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Stereochemical Studies. XVII.[1] Nitrous Acid Deaminations of (R)-α-Methylphenylalanine and Its Methyl Ester in Acetic Acid[2]

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Detailed examinations on nitrous acid deamination of (*R*)-α-methylphenylalanine methyl ester (I) in acetic acid have shown that elimination (68%), substitution (21%), hydrogen migration (8%), and phenyl migration (3%) products were obtained. The stereochemical courses of these products were also clarified. Substitution reactions giving α-hydroxy ester (VIII) and α-acetoxy ester (IX) proceeded with net retention, while migration reactions proceeded with net inversion at their migration termini, as shown in Table I. Nitrous acid deamination of (*R*)-α-methylphenylalanine (II) in acetic acid was also examined as shown in Table II.

Reactions of nitrous acid or of nitrosyl halides with optically active α-amino acids are reported[4] to exclusively give the corresponding α-substituted acids with retention of configuration, due to participation of the neighboring carboxylate group. Reactions with α-amino acid esters are reported[4] to proceed with racemization together with excess inversion about the asymmetric α-carbon atom due to the lack of participation of the neighboring ester group. Exceptions[4] to this generalization have been reported in reactions of those optically active α-amino acids having no hydrogen or having an aryl group at the asymmetric α-carbon atom. Thus, it was reported[5] that completely optically inactive products were obtained on treatment of optically active α-amino-α methylbutyric acid (isovaline) with nitrous acid or nitrosyl bromide. It was also reported[4b,6] that the reaction of nitrous acid with optically active phenylglycine afforded mandelic acid with retention accompanied by extensive racemization.

The present paper is concerned with nitrous acid deaminations of (*R*)-α-methylphenylalanine methyl ester (I) and (*R*)-α-methylphenylalanine (II) in acetic acid, and is the first example of detailed analyses of deaminations of α-amino acid derivatives having tertiary carbinamine structures. The present system possesses the following peculiar advantages for the study of deamination reactions. (1) Nitrous acid deaminations of (*S*)-phenylalanine ethyl ester (III) and (*S*)-phenylalanine (IV) in acetic acid have been thoroughly studied,[7] and differences in the reactivity of the secondary and tertiary cationic centers can be assessed. (2) Only three examples have been reported on the stereochemistry of substitution reactions in deaminations of acylic tertiary carbinamines, in which the reactions of α-amino-α-methylbutyric acid[5] described above, and α-naphthylphenyl-*p*-tolylmethylamine[8] are reported to

1) Part XVI: M. Taniguchi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 1438 (1972).
2) A part of this work was presented at the 91st Annual Meeting of the Pharmaceutical Society of Japan, Fukuoka, April 1971.
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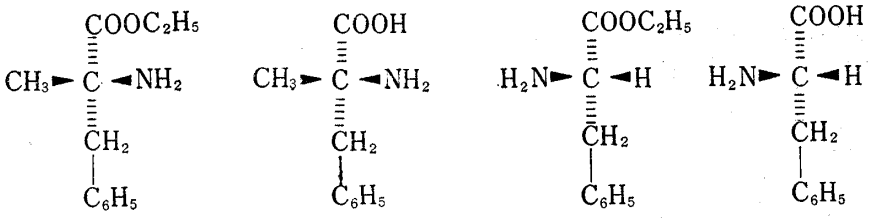
4) *a*) A Neuberger, "Advances in Protein Chemistry," Vol. 4, ed. by M.L. Anson and J.T. Edsall, Academic Press, New York, 1948, p. 333; *b*) P. Brewster, F. Hiron, E.D. Hughes, C.K. Ingold, and P.A.D.S. Rao, *Nature*, **166**, 179 (1950).
5) E. Fischer and R. von Gravenitz, *Ann.*, **406**, 1 (1914).
6) *a*) E. Fischer and O. Weichbold, *Ber.*, **41**, 1286 (1908); *b*) A. McKenzie and G.W. Clough, *J. Chem. Soc.*, **95**, 777 (1909).
7) *a*) S. Yamada, T. Kitagawa, and K. Achiwa, *Tetrahedron Letters*, **1967**, 3007; *b*) K. Koga, C.C. Wu, and S. Yamada, *ibid.*, **1971**, 2283; *c*) K. Koga, C.C. Wu, and S. Yamada, *ibid.*, **1971**, 2287.
8) C.L. Arcus, J. Kenjon, and S. Levin, *J. Chem. Soc.*, **1951**, 407.

proceed with racemization, while the reactions of 2-phenyl-2-butylamine[9] are reported to proceed to complete retention depending upon the methods of deamination. (3) There is no report[10] on the stereochemistry of the migration reaction to the acyclic tertiary cationic center in deamination.



