochemical course in the reduction of ketones having a functional group at β-position to the carbonyl group.[4c,5b,f]



XXXVII

threo (major diastereomer)

As to the degree of 1,2-asymmetric induction, they are far greater in the reduction of I and II than in that of III and IV. Although it is not certain that the influence of one mole of hydrochloric acid in the reduction of I and II is, we believe, from the synthetic point of view, that there is a high degree of 1,2-asymmetric induction in the sodium borohydride reduction of α-amino ketone hydrochloride and β-amino ketone hydrochloride to the corresponding *erythro*-isomer and *threo*-isomer, respectively. Also, the effect of the -NH_2HCl group on the degree of 1,2-asymmetric induction is similar whether the group is situated at α- or β-position to the carbonyl group.

Finally, stereoselectivity is decreased in the reduction of ketones with functional groups both at α- and β-positions to the carbonyl group. This is a reasonable supposition because the effect of the group at α-position on the direction of 1,2-asymmetric induction is opposite to that at β-position, which results in cancellation of these effects on each other.

Experimental[19]

Materials——$NaBH_4$ was purchased from Kawaken Fine Chemicals Co. Ltd., and its purity was assumed to be 95%. Commercial AcOH of special grade was used as a solvent in determining the ratios of diastereomers by NMR spectroscopy.

19) All melting and boiling points are uncorrected. IR spectra were measured with a Koken DS-402G spectrometer. NMR spectra were measured with a JNM 3H-60 spectrometer operating at 60 MHz or with a Varian A-100 spectrometer operating at 100 MHz using TMS as an internal standard. Analytical gas chromatography was performed with a Shimadzu Gas Chromatograph GC-1B equipped with a hydrogen flame ionization detector. Preparative gas chromatography was performed with the same instrument equipped with an automatic preparative attachment and a thermal conductivity detector. Microanalyses and spectral measurements were performed by the members of the Central Analysis Room of this Faculty.

2-Aminopropiophenone Hydrochloride (I)——mp 184—185° (decomp.) (reported[8] mp 183—184° (decomp.)). IR ν_{max}^{KBr} cm^{-1}: 1692 (C=O). *Anal.* Calcd. for $C_9H_{11}ON \cdot HCl$: N, 7.55. Found: N, 7.65.

2-Methoxypropiophenone (III)——bp 103—105° (7 mmHg) (reported[9] bp 76—77° (0.8 mmHg)). IR $\nu_{max}^{liq.}$ cm^{-1}: 2805 (OCH_3). 1695 (C=O).

Semicarbazone: mp 151—153°. *Anal.* Calcd. for $C_{11}H_{15}O_2N_3$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.96; H, 6.91; N, 19.17.

3-Hydroxy-2-methylpropiophenone (IV)——bp 136—137° (3 mmHg) (reported[10] bp 116—117° (1.5—2.0 mmHg)). IR $\nu_{max}^{liq.}$ cm^{-1}: —3400 (OH), 1685 (C=O).

2,4-Dinitrophenylhydrazone: mp 150—152°. *Anal.* Calcd. for $C_{16}H_{16}O_5N_4$: C, 55.81; H, 4.68; N, 16.27. Found: C, 55.82; H, 4.52; N, 16.12.

2-Amino-3-hydroxypropiophenone Hydrochloride (V)——mp 164—165° (decomp.) (reported[11] mp 164°). IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O). *Anal.* Calcd. for $C_9H_{11}O_2N \cdot HCl$: N, 6.95. Found: N, 6.90.

N(2-Methyl-3-oxo-3-phenylpropyl)phthalimide (XVII)——$SOCl_2$ (7.8 g, 65.6 mmoles) was added to a solution of IV (7.0 g, 43.7 mmoles) in benzene (50 ml) under stirring and the whole was allowed to stand at room temperature overnight. After evaporation to dryness, the residue was heated with phthalimide (6.5 g, 44 mmoles) and K_2CO_3 (3.1 g, 22 mmoles) at 180—200° for 3 hr. The reaction mixture was taken up in $CHCl_3$, washed with 10% aq. NaOH, 10% aq. HCl, H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the $CHCl_3$ gave a solid, which was recrystallized from benzene–hexane to colorless prisms of XVII (7.3 g, 57% yield), mp 74—76.5°. IR ν_{max}^{KBr} cm^{-1}: 1772, 1717 (phthalimide), 1678 (C=O). *Anal.* Calcd. for $C_{18}H_{15}O_3N$: N, 4.78. Found: N, 4.62.

3-Amino-2-methylpropiophenone Hydrochloride (II)——A solution of XVII (7.0 g) in AcOH (70 ml) and conc. HCl (50 ml) was refluxed for 8 hr, then evaporated to dryness. The residue was taken up in cold H_2O (*ca.* 100 ml), after which insoluble materials were filtered off and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH–ether to the colorless powder of II (2.1 g, 44% yield), mp 122—123.5°. IR ν_{max}^{KBr} cm^{-1}: 1677 (C=O). *Anal.* Calcd. for $C_{10}H_{13}ON \cdot HCl$: C, 60.15; H, 7.07; N, 7.02. Found: C, 60.23; H, 6.86; N, 7.23.

2,3-Diaminopropiophenone Dihydrochloride (VI)——N(3-Oxo-3-phenyl-2-phthalimidopropyl)phthalimide (XVIII) (mp 206—208°, reported mp 203—205°,[20a] 210°[20b]) (10.3 g) was dissolved in AcOH (145 ml) and conc. HCl (66 ml), and the whole was refluxed for 10 hr. The reaction mixture was evaporated *in vacuo* to dryness, after which the residue was dissolved again in AcOH (145 ml) and conc. HCl (66 ml). The solution was refluxed for 3 hr, then evaporated to dryness *in vacuo*. 10% aq. HCl (150 ml) and H_2O (80 ml) were added to the residue, and the insoluble materials were filtered off. The filtrate was washed with AcOEt and benzene. The aqueous layer was treated with charcoal and filtered. The filtrate was evaporated to dryness *in vacuo* to give a solid, which was recrystallized from MeOH–ether to colorless leaflets of VI (1.9 g, 33% yield), mp 221—221.5° (decomp.). IR ν_{max}^{KBr} cm^{-1}: 1705 (C=O). *Anal.* Calcd. for $C_9H_{12}ON_2 \cdot 2HCl$: C, 45.58; H, 5.95; N, 11.81. Found: C, 45.43; H, 6.17; N, 11.93.