I II III IV

Chart 1

Result and Discussion

Starting Materials and Products

Optically pure I and II were prepared according to the reported method,[11] then were diazotized with sodium nitrite in acetic acid. Analyses by gas chromatography showed that the products contained several components, which were separated by column chromatography and preparative gas chromatography. These were identified as shown in Table I and II.

Table I. Results of Nitrous Acid Deamination of I in AcOH

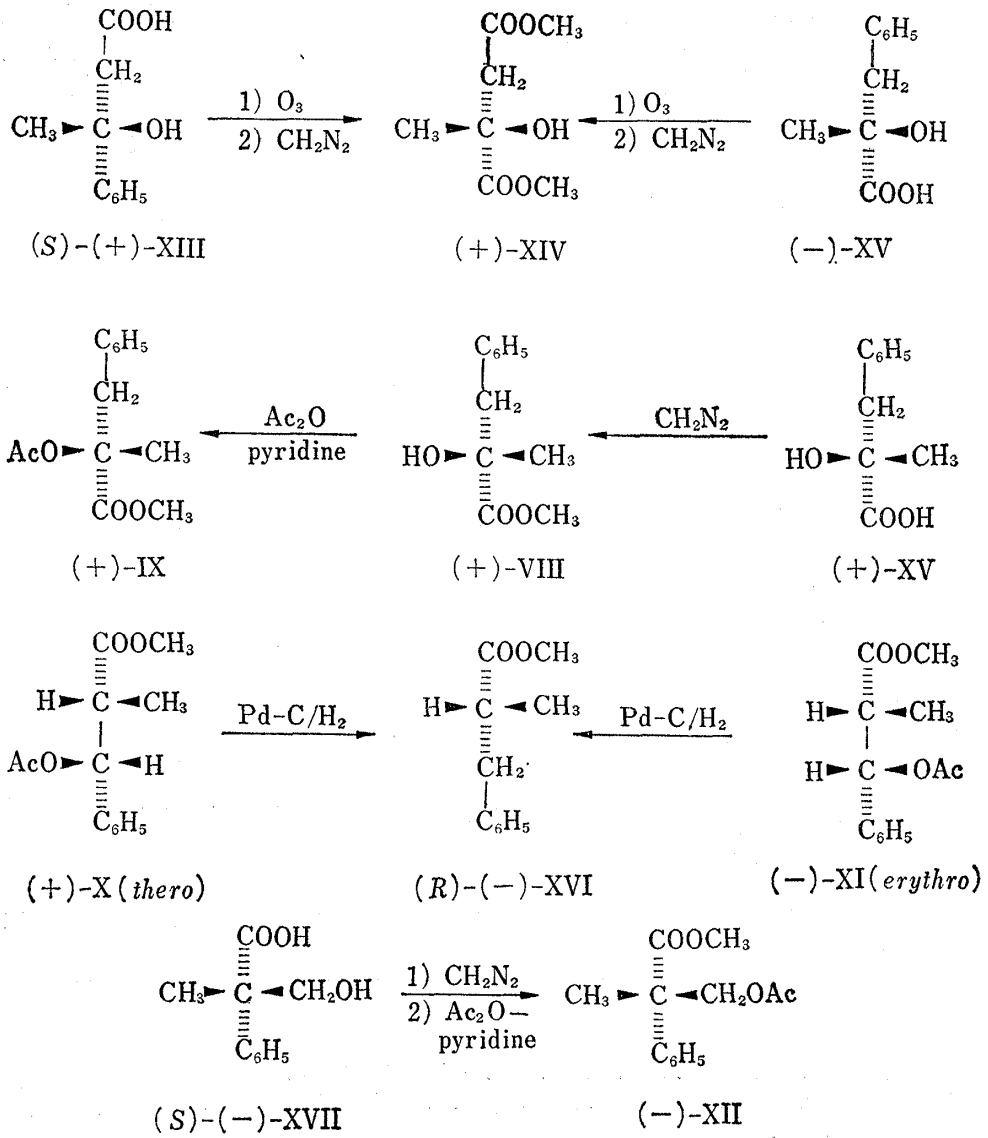
Compounds	Structure	Ratio (%)	$[\alpha]_D^{20}$ (in benzene)	Stereochemistry	Type of reaction
V	C_6H_5-CH_2-$C(=CH_2)$-$COOCH_3$	28			elimination (68%)
VI	C_6H_5, H, $C(=C)$, $COOCH_3$, CH_3	25		*cis*	
VII	C_6H_5, H, $C(=C)$, CH_3, $COOCH_3$	15		*trans*	
VIII	C_6H_5-CH_2-$C(CH_3)(OH)$-$COOCH_3$	6	+ 7.5°	60% net ret.	substitution (21%)
IX	C_6H_5-CH_2-$C(CH_3)(OAc)$-$COOCH_3$	15	+ 4.2°	10% net ret.	
X	C_6H_5-$CH(OAc)$-$CH(CH_3)$-$COOCH_3$ (*threo*)	4	+24.7°	63% net inv.[a]	H migration (8%)
XI	C_6H_5-$CH(OAc)$-$CH(CH_3)$-$COOCH_3$ (*erythro*)	4	−34.6°	63% net inv.[a]	
XII	C_6H_5-$C(CH_3)(CH_2OAc)$-$COOCH_3$	3	− 4.2°	27% net inv.	C_6H_5 migration (3%)

a) stereochemical result at migration terminus

9) E.H. White and J.E. Stuber, *J. Am. Chem. Soc.*, **85**, 2168 (1963).
10) *cf.* L. Friedman, "Carbonium Ions," Vol. 2, ed. by G.A. Olah and P. von R. Schleyer, Wiley-Interscience, New York, 1970, p. 672.
11) S. Yamada, S. Terashima, and K. Achiwa, *Chem. Pharm. Bull.* (Tokyo), **14**, 1138 (1966).

Table II. Results of Nitrous Acid Deamination of II in AcOH followed by Treatment of the Products with Diazomethane

Compounds	Structure	Ratio(%)	$[\alpha]_D^{20}$(in benzene)	Stereochemistry	Type of reaction
V	C_6H_5-CH_2-$C(=CH_2)$-$COOCH_3$	3			elimination (10%)
VI	C_6H_5, H, $COOCH_3$, CH_3	4		*cis*	
VII	C_6H_5, H, CH_3, $COOCH_3$	3		*trans*	
VIII	C_6H_5-CH_2-$C(CH_3)(OH)$-$COOCH_3$	2			substitution (90%)
IX	C_6H_5-CH_2-$C(CH_3)(OAc)$-$COOCH_3$	88	+9.6°	27% net ret.	



(S)-(+)-XIII (+)-XIV (−)-XV

(+)-IX (+)-VIII (+)-XV

(+)-X (*thero*) (R)-(−)-XVI (−)-XI (*erythro*)

(S)-(−)-XVII (−)-XII

Chart 2

Absolute configurations of substitution products (VIII, IX) and migration products (X, XI, XII) were determined as shown in Chart 2. Thus, (*S*)-(+)-3-hydroxy-3-methyl-3-phenylpropionic acid ((*S*)-(+)-XIII), whose absolute configuration is known,[12] was led to (+)-dimethyl 2-methylmalate ((+)-XIV), which was similarly prepared from (−)-2-hydroxy-2-methyl-3-phenylpropionic acid ((−)-XV). However, (+)-XV afforded (+)-methyl 2-hydroxy-2-methyl-3-phenylpropionate ((+)-VIII) and (+)-methyl 2-acetoxy-2-methyl-3-phenylpropionate ((+)-IX). Therefore, (+)-VIII and (+)-IX must belong to (*R*)-series. Diastereomeric configurations of (+)-methyl *threo*-3-acetoxy-2-methyl-3-phenylpropionate ((+)-X) and (−)-methyl *erythro*-3-acetoxy-2-methyl-3-phenylpropionate ((−)-XI) were determined by comparing the corresponding *erythro*-racemate.[13] Their absolute configurations were determined by leading them to (−)-methyl (*R*)-2-methyl-3-phenylpropionate ((*R*)-(−)-XVI)[14] by catalytic hydrogenolysis with palladium-charcoal. The absolute configuration of (−)-methyl 3-acetoxy-2-methyl-2-phenylpropionate ((−)-methyl O-acetyl-α-methyltropate) ((−)-XII) was determined to be (*S*) by preparing it from (*S*)-(−)-3-hydroxy-2-methyl-2-phenylpropionic acid ((*S*)-(−)-α-methyltropic acid) ((*S*)-(−)-XVII) of known absolute configuration.[15] Details on estimations of the maximum rotations of these compounds are given in the experimental section.