3-Hydroxy-2-methoxypropiophenone (VII)——A suspension of 2-methoxyacetophenone (XIX) (bp 116—119° (15 mmHg)) (6.5 g, 43 mmoles), paraformaldehyde (2.6 g, 86 mmoles), MeOH (100 ml), H_2O (50 ml), and Ca $(OH)_2$ (150 mg, 2 mmoles) was refluxed for 30 min. The reaction mixture became a clear solution. Na_2SO_3 (5.4 g, 43 mmoles) was added to the solution and then the solution was made acidic with 10% aq. H_2SO_4. The reaction mixture was concentrated to about one-third of its volume under reduced pressure, and extracted with $CHCl_3$. Dried $CHCl_3$ extracts were evaporated, *in vacuo* to dryness, and the residual oil (6.5 g) was chromatographed on silica gel (130 g) with 2.5% EtOH–$CHCl_3$ to give colorless oil of VII (3.1 g, 40% yield). IR $\nu_{max}^{liq.}$ cm^{-1}: 3400 (OH), 2830 (OCH_3), 1690 (C=O).

2,4-Dinitrophenylhydrazone: mp 195—196°. *Anal.* Calcd. for $C_{16}H_{16}O_3N_4$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.04; H, 4.41; N, 15.59.

N(2-Methoxy-3-oxo-3-phenylpropyl)benzamide (XX)——A mixture of XIX (18.6 g, 124 mmoles), benzylamine hydrochloride (17.8 g, 124 mmoles) and 35% aq. formalin (12.6 ml) was heated on a water-bath for 1.5 hr. The reddish brown reaction mixture was evaporated to dryness under reduced pressure. The residue was mixed with H_2O (*ca.* 500 ml) and the whole was washed with ether. The aqueous layer was made alkaline with K_2CO_3, and extracted with benzene. The benzene solution was washed with H_2O, and extracted with 10% aq. HCl. Evaporation of the aqueous HCl solution *in vacuo* to dryness afforded a yellowish-brown viscous oil (14.0 g). The oil was dissolved in EtOH (130 ml) and hydrogenated at the atmospheric pressure of H_2 with 5% Pd-C (4 g) until 1485 ml of H_2 was absorbed. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in H_2O, after which some insoluble materials were filtered off, then the filtrate was made alkaline with K_2CO_3. Extraction with ether followed by evaporation of the dried ether solution afforded a viscous oily residue, which was mixed with benzoyl chloride (14.1 g, 100 mmoles) in pyridine (100 ml) and the whole was allowed to stand at room temperature overnight. From the usual work up, a neutral fraction was obtained as a viscous oil

20) *a*) M.C. Rebstock, *J. Org. Chem.*, **19**, 851 (1954); *b*) K. Yee-sheng, P. Pei-chuan, L. Sheun-hsing, C. Chi-hao, and H. Hsiu-yung, *Scientia Sinica*, **7**, 738 (1958).

(15.1 g). This was dissolved in a solution of NaOH (2.0 g) in MeOH (200 ml), and the whole was refluxed for 1.5 hr. Evaporation of the solvent to dryness *in vacuo* gave a residue, which was taken up in $CHCl_3$. The $CHCl_3$ suspension was washed with 10% aq. HCl, 10% aq. NaOH, H_2O, dried, and evaporated to give an oil (10.5 g), which was dissolved in AcOH (30 ml). Under ice-cooling, a solution of CrO_3 (3.72 g, 37.2 mmoles) in AcOH (15 ml) and H_2O (5 ml) was added, and the whole was allowed to stand for 4 hr under ice-cooling. The reaction mixture was poured into ice–water, and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with 10% aq. NaOH, H_2O and dried. Evaporation of the $CHCl_3$ *in vacuo* gave an oil (7.9 g) which became semi-solid on scratching. Recrystallization from AcOEt–hexane afforded crude XX (4.3 g, 12% yield) of mp 111—114°. Recrystallizations from benzene–hexane raised the mp to 118—119° of colorless fine needles. IR ν_{max}^{KBr} cm^{-1}: 3380 (NH), 1688 (C=O), 1646, 1532 (amide). *Anal.* Calcd. for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.27; H, 6.01; N, 5.01.

3-Amino-2-methoxypropiophenone Hydrochloride (VIII)——A mixture of XX (3.54 g) and *ca.* 18% aq. HCl (50 ml) was refluxed for 6 hr. After cool, the reaction mixture was washed with ether, then was evaporated *in vacuo* to dryness to give a solid. Recrystallization of this solid from EtOH–isopropyl ether afforded crude VIII (940 mg, 35% yield) of mp —113°. Recrystallizations from the same solvent system raised the mp to 118°. IR ν_{max}^{KBr} cm^{-1}: 1695 (C=O). *Anal.* Calcd. for $C_{10}H_{13}O_2N \cdot HCl$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.69; H, 6.42; N, 6.47.

***threo*-2-Amino-1-phenyl-1-propanol (DL-Norpseudoephedrine) (*threo*-IX)**——mp 75.5—76.5° (reported mp 71°,[12] 76.8—77.5°[14a]). NMR (in AcOH, 60 MHz) τ: 8.90 (3H, doublet, J=6.8 Hz, $C\underline{H}_3$-CH-), ~6.4 (1H, multiplet, CH_3-$C\underline{H}(NH_2)$-CH-), 5.33 (1H, doublet, J=9.7 Hz, C_6H_5-$C\underline{H}$(OH)-CH-), 2.68 (5H, singlet, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_9H_{13}ON$: N, 9.26. Found: N, 9.04.

***erythro*-2-Amino-1-phenyl-1-propanol (DL-Norephedrine) (*erythro*-IX)**——mp 100—101.5° (reported mp 100—101.5°[6]). NMR (in AcOH, 60 MHz) τ: 8.90 (3H, doublet, J=6.3 Hz, $C\underline{H}_3$-CH-), —6.3 (1H, multiplet, CH_3-$C\underline{H}(NH_2)$-CH-), 4.80 (1H, doublet, J=2.4 Hz, C_6H_5-$C\underline{H}$(OH)-CH-), 2.67 (5H, singlet, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_9H_{13}ON$: N, 9.26. Found: N, 9.30.

***threo*-2-Amino-1-phenyl-1,3-propanediol(*threo*-XIII)**——*threo*-Phenylserine ethyl ester hydrochloride (mp 138—139.5°, reported[13] mp 140°) was reduced with $NaBH_4$[21] to *threo*-XIII of mp 87—89° (reported[13] mp 88—89°). NMR (in AcOH, 100 MHz) τ: 5.16 (1H, C_6H_5-$C\underline{H}$(OH)-CH-). *Anal.* Calcd. for $C_9H_{13}O_2N$: N, 8.38. Found: N, 8.50.

***erythro*-2-Amino-1-phenyl-1,3-propanediol (*erythro*-XIII)**——*erythro*-Phenylserine ethyl ester hydrochloride (mp 175.5—176° (decomp.), reported[13] mp 175—176° (decomp.)) was reduced with $NaBH_4$[21] to *erythro*-XIII of mp 104° (reported[13] mp 104—105°) as colorless thin plates. NMR (in AcOH, 100 MHz) τ: 4.86 (1H, C_6H_5-$C\underline{H}$(OH)-CH-). *Anal.* Calcd. for $C_9H_{13}O_2N$: N, 8.38. Found: N, 8.50.

***erythro*-2-Methyl-3-phenylhydracrylic Acid Hydrazide(*erythro*-XXII)**——A diastereomeric mixture of methyl 2-methyl-3-phenylhydracrylate (XXI) (32.5 g, 0.167 mole) prepared according to the reported method[14] was mixed with hydrazine hydrate (19.5 g, 0.488 mole) at room temperature, and the whole was agitated until it solidified. After standing at room temperature for 2 days, the whole was recrystallized from 140 ml of H_2O. The deposited crystals were recrystallized from EtOH to afford colorless needles of *erythro*-XXII (11.6 g, 36% yield) of mp 194—195° (reported[14b] mp 196°). IR ν_{max}^{KBr} cm^{-1}: 1633, 1538 (hydrazide). *Anal.* Calcd. for $C_{10}H_{14}O_2N_2$: N, 14.42; Found: N, 14.70.

By evaporating the above aqueous mother liquor to dryness, followed by recrystallizing the residue twice from EtOH, the corresponding *threo*-XXII (10.6 g, 33% yield) was obtained as colorless fine needles of mp 138—139°.

***erythro*-2-Methyl-3-phenylhydracrylic Acid (*erythro*-XIII)**——A mixture of *erythro*-XXII (1.0 g) in 20% aq. KOH (30 ml) and EtOH (10 ml) was refluxed for three and one-third hr. After cool, the reaction mixture was brought to pH 1 with conc. HCl, and the whole was extracted with ether. On evaporation of the dried ethereal extracts, a pale brown solid was obtained. Recrystallizations of this solid from benzene–hexane followed by recrystallization from AcOEt-hexane afforded colorless prisms of *erythro*-XXIII (640 mg, 69% yield) of mp 94.5—95.5° (reported[14a] mp 96.5—97.5°). *Anal.* Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.75; H, 6.66.

Methyl *erythro*-2-Methyl-3-phenylhydracrylate (*erythro*-XXIV)——a) A diastereomeric mixture of methyl 2-methyl-3-phenylhydracrylate (XXI) (3.0 g) was dissolved in hexane (300 ml) at room temperature, and the solution was cooled to —20°. Colorless fine needles of *erythro*-XXIV (420 mg, 14% yield) were obtained and identified with the specimen obtained in b).

b) *erythro*-XXIV was prepared from *erythro*-XXIII according to the reported method,[14a] mp 49.5—51.5° (reported[14a] mp 43—46°). IR ν_{max}^{KBr} cm^{-1}: 3466 (OH), 1714 (ester). *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.03; H, 7.27. Found: C, 68.24; H, 7.11.

***erythro*-2-Methyl-3-phenylhydracrylamide(*erythro*-XXV)**——a) A solution of *erythro*-XXIV (420 mg) in 18% NH_3 in MeOH (25 ml) was sealed tightly and allowed to stand at about 35° for 4 days. After evaporating to dryness *in vacuo*, the residue was recrystallized from AcOEt–hexane to afford colorless prisms of

21) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), 13, 995 (1965).

erythro-XXV (320 mg, 82% yield) of mp 133.5—135°. IR ν_{max}^{KBr} cm^{-1}: 3350, 3175 (OH and NH), 1675, 1617 (amide). *Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.97; H, 7.17; N, 7.83.

b) A mixture of diastereomers of methyl 2-methyl-3-phenylhydracrylate (XXI) (910 mg) was treated as in a), and the crude product was recrystallized from EtOH (5 ml) to give colorless prisms of *erythro*-XXV (140 mg, 17% yield), mp 133—134.5°. This sample was shown to be identical with the sample prepared in a) by IR and mixed mp test.