Mechanistic Considerations

From the data in Table I, the following five points should be mentioned for the reaction of I in acetic acid. (1) The amount of olefins (V, VI, VII) constitutes 68% of the total products, in contrast to 14—16% in the reaction of III.[7a] (2) The amount of substitution products (VIII, IX) is two-thirds of the non-olefinic products. (3) The phenyl migration reaction is a minor reaction (3%) in I, but a moderate reaction (24%) in III.[7a] (4) Stereochemical results of substitution reactions giving VIII and IX are net retention, in contrast to net inversion in III.[7a] (5) Migration reactions giving X, XI, and XII have net inversions at their migration termini.

Chart 3 represents three conformations (XVIII, XIX, XX) of the diazonium ions from I, three conformations (XXI, XXII, XXIII) of the corresponding carbonium ions, and possible reaction products; since (1) elimination and migration will occur when groups are anti-parallel in diazonium ions, (2) while the group is eclipsed with the neighboring vacant *p*-orbital in the carbonium ions, and (3) since substitution will occur from all of them. Although interconversions between these rotamers will occur to some extent, the general principle for the reaction of I is explanable with these models.

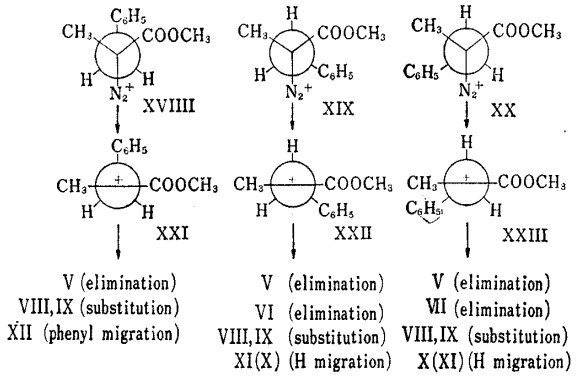


Chart 3

The nitrous acid deamination mechanism of III in acetic acid has already been proposed.[7a] The most important difference between the reactions of I and III may be that initially formed ion is tertiary in the former, while secondary in the latter. The tertiary ion is thought to be thermodynamically more stable than the corresponding secondary ion, and the tertiary ion is considered to be more highly difficult to react with nucleophiles than

12) S. Mitsui, K. Konno, I. Onuma, and K. Shimizu, *Nippon Kagaku Zasshi*, **85**, 437 (1964).
13) *a*) H.E. Zimmerman and J. English, Jr., *J. Am. Chem. Soc.*, **76**, 2291 (1954); *b*) J. Wein, *Acta Chem. Acad. Sci. Hung.*, **17**, 181 (1958); *c*) K. Koga and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 526 (1972).
14) *cf.* A.W. Schrecker, *J. Org. Chem.*, **22**, 33 (1957).
15) J. Knabe, H. Junginger, and W. Geismar, *Ann.*, **739**, 15 (1970).

the secondary ion due to steric hindrance. These phenomena are considered to be responsible for formation of the large amount of olefins (V, VI, VII), and for formation of the major portion of substitution products (VIII, IX) among the non-olefinic products. A small proportion of the phenyl migration product (XII) is also considered to be due to the need to form an unstable primary cation of the neopentyl type.

Stereochemically the conformations depicted in Chart 3 suggest that the phenyl migration product (XII) and hydrogen migration products (X, XI) were obtained with net inversion at their migration termini. It also seems reasonable that the substitution reaction to give α-hydroxy ester (VIII) occurred with relatively high net retention, because the reaction is intramolecular in nature[9] due to the attack of water produced in the diazotization step. Interestingly, the substitution reaction to give α-acetoxy ester (IX) occurred with 10% net retention. Conformer XXI may be expected to give IX with retention due to steric hindrance of the phenyl group, while the others will give IX with low net inversion. We presume that conformer XXI plays a dominant role in the formation of IX, because the routes to VI, VII, X, and XI from XXI are prohibited and the route to XII from XXI is also restricted. Therefore, the shielding effect of the leaving nitrogen is overcome by the conformational effect.

Results in Table II on the deamination of II in acetic acid followed by esterification are interesting in that olefins (V, VI, VII) are also produced along with the corresponding substitution products (VIII, IX), and in that the stereochemistry of the substitution reaction to give IX is of relatively low net retention. These results may be the consequence of incomplete participation of the neighboring carboxylate group, due to formation of a relatively stable tertiary carbonium ion and steric effect.

Finally, the deamination reaction has been shown to be highly dependent on the solvent used.[7b,c] Thus, studies on the reactions of I and II in solvents of various nucleophilicities will be reported in the future.

Experimental[16]

(*R*)-(−)-α-Methylphenylalanine Methyl Ester (I)——A suspension of (+)-N-acetyl-(*R*)-α-methylphenylalanine ($[\alpha]_D^{25}$ +76.2° (*c*=1.607, MeOH), reported[11] $[\alpha]_D^{20}$ +79.3° (*c*=1.082, MeOH)) (18.0 g) in 10% HCl (360 ml) was refluxed for 4 hr. The resulting solution was evaporated to dryness *in vacuo*, then the residue was dissolved in MeOH (180 ml). $SOCl_2$ (58 g) was added dropwise to this solution under ice-cooling. The resulting solution was refluxed for 8 hr, then evaporated to dryness *in vacuo*. The residue was dissolved in H_2O (150 ml) and basified with excess K_2CO_3, then the whole was extracted four times with benzene. Evaporation of the dried benzene extracts *in vacuo* gave an oil, which was distilled to give I (13.6 g, 86.7%), as a colorless liquid of bp 124—125° (10 mmHg), $[\alpha]_D^{24}$ −4.33° (*c*=3.05, MeOH). IR γ_{max}^{film} cm^{-1}: 1734 (ester). NMR (in CCl_4) τ: 8.72 (3H, s, C-C<u>H</u>$_3$), 8.6 (2H, s, -N<u>H</u>$_2$), 7.29 and 7.02 (2H, AB q, *J*=12.8 Hz, C_6H_5-C<u>H</u>$_2$), 6.44 (3H, s, -COOC<u>H</u>$_3$), 2.9 (5H, s, C_6<u>H</u>$_5$-). *Anal.* Calcd. for $C_{11}H_{15}O_2N$: N, 7.25. Found: N, 7.42.

(*R*)-(+)-α-Methylphenylalanine (II)——Prepared from (+)-N-acetyl-(*R*)-α-methylphenylalanine, as described above, in the usual manner. $[\alpha]_D^{20}$ +20.1° (*c*=1.066, H_2O). *Anal.* Calcd. for $C_{10}H_{13}O_2N$: N, 7.82. Found: N, 7.75.

Nitrous Acid Deamination of I in AcOH——$NaNO_2$ (13.3 g, 0.193 mole) was added in portions during 8 hr at 20—22° to a solution of I (33.7 g, 0.175 mole) in AcOH (580 ml), then the whole was allowed to stand at room temperature overnight. The reaction mixture was evaporated *in vacuo* below 50°. The residue was mixed with H_2O (200 ml), then the whole was extracted with benzene. The benzene extracts were washed successively with 10% HCl, sat. NaCl, 10% Na_2CO_3, and sat. NaCl. Evaporation of the dried

16) All melting and boiling points are uncorrected. Infrared (IR) spectra were measured with a spectrometer, Model DS-402G, Japan Spectroscopic Co., Ltd. Nuclear magnetic resonance (NMR) spectra were measured with a spectrometer, Model 3H-60, Japan Electron Optics Lab., using tetra methyl silane (TMS) as an internal standard. Optical rotations were measured with a Yanaco automatic polalimeter, Model OR-50. Optical rotatory dispersion measurements were carried out with a spectrometer, Model ORD/UV-5, Japan Spectroscopic Co., Ltd. A preparative gas chromatograph, Perkin-Elmer F-21, was used to isolate the products. Microanalyses and spectral measurements were performed by members of the Central Analysis Room of this faculty.

benzene solution left a yellow liquid (36.3 g). Gas chromatographic analysis using acenaphthene as an internal standard showed that the products (81% yield based on the unrecovered I) were composed of the following eight compounds: (values in parentheses are molar ratios of the products). V (28%), VI (25%), VII (15%), VIII (6%), IX (15%), X (4%), XI (4%), and XII (3%).

From the above 10% HCl washings, the starting material (I) (1.40 g, 4%) was recovered.

Isolation of Products from the Deamination of I——Deamination products (35.0 g) from I were chromatographed on silica gel (500 g) with benzene. The initially eluted part (19.3 g) was a mixture of olefins (V, VI, VII). The second part (5.0 g) was a mixture of products, in which IX was predominant. The third part (8.3 g) was a mixture of non-olefinic products.

The initially eluted part (10.0 g) was re-chromatographed on silica gel (1500 g) with benzene–hexane (1:1) to give V in its pure form, and VI and VII as a mixture.

The second part (5.0 g) was re-chromatographed on silica gel (500 g) with benzene to give IX in its pure form.

The third part (7.16 g) was subjected to preparative gas chromatography (column: 10% PEGA on Chromosorb WAW, 8 mm×4.5 m; temperature: 185°) to give VIII, X, XI, and XII as pure forms.