***erythro*-3-Amino-2-methyl-1-phenyl-1-propanol (*erythro*-X)**——A solution of *erythro*-XXV (200 mg, 1.12 mmoles) in THF (20 ml) was added dropwise to a suspension of $LiAlH_4$ (220 mg, 5.6 mmoles) in THF (30 ml), and the whole was refluxed for 5 hr. A mixture of 10% aq. NaOH (0.37 ml) and H_2O (0.63 ml) was added to the reaction mixture. Deposited precipitates were filtered off, and washed with a small amount of THF. The combined filtrate and washings were evaporated to dryness *in vacuo*, and the residue was dissolved in 10% aq. HCl. This aqueous solution was washed with ether, then evaporated to dryness *in vacuo*. The residue was taken up in $CHCl_3$, and $CHCl_3$ saturated with NH_3 was added in excess after which the deposited precipitates were filtered off. Evaporation of the filtrate *in vacuo* left the colorless oil of *erythro*-X (170 mg, 92% yield). NMR (in AcOH, 60 MHz) τ: 9.26 (3H, doublet, J=6.8 Hz, C$\underline{H}_3$-CH-), 5.50 (1H, doublet, J=8.6 Hz, C_6H_5-C$\underline{H}$(OH)-CH-), 2.71 (5H, singlet, $C_6\underline{H}_5$-).

erythro-5-Methyl-6-phenyl-1,3-oxazin-2-one: A mixture of *erythro*-X (830 mg, 5 mmoles) in benzene (30 ml), 10% aq. KOH (13 ml) and 24% (w/w) $COCl_2$ in toluene (7.0 ml) was shaken vigorously for 30 min. The organic layer was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was recrystallized from benzene–hexane to *erythro*-5-methyl-6-phenyl-1,3-oxazin-2-one (690 mg, 72% yield) of mp 152—157°. Further recrystallization from the same solvent raised the mp to 157—159°. IR ν_{max}^{KBr} cm^{-1}: 3260 (NH), 1700 (C=O). NMR (in $CDCl_3$, 60 MHz) τ: 9.20 (3H, doublet, J=6.8 Hz, C$\underline{H}_3$-CH-), 5.15 (1H, doublet, J=10.1 Hz, C_6H_5-C$\underline{H}$(O-)-CH-), 2.66 (5H, singlet, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_{11}H_{13}O_2N$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.20; H, 7.15; N, 7.46.

***threo*-3-Amino-2-methyl-1-phenyl-1-propanol (*threo*-X)**——A mixture of II (1.9 g, 10 mmoles) and $NaBH_4$ (600 mg, 15 mmoles) in EtOH (60 ml) was allowed to stand at room temperature overnight. The reaction mixture was brought to pH 3 with 10% aq. HCl. Deposited precipitates were filtered off, and the filtrate was evaporated to dryness. The residue was taken up in $CHCl_3$ and $CHCl_3$ saturated with NH_3 was added in excess. Deposited precipitates were filtered off, and the filtrate was evaporated to dryness *in vacuo* to give a solid. The solid was recrystallized twice from isopropyl ether, three times from benzene–hexane to afford colorless needles of *threo*-X (260 mg, 13% yield) of mp 93—94°. NMR (in AcOH, 60 MHz) τ: 9.17 (3H, doublet, J=6.8 Hz, C$\underline{H}_3$-CH-), 4.95 (1H, doublet, J=3.8 Hz, C_6H_5-C$\underline{H}$(OH)-CH-), 2.61 (5H, singlet, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_{10}H_{15}ON$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.57; H, 9.15; N, 8.52.

***erythro*-2-Methyl-1-phenyl-1,3-propanediol (*erythro*-XII)**——A suspension of *erythro*-XXIII (950 mg, 5.3 mmoles) and $LiAlH_4$ (640 mg, 16 mmoles) in THF (100 ml) was refluxed for 3 hr and the whole was allowed to stand at room temperature overnight. A solution of 10% aq. NaOH (1.0 ml) and H_2O (1.6 ml) was added to the reaction mixture, and the deposited precipitates were filtered off. Evaporation of the filtrate *in vacuo* afforded an oily residue, which was chromatographed on alumina (100 g) with $CHCl_3$–benzene (95: 5) to give *erythro*-XII (700 mg, 80% yield) as a colorless liquid. NMR (in AcOH, 60 MHz) τ: 9.34 (3H, doublet, J=6.8 Hz, C$\underline{H}_3$-CH-), 5.50 (1H, doublet, J=7.5 Hz, C_6H_5-C$\underline{H}$(OH)-CH-), 2.68 (5H, singlet, $C_6\underline{H}_5$-).

erythro-2,2,5-Trimethyl-4-phenyl-1,3-dioxane (*erythro*-XXXIII): A mixture of *erythro*-XII (300 mg), anhyd. $CuSO_4$ (1.0 g) and dehyd. acetone (20 ml) was stirred at room temperature for 4 days. Insoluble materials were filtered off, and washed with a small amount of acetone. The filtrate and the washings were combined and evaporated to dryness *in vacuo*. The oily residue was chromatographed on silica gel (32 g) with AcOEt–benzene (1: 2) to give *erythro*-XXXIII (230 mg, 54% yield) as a colorless oil, bp 150—152° (30 mmHg). NMR (in CCl_4, 60 MHz) τ: 9.42 (3H, doublet, J=7.1 Hz, C$\underline{H}_3$-CH-), 8.61 (3H, singlet, C$\underline{H}_3$-C), 8.53 (3H, singlet, C$\underline{H}_3$-C), —8.1 (1H, multiplet, CH_3-C$\underline{H}$(CH_2-)-CH-), 5.70 (1H, doublet, J=10.5 Hz, C_6H_5-C$\underline{H}$(O-)-CH-), 2.67 (5H, singlet, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.72; H, 8.81.

erythro-5-Methyl-2-(*p*-nitrophenyl)-4-phenyl-1,3-dioxane (*erythro*-XXXIV): A solution of *erythro*-XII (700 mg, 4.2 mmoles), *p*-nitrobenzaldehyde (750 mg, 5 mmoles) and conc. H_2SO_4 (1 drop) in dehyd. xylene (50 ml) was evaporated to dryness *in vacuo* under water bath heating. Dehyd. xylene (50 ml) was added to the residue again, and the whole was evaporated in the same manner. The residue was taken up in benzene, washed with aq. $NaHSO_3$, H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the benzene *in vacuo* afforded a solid, which was recrystallized from benzene–hexane to give pale yellow prisms of *erythro*-XXXIV (760 mg, 60% yield) of mp 120—123°. Two recrystallizations from the same solvent system raised the mp to 122—123°. NMR (in $CDCl_3$, 60 MHz) τ: 9.32 (3H, doublet, J=6.8 Hz, C$\underline{H}_3$-CH-), 7.6—8.2 (1H, multiplet, CH_3-C$\underline{H}$(CH_2-)-CH-), 6.30 (1H, triplet, J=10.8 Hz, -O-C$\underline{H}_2$-CH-), 5.70 (1H, doublet-doublet, J=10.8 and 4.5 Hz, -O-C$\underline{H}_2$-CH-), 5.58 (1H, doublet, J=9.8 Hz, C_6H_5-C$\underline{H}$(O-)-CH-), 4.26 (1H, singlet, -O-C$\underline{H}$(C_6H_5)-O-), 1.7—2.8 (9H, multiplet, $C_6\underline{H}_5$- and -$C_6\underline{H}_4$-). *Anal.* Calcd. for $C_{17}H_{17}O_4N$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.09; H, 5.71; N, 4.77.