Methyl 2-Benzylacrylate (V)——The sample obtained as a pure form by the chromatography described above was distilled under reduced pressure to give V (0.45 g) as a colorless liquid of bp 92—96° (8 mmHg). IR ν_{max}^{film} cm^{-1}: 1726 (ester), 1633 (double bond). NMR (in CCl_4) τ: 6.45 (2H, s, C_6H_5-C$\underline{H}_2$-), 6.38 (3H, s, -COOC$\underline{H}_3$), 4.66 (1H, m, –C$\underline{H}$H). 3.87 (1H, m, –CH$\underline{H}$), 2.86 (5H, s, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 74.81; H, 6.76. Spectral data for this compound are reported in the literature.[17]

Methyl *cis*-α-Methylcinnamate (VI) and Methyl *trans*-α-Methylcinnamate (VII)——a) Isolation as a mixture of VI and VII from the deamination products of I. The sample was obtained from the deamination mixture by the chromatography described above. NMR spectral comparisons with the reported value[18] as well as with the sample prepared in b) showed that this sample was a mixture of VI and VII. NMR (in CCl_4) τ: 7.96 (3H, d, J=1.5 Hz, =C-C$\underline{H}_3$), 6.30 (3H, s, -COOC$\underline{H}_3$). 2.76 (5H, s, $C_6\underline{H}_5$-), 2.44 (1H, m, C_6H_5-C$\underline{H}$=) for VII, and 8.01 (3H, d, J=1.5 Hz, =C-C$\underline{H}_3$), 6.50 (3H, s, -COOC$\underline{H}_3$), 3.46 (1H, s, C_6H_5-CH=), 2.87 (5H, s, $C_6\underline{H}_5$-) for VI.

b) Authentic Sample of VII: *trans*-α-Methylcinnamic acid, prepared according to the reported method,[19] was esterified to give a colorless solid of bp 106—110° (6 mmHg), mp 36.5—38.5° (reported[18] mp 37—39°). NMR (in CCl_4) τ: 7.93 (3H, d, J=1.5 Hz, =C-C$\underline{H}_3$), 6.24 (3H, s, -COOC$\underline{H}_3$), 2.70 (5H, s, $C_6\underline{H}_5$-), 2.42 (1H, m, C_6H_5-C$\underline{H}$=). *Anal.* Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 75.13; H, 6.77.

Methyl 2-Hydroxy-2-methyl-3-phenylpropionate (VIII)——Preparative gas chromatography of the deamination products of I, as described above, afforded (+)VIII (800 mg) as a liquid. This was purified by chromatography on silica gel (20 g) with benzene, followed by distillation under reduced pressure to a cololess liquid, (600 mg) of bp 91—97° (2 mmHg), $[\alpha]_D^{20}$ +7.46° (c=2.198, benzene). IR ν_{max}^{film} cm^{-1}: 3520 (OH), 1736 (ester). NMR (in CCl_4) τ: 8.62 (3H, s, C-C$\underline{H}_3$), 6.8 (1H, s, OH), 7.15 and 7.07 (2H, AB q, J=13.5 Hz, C_6H_5-C$\underline{H}_2$-), 6.42 (3H, s, -COOC$\underline{H}_3$), 2.88 (5H, s, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.28; H, 7.43.

O-Acetate (IX): Prepared in the usual manner to give a colorless liquid of bp 111—116° (3 mmHg). Identified with the sample below by its IR and NMR spectra. Optical rotation of this sample was α_D^{20} +2.212° (l=0.1, neat), $[\alpha]_D^{20}$ +23.9° (c=2.760, benzene), corresponding to 60% R.

Methyl 2-Acetoxy-2-methyl-3-phenylpropionate (IX)——a) Isolation from the Deamination Products of I: The sample obtained as a pure form from the deamination products of I by the chromatography descrived above was distilled under reduced pressure to give (+)IX (1.6 g) as a colorless liquid of bp 132—138° (8 mmHg), $\alpha_D^{19.5}$ +0.348 (l=0.1, neat), $[\alpha]_D^{19.5}$ +4.15° (c=2.362, benzene), $[\alpha]_{350}^{26}$ +18.4° (c=2.014, benzene), corresponding to 10% R. IR ν_{max}^{film} cm^{-1}: 1745 (ester), 1250 (acetate). NMR (in $CDCl_3$) τ: 8.59 (3H, s, C-C$\underline{H}_3$), 8.03 (3H, s, -COOC$\underline{H}_3$), 7.00 and 6.76 (2H, AB q, J=13.5 Hz, C_6H_5-C$\underline{H}_2$-), 6.38 (3H, s, -COOC$\underline{H}_3$), 2.85 (5H, s, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.79; H, 7.05.