***threo*-2-Methyl-1-phenyl-1,3-propanediol O,O-Di-*p*-nitrobenzoate (*threo*-XXVI)**——Ketone (IV) (6.56 g, 40 mmoles) was reduced with $NaBH_4$ (800 mg, 20 mmoles) in EtOH (100 ml) at room temperature and

treated as usual to give an oily product (6.18 g). This oil was mixed with *p*-nitrobenzoyl chloride (15.2 g, 81.8 mmoles) in pyridine (150 ml). The whole was heated on a water-bath for 4 hr, then was kept at room temperature overnight. The pyridine was evaporated *in vacuo*, after which residue was taken up in $CHCl_3$, washed with 10% aq. NaOH, H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the $CHCl_3$ afforded a pale yellow oil (7.5 g), which was treated again with *p*-nitrobenzoyl chloride (7.6 g, 41 mmoles), as above. The oily neutral fraction was dissolved in hot benzene (*ca.* 100 ml) and was allowed to cool to room temperature to give a solid (4.89 g). This solid was recrystallized 6 times from benzene to give pale yellow prisms of *threo*-XXVI (1.30 g, 7% yield based on IV), mp 156—157°. IR ν_{max}^{KBr} cm^{-1}: 1726, 1721 (ester), 1532, 1351 (nitro), 1269 (ester). *Anal.* Calcd. for $C_{24}H_{20}O_8N_2$: C, 62.02; H, 4.34; N, 6.03. Found: C, 62.18; H, 4.60; N, 5.82.

***threo*-2-Methyl-1-phenyl-1,3-propanediol (*threo*-XII)**——A solution of *threo*-XXVI (930 mg, 2 mmoles) and NaOH (220 mg, 5.5 mmoles) in EtOH (30 ml) and H_2O (3 ml) was refluxed for 1.5 hr, then evaporated *in vacuo* to dryness. The residue was dissolved in H_2O (15 ml) and extracted continuously with ether. The ether was dried and evaporated to dryness to give *threo*-XII (310 mg, 93% yield) as an oil. NMR (in AcOH, 60 MHz) τ: 9.17 (3H, doublet, J=6.8 Hz, $C\underline{H}_3$-CH-), —6.4 (2H, multiplet, -CH-$C\underline{H}_2O$-), 5.05 (1H, doublet, J=4.2 Hz, C_6H_5-$C\underline{H}$(OH)-CH-), 2.70 (5H, singlet, $C_6\underline{H}_5$-).

threo-2,2,5-Trimethyl-4-phenyl-1,3-dioxane (*threo*-XXXII): This sample was prepared from *threo*-XII using a procedure similar to the synthesis of *erythro*-XXXII, then it was distilled at 25 mmHg with a bath temperature of 160—170°. NMR (in CCl_4, 60 MHz) τ: 9.22 (3H, doublet, J=6 Hz, $C\underline{H}_3$-CH-), 6.36 (1H, doublet-doublet, J=11.3 and 1.5 Hz, -O-$C\underline{H}_2$-CH-), 5.75 (1H, doublet-doublet, J=11.3 and 2.3 Hz, -O-$C\underline{H}_2$-CH-), 4.91 (1H, doublet, J=2.3 Hz, C_6H_5-$C\underline{H}$(O-)-CH-), 2.76 (5H, singlet, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found C, 75.51; H, 8.79.

***threo*-2,3-Diamino-1-phenyl-1-propanol (*threo*-XIV)**——*threo*-Phenylserine amide (mp 123.5—124.5° (reported[15] mp 118—120°), IR ν_{max}^{KBr} cm^{-1}: 3350, 3200 (OH and NH), 1667, 1606 (amide)) (1.08 g, 6 mmoles) was reduced with $LiAlH_4$ (1.65 g, 42 mmoles) in THF (80 ml) in the usual manner to give *threo*-XIV (440 mg, 56% yield) as a colorless liquid. NMR (in AcOH, 60 MHz) τ: 5.00 (1H, doublet, J=*ca.* 6 Hz, C_6H_5-$C\underline{H}$(OH)-CH-).

N^2,N^3-Dibenzamide: A solution of *threo*-XIV (440 mg, 2.66 mmoles) and benzoyl chloride (1.31 g, 9.3 mmoles) in pyridine (30 ml) was refluxed for 3 hr, and evaporated to dryness. The residue was taken up in $CHCl_3$, washed with 10% aq. HCl, satd. aq. $NaHCO_3$, H_2O, dried over anhyd. Na_2SO_4, and the $CHCl_3$ solution was evaporated to dryness *in vacuo* to afford an oil (890 mg). This oil was dissolved in a solution of KOH (170 mg, 3 mmoles) in EtOH (17 ml) and the whole was refluxed for 2.5 hr. After evaporation of the solvent, the residue was taken up in $CHCl_3$, washed with satd. aq. $NaHCO_3$, 10% aq. HCl, H_2O, dried, and evaporated to give a solid. Recrystallization of the solid from EtOH afforded colorless needles of N^2,N^3-dibenzamide (590 mg, 60% yield) of mp 195—197°. Recrystallizations twice from EtOH raised the mp to 199—200°. *Anal.* Calcd. for $C_{23}H_{22}O_3N_2$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.50; H, 5.93; N, 7.42.