b) Optically pure authentic sample: Optically pure (*R*)-(+)-2-hydroxy-2-methyl-3-phenylpropionic acid ((*R*)-(+)-XV) (mp 117.5—119°, $[\alpha]_D^{17}$ +16.4° (c=5.658, dioxane), reported[20] mp 118—119.5°, $[\alpha]_D$ +17.0° (c=5.595, dioxane)), prepared according to the reported method,[20] was esterified with CH_2N_2 and acetylated with Ac_2O–pyridine in the usual manner to give (*R*)-(+)-IX as a colorless liquid of bp 109—115° (2 mmHg), $\alpha_D^{19.5}$ +3.688° (l=0.1, neat), $[\alpha]_D^{19.5}$ +39.4° (c=2.306, benzene), $[\alpha]_{350}^{22}$ +170° (c=1.638, benzene). This sample was identified with the sample prepared in a) by IR and NMR spectral comparisons.

Methyl *threo*-3-Acetoxy-2-methyl-3-phenylpropionate (X)——Preparative gas chromatography of the deamination products of I, as described above, afforded (+)X (420 mg) as a liquid. This was purified by chromatography on silica gel (15 g) with benzene, followed by distillation under reduced pressurs to a colo-

17) I. Tabushi, K. Okazaki, and R. Oda, *Tetrahedron*, **24**, 4401 (1969).
18) H. Kashiwagi, N. Nakagawa, and J. Niwa, *Bull. Chem. Soc. Japan*, **36**, 410 (1963).
19) Y. Urushibara and M. Hirota, *Nippon Kagaku Zasshi*, **82**, 354 (1961).
20) A.G. Davis, F.M. Ebeid, and J. Kenyon, *J. Chem. Soc.*, **1957**, 3154.

rless liquid (300 mg) of bp 110—114° (3 mmHg), $[\alpha]_D^{20}$ +24.7° (c=1.312, benzene). IR ν_{max}^{film} cm^{-1}: 1745 (ester), 1230 (acetate). NMR (in CCl_4) τ: 8.89 (3H, d, J=7.0 Hz, CH-C<u>H</u>$_3$), 8.01 (3H, s, OCOC<u>H</u>$_3$), 6.95—7.42 (1H, m, -CH-C<u>H</u>-CH$_3$), 6.52 (3H, s, -COOC<u>H</u>$_3$), 4.07 (1H, d, J=6.5 Hz, C_6H_5-C<u>H</u>-), 2.84 (5H, s, C_6<u>H</u>$_5$-). *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.79; H, 6.66.

Catalytic hydrogenolysis to XVI with the Pd-C described below proved that this sample was 63% optically pure.

Methyl *erythro*-3-Acetoxy-2-methyl-3-phenylpropionate (XI)——a) Isolation from the Deamination Products of I: Preparative gas chromatography of the deamination products of I, as described above, afforded (−)XI (510 mg) as a solid. This was purified by chromatography on silica gel (20 g) with benzene, followed by distillation under reduced pressure to a colorless solid (320 mg) of bp 106° (1 mmHg), mp 50—51.5°, $[\alpha]_D^{20}$ −34.6° (c=2.188, benzene). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1748 (ester), 1227 (acetate). NMR (in CCl_4) τ: 9.10 (3H, d, J=7.0 Hz, CH-C<u>H</u>$_3$), 8.07 (3H, s, -OCOC<u>H</u>$_3$), 7.35—6.85 (1H, m, -CH-C<u>H</u>-CH$_3$), 6.32 (3H, s, -COOC<u>H</u>$_3$). 4.27 (1H, d, J=9.5 Hz, C_6H_5-C<u>H</u>-), 2.76 (5H, s, C_6<u>H</u>$_5$-). *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.96; H, 6.64.

Catalytic hydrogenolysis to XVI with the Pd-C described below proved that this sample was 63% optically pure.

b) Racemic Authentic Sample: Racemic methyl *erythro*-3-hydroxy-2-methyl-3-phenylpropionate of mp 50—52° (reported mp 43—46°,[13a] 49.5—51.5°[13c]) was acetylated with Ac_2O–pyridine in the usual manner to give (±)XI as a colorless solid of bp 140—146° (6 mmHg), mp 56.5—58°. Its IR and NMR spectra were identical with those of the sample prepared in a). *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.06; H, 6.72.