A Mixture of Diastereomeric Methyl 2-Methoxy-3-phenylhydracrylate (XXVII)——A solution of Et_2NH (22.0 g, 0.3 mole) in ether (40 ml) was added to a Grignard solution prepared from EtBr (32.7 g, 0.3 mole) and Mg (7.3 g, 0.3 atom) in ether (120 ml), and the whole was stirred at room temperature for 30 min and at reflux temperature for 30 min. After cooling to −5°, a solution of benzaldehyde (10.6 g, 0.1 mole) and methyl methoxyacetate (10.4 g, 0.1 mole) in ether (90 ml) was added to the above solution, and the whole was stirred at −5° for 2 hr. Initially, a viscous creamy oil separated, which gradually became powder-like precipitates. The reaction mixture was decomposed with satd. aq. NH_4Cl (30 ml), the insolubles were filtered off and washed with ether. The combined filtrate and the washings were successively washed with 10% aq. H_2SO_4, satd. aq. $NaHSO_3$, satd. aq. $NaHCO_3$, and satd. aq. NaCl. Evaporation of the dried ether solution followed by distillation of the residue at reduced pressure afforded XXVII (3.1 g, 15% yield), bp 120—130° (3 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: —3400 (OH), 2815 (OCH_3), 1745 (ester).

***erythro*-2-Methoxy-3-phenylhydracrylamide (*erythro*-XXVIII)**——A solution of XXVII (4.67 g) in MeOH (100 ml) satd. with NH_3 was closed tightly and allowed to stand at *ca.* 30° for 2 days. Evaporation of the solvent *in vacuo* gave a solid, which was recrystallized from AcOEt to afford crude *erythro*-XXVIII (2.1 g, 48.5% yield) as colorless prisms of mp 153—155°. Two recrystallizations from AcOEt afforded colorless prisms of mp 157.5—158.5°. IR ν_{max}^{KBr} cm^{-1}: 3375, 3190 (OH and NH), 2815 (OCH_3), —1640 (amide). *Anal.* Calcd. for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.63; H, 6.93; N, 7.10.

***erythro*-2-Methoxy-3-phenylhydracrylic Acid (*erythro*-XXIX)**——A mixture of *erythro*-XXVIII (780 mg) and 10% aq. HCl (15 ml) was refluxed for 2.5 hr. After cool, the reaction mixture was extracted continuously with ether. The ether was dried and evaporated to give a solid, which was recrystallized from $CHCl_3$–hexane to colorless plates of *erythro*-XXIX (470 mg, 60% yield) of mp 104—107°. Further recrystallizations raised the mp to 104.5—107°. *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.35; H, 6.04.

***erythro*-2-Methoxy-1-phenyl-1,3-propanediol (*erythro*-XV)**——The reduction of *erythro*-XXIX (310 mg, 1.58 mmoles) with $LiAlH_4$ (165 mg, 4.32 mmoles) in THF (50 ml) was performed in the usual manner to give *erythro*-XV (280 mg, 97% yield) as a colorless oil. NMR (in AcOH, 60 MHz) τ: 6.71 (3H, singlet, -$OC\underline{H}_3$), 5.08 (1H, doublet, J=5.4 Hz, C_6H_5-$C\underline{H}$(OH)-CH-), 2.61 (5H, singlet, $C_6\underline{H}_5$-).

erythro-2,2-Dimethyl-5-methoxy-4-phenyl-1,3-dioxane (*erythro*-XXXI): This sample was prepared from *erythro*-XV in a manner similar to the synthesis of *threo*-XXXI described below, then it was distilled at 21 mmHg under a bath temperature of 160—170° to *erythro*-XXXI in 86% yield. NMR (in CCl_4, 60 MHz) τ: 8.62 (3H, singlet, C$\underline{H}_3$-C), 8.52 (3H, singlet, C$\underline{H}_3$-C), 7.02 (3H, singlet, -OC$\underline{H}_3$), 5.53 (1H, doublet, J=9 Hz, C_6H_5-C$\underline{H}$(O-)-CH-), 2.72 (5H, singlet, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.01; H, 8.33.

erythro-5-Methoxy-2-(*p*-nitrophenyl)-4-phenyl-1,3-dioxane (*erythro*-XXXII): A solution of *erythro*-XV (260 mg, 1.4 mmoles), *p*-nitrobenzaldehyde (230 mg, 1.5 mmoles) and conc. H_2SO_4 (1 drop) in dehyd. xylene was treated as in the synthesis of *erythro*-XXXIV, and the product was recrystallized from hexane to afford pale yellow prisms of *erythro*-XXXII (220 mg, 50% yield) of mp 96—98°. IR ν_{max}^{KBr} cm^{-1}: 2835 (OCH_3), 1516, 1356 (nitro). NMR (in $CDCl_3$, 100 MHz) τ: 6.98 (3H, singlet, OC$\underline{H}_3$), 6.37 (1H, triplet, J=10.2 Hz, -O-C$\underline{H}_2$-CH-), 5.64 (1H, doublet-doublet, J=5.0 and 10.2 Hz, -O-C$\underline{H}_2$-CH-), 5.57 (1H, doublet, J=8.1 Hz, C_6H_5-C$\underline{H}$(O-)-CH-), 4.47 (1H, singlet, -O-C$\underline{H}$(C_6H_4-NO_2)-O-). *Anal.* Calcd. for $C_{17}H_{17}O_5N$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.95; H, 5.53; N, 4.49.

***threo*-2-Methoxy-1-phenyl-1,3-propanediol O,O-Di-*p*-nitrobenzoate (*threo*-XXX)**——The ketone (VII) (3.0 g, 16.7 mmoles) was reduced with $NaBH_4$ (680 mg, 17 mmoles) in EtOH (80 ml) at room temperature and treated in the usual manner to afford an oily product, which was mixed with *p*-nitrobenzoyl chloride (7.4 g, 40 mmoles) in pyridine (100 ml), and the whole was refluxed for 4 hr. The pyridine was evaporated *in vacuo* and the residue was treated as usual to give an oil (6.5 g) as a neutral component. The oil was dissolved in AcOEt (50 ml), then hexane (*ca.* 50 ml) was added and the whole was allowed to stand at room temperature overnight. The deposited solid (2.29 g) of mp 99—103° was recrystallized 6 times from AcOEt to give pale yellow prisms of *threo*-XXX (0.73 g, 14% yield) of mp 162.5—164°. IR ν_{max}^{KBr} cm^{-1}: 2830 (OCH_3), 1732 (ester), 1526, 1351 (nitro). *Anal.* Calcd. for $C_{24}H_{20}O_9N_2$: C, 60.00; H, 4.20; N, 5.83. Found: C, 59.69; H, 4.17; N, 5.91.