Methyl 3-Acetoxy-2-methyl-2-phenylpropionate (Methyl O-Acetyl-α-methyltropate) (XII)——a) Isolation from the deamination products of I: Preparative gas chromatography of the deamination products of I: Preparative gas chromatography of the deamination products of I, as described above, afforded (−)XII (190 mg). This was purified by chromatography on silica gel (15 g) with benzene to give a colorless liquid, $[\alpha]_D^{20}$ −4.24° (c=1.840, benzene), $[\alpha]_{350}^{22}$ −19.5° (c=0.872, benzene), corresponding to 27% S based on the value of the sample prepared in b).

b) Optically Pure Authentic Sample: Optically pure (*S*)-(−)-3-hydroxy-2-methyl-2-phenylpropionic acid (*S*)(−)α-methyltropic acid ((*S*)-(−)-XVII) (mp 87—89°, $[\alpha]_D^{19.5}$ −29.9° (c=1.998, EtOH), reported[21] mp 89—90°, $[\alpha]_D^{20}$ −28.3° (c=2, EtOH)), prepared according to the reported method,[21] was esterified with CH_2N_2, then acetylated with Ac_2O–pyridine in the usual manner to give (*S*)-(−)-XII as a colorless liquid of bp 118—123° (2 mmHg), $\alpha_D^{19.5}$ −2.899° (l=0.1, neat), $[\alpha]_D^{19.5}$ −17.5° (c=2.296, benzene), $[\alpha]_{350}^{24}$ −71.7° (c=2.682, benzene). This sample showed IR and NMR spectra identical with those of the sample prepared in a). IR ν_{max}^{film} cm^{-1}: 1744 (ester), 1238 (acetate). NMR (in CCl_4) τ: 8.43 (3H, s, C-C<u>H</u>$_3$), 8.08 (3H, s, OCO-C<u>H</u>$_3$), 6.41 (3H, s, -COOC<u>H</u>$_3$), 5.72 and 5.50 (2H, AB q, J=10.8 Hz, -C<u>H</u>$_2$OAc), 2.82 (5H, s, C_6<u>H</u>$_5$-). *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.25; H, 6.81.

Dimethyl 2-Methylmalate (XIV)——a) From (*S*)(+)-XIII: O_3 gas was introduced at room temperature for 39 hr to a solution of (*S*)-(+)-3-hydroxy-3-methyl-3-phenylpropionic acid[12] ($[\alpha]_D^{20}$ +11.0° (c=3.004, EtOH)) (1.30 g) in AcOH (50 ml). 30% H_2O_2 (3 ml) was added to this solution then the whole was allowed to stand at room temperature for 2 hr. After decomposing the excess H_2O_2 by adding Pt, the reaction mixture was filtered, then the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in MeOH-ether, to which a solution of excess CH_2N_2 in ether was added. After decomposing the excess CH_2N_2 with HCOOH, the solution was washed with sat. $NaHCO_3$, sat. NaCl, then dried over anhyd. Na_2SO_4. Evaporation of the solvent *in vacuo* gave an oil (1.1 g), which was chromatographed on silica gel with benzene-CH_2Cl_2 to give (+)-XIV (220 mg) as a colorless liquid, $[\alpha]_D^{20}$ +5.15° (c=3.302, MeOH). This sample showed IR and NMR spectra identical with those of the sample prepared in c.).

b) From (−)-XV: (−)-2-Hydroxy-2-methyl-3-phenylpropionic acid ((−)XV) ($[\alpha]_D^{19.5}$ −12.6° (c=1.94, dioxane)) (2.0 g) was treated as in a) to give (+)XIV (190 mg) as a colorless liquid, $[\alpha]_D^{20}$ +4.48° (c=3.262, MeOH). This sample showed IR and NMR spectra identical with those of the sample prepared in c).

c) Racemic Authentic Sample: Racemic 2-methylmalic atid[22] (2.0 g) was esterified with CH_2N_2 in the usual manner to give dimethyl 2-methylmalate ((±)XIV) (1.6 g, 60% yield) as a colorless liquid of bp 87—89° (5 mmHg). IR ν_{max}^{film} cm^{-1}: 3510 (OH), 1745 (ester). NMR (in CCl_4) τ: 8.64 (3H, s, C-C<u>H</u>$_3$), 7.38 and 7.20 (2H, AB q, J=16.5 Hz, -C<u>H</u>$_2$-), 6.35 (3H, s, COOC<u>H</u>$_3$), 6.25 (3H, s, -