***threo*-2-Methoxy-1-phenyl-1,3-propanediol (*threo*-XV)**——A solution of *threo*-XXX (1.25 g, 2.6 mmoles) and NaOH (240 mg, 6 mmoles) in EtOH (34 ml) and H_2O (5 ml) was refluxed for 1.5 hr, then evaporated to dryness. The residue was dissolved in H_2O (15 ml) and the whole was extracted continuously with ether. The ether extracts was dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo* to afford *threo*-XV (460 mg, 97% yield) as a colorless oil. NMR (in AcOH, 60 MHz) τ: 6.59 (3H, singlet, -OC$\underline{H}_3$), 5.08 (1H, doublet, J=5.4 Hz, C_6H_5-C$\underline{H}$(OH)-CH-), 2.61 (5H, singlet, $C_6\underline{H}_5$-).

threo-2,2-Dimethyl-5-methoxy-4-phenyl-1,3-dioxane (*threo*-XXXI): A mixture of *threo*-XV (280 mg), anhyd. $CuSO_4$ (800 mg) and dehyd. acetone (20 ml) was stirred at room temperature for 3 days. Insoluble materials were filtered off, and washed with a small amount of acetone. The combined filtrate and the washings were evaporated to dryness. The residual oil (270 mg) was chromatographed on silica gel (27 g) with benzene–AcOEt (2: 1) to give *threo*-XXXI (180 mg, 53% yield) as a colorless oil which was distilled at 24 mmHg under a bath temperature of 160—180°. NMR (in CCl_4, 60 MHz) τ: 8.56 (6H, singlet, C$\underline{H}_3$-C-C$\underline{H}_3$), 7.03 (3H, singlet, -OC$\underline{H}_3$), 5.10 (1H, doublet J=2.3 Hz, C_6H_5-C$\underline{H}$(O-)-CH-), 2.68 (5H, singlet, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.98; H, 8.10.

threo-5-Methoxy-2-(*p*-nitrophenyl)-4-phenyl-1,3-dioxane (*threo*-XXXII): This sample was prepared from *threo*-XV in a manner similar to the synthesis of *erythro*-XXXIV. Recrystallizations from hexane afforded *threo*-XXXII in 60% yield as pale yellow prisms of mp 133.5—135°. IR ν_{max}^{KBr} cm^{-1}: 2820 (OCH_3), 1523, 1346 (nitro). NMR (in $CDCl_3$, 100 MHz) τ: 6.83 (3H, singlet, -OC$\underline{H}_3$), —5.81 (1H, doublet-doublet, J=12.3 and 1.8 Hz, -O-C$\underline{H}_2$-CH-), —5.44 (1H, doublet-doublet, J=12.3 and 1.8 Hz, -O-C$\underline{H}_2$-CH-), 4.91 (1H, doublet, J=2.1 Hz, C_6H_5-C$\underline{H}$(O-)-CH-), 4.16 (1H, singlet, -O-C$\underline{H}$(C_6H_4-NO_2)-O-). *Anal.* Calcd. for $C_{17}H_{17}O_5N$: C, 64.75; H, 5.43; N, 4.44. Found: C, 65.02; H, 5.56; N, 4.25.

***erythro*-3-Amino-2-methyl-1-phenyl-1-propanol (*erythro*-XVI)**——A mixture of *erythro*-XXVIII (255 mg, 1.31 mmoles) and $LiAlH_4$ (250 mg, 6.55 mmoles) in THF (45 ml) was refluxed for 5 hr, then left at room temperature overnight. A solution of 10% aq. NaOH (0.4 ml) and H_2O (0.85 ml) was added to the reaction mixture. The insoluble materials were filtered off, and washed with a small amount of THF. The filtrate and the washings were combined and evaporated *in vacuo* to leave an oil, which was dissolved in 10% aq. HCl (20 ml). After washing with $CHCl_3$ and benzene, the aqueous layer was evaporated to dryness *in vacuo* and the residue was taken up in $CHCl_3$. NH_3 gas in excess was introduced to the $CHCl_3$ solution. Deposited precipitates were filtered off and washed with a small amount of $CHCl_3$. Evaporation of the combined filtrate and the washings *in vacuo* to dryness gave *erythro*-XVI (185 mg, 79% yield) as a pale yellow liquid. NMR (in AcOH, 60 MHz) τ: 6.65 (3H, singlet, -OC$\underline{H}_3$), 5.00 (1H, doublet, J=4.5 Hz, C_6H_5-C$\underline{H}$(OH)-CH-), 2.67 (5H, singlet, $C_6\underline{H}_5$-).

erythro-5-Methoxy-6-phenyl-1,3-oxazin-2-one: A mixture of *erythro*-XVI (350 mg, 1.93 mmoles) in benzene (10 ml), 10% aq. KOH (5.6 ml) and 19% (w/w) $COCl_2$ solution in toluene (3.5 ml) was shaken vigorously for 10 min. The organic layer was separated, washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was recrystallized from benzene–hexane to afford *erythro*-5-methoxy-6-phenyl-1,3-oxazin-2-one (190 mg, 45% yield) of mp 148.5—150°. IR ν_{max}^{KBr} cm^{-1}: 2825 (OCH_3), 1706 (C=O). *Anal.* Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.70; H, 7.24; N, 6.61.

***erythro*-2-Methoxy-1-phenyl-1-propanol (*erythro*-XI)**——A diastereomeric mixture of 2-methoxy-1-phenyl-1-propanol, obtained form III by $LiAlH_4$ reduction in the usual manner, was subjected to preparative gas chromatography using a column of 20% carbowax 20M on C-22 (1 cm in diameter and 4.5 m in length) at 198° Of the two incompletely separated peaks that appeared at t_R 45 min to t_R 60 min, the latter peak (t_R 55 min to t_R 60 min) was collected and distilled to give *erythro*-XI of bp 104—105° (5 mmHg). Gas chromatographic analysis showed that the diastereomeric purity of this sample was not less than 97%. IR $\nu_{max}^{liq.}$ cm^{-1}: 3440 (OH), 2830 (OCH_3). NMR (in AcOH, 60 MHz) τ: 8.96 (3H, doublet, J=6.3 Hz, $C\underline{H}_3$-CH-), 6.65 (3H, singlet, -$OC\underline{H}_3$), ~6.3 (1H, multiplet, CH_3-C$\underline{H}$(OCH_3)-CH-), 5.09 (1H, doublet, J=4.5 Hz, C_6H_5-C$\underline{H}$(OH)-CH-), 2.70 (5H, singlet, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.23; H, 8.43.

***erythro*-1,2-Dimethoxy-1-phenylpropane (*erythro*-XXXV)**——a) A suspension of NaH (obtained from 1.06 g (22 mmoles) of a 50% oil dispersion by washing it with dehyd. xylene and dioxane) in dioxane (20 ml) was added to a solution of *erythro*-1-phenyl-1,2-propanediol (mp 92—93°, reported[18] mp 91—92°) (1.40 g, 9.2 mmoles) in dioxane (30 ml), and the whole was stirred at room temperature for 40 min. CH_3I (4.9 ml, *ca.* 80 mmoles) was added to this mixture and the whole was allowed to stand at room temperature overnight. Insoluble materials were filtered off, and the filtrate was evaporated to dryness under reduced pressure. The reddish-yellow residue was subjected to column chromatography on silica gel with benzene to give a pale yellow oil (1.1 g), which was distilled to the colorless oil of *erythro*-XXXV (900 mg, 54% yield) of bp 88—89° (9 mmHg). IR $\nu_{max}^{liq.}$ cm^{-1}: 2820 (OCH_3), 1114 (ether). NMR (in CCl_4, 60 MHz) τ: 8.87 (3H, doublet, J=6 Hz, $C\underline{H}_3$-CH-), 6.91 (3H, singlet, -$OC\underline{H}_3$), 6.81 (1H, singlet, -$OC\underline{H}_3$), ~6.7 (1H, multiplet, CH_3-C$\underline{H}$-(OCH_3)-CH-), 6.05 (1H, doublet, J=6 Hz, C_6H_5-C$\underline{H}$(OCH_3)-CH-), 2.77 (5H, singlet, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.06; H, 8.96.

b) *erythro*-XI (1.40 g, 8.4 mmoles) obtained as above was treated with NaH (480 mg as a 50% oil dispersion, 10 mmoles) and CH_3I (2.5 ml, *ca.* 40 mmoles) in dioxane (50 ml) as in a) to give *erythro*-XXXV (310 mg, 20% yield) as a colorless liquid. This sample was shown to be identical with the sample obtained in a) by comparing their IR and NMR spectra.

Examination of the NMR Method for Analyses of the Ratios of Diasteromeric Mixture of *threo*-XI and *erythro*-XI——Sample of known compositions of diasteromers(sample a: 99.3 mg of *erythro*-IX and 11.0 mg of *threo*-IX in 0.55 ml of AcOH; sample b: 230.3 mg of *erythro*-IX and 10.6 mg of *threo*-IX in 1.20 ml of AcOH) were prepared and their NMR spectra (100 MHz)[19] were measured at τ 4 to 6, several times. Doublet peaks at τ 4.80 (corresponding to *erythro*-IX) and at τ 5.33 (corresponding to *threo*-IX) in the chart were cut out, and their weights were measured. A shown in Table IV, per cent compositions of the calculated and the found agreed within 2%. The existence of *threo*-IX in sample b could also be detected by NMR operating at 60 MHz.[19]

Table IV. Estimations of Diastereomeric Ratios by NMR

Sample		Calcd.(%)	Found (%)							Mean (%)
a	*erythro*-IX	90.0	89.3,	89.0,	89.3,	88.8,	88.8,	89.4,	88.7	89.0
	threo-IX	10.0	10.7,	11.0,	10.7,	11.2,	11.2,	10.6,	11.3	11.0
b	*erythro*-IX	95.6	94.1,	93.3,	94.5,	94.0,	93.9,	93.8,	92.7	93.9
	threo-IX	4.4	5.9,	6.7,	5.5,	6.0,	6.1,	6.2,	7.3	6.1

General Procedure for the Reduction of Ketones (I—VIII) with Sodium Borohydride——Reduction of ketones (1 mmoles) was carried out with $NaBH_4$ (3 mmoles for III, IV, and VII, 4 mmoles for I, II, V, and VIII, 5 mmoles for VI) in EtOH (20 ml) at reflux and ice-cooling (1—4°) temperatures. The reaction time was 5 hr at reflux temperature, or 3 days at ice-cooling temperature. The reaction mixture was brought to pH 3 with 10% aq. HCl. Precipitates were filtered off, washed with a small amount of EtOH, and the combined filtrate and the washings were evaporated under reduced pressure. The residue was dissolved in H_2O, made alkaline with aq. K_2CO_3 when the reduction products were basic substances, and the whole was extracted continously with ether. The ether solution was dried over anhyd. Na_2SO_4, then evaporated to dryness under reduced pressure. Reduction products thus obtained were subjected to the above analytical procedures. In all experiments, the chemical yields of this reduction were not less than 94%, except for 85% for VI.

Results of Analyses of the Ratios of Diastereomers——Results are shown in Table III. Ratios of diastereomeric mixture in the reduction products of VII were determined from their O,O-diacetates by gas chromatography using 5% PEGA on Diasolid L. Ratios of the diastereomeric mixture in the reduction products of VIII are given as rough measurements due to the incomplete separation of diastereomeric signals in their NMR spectra.

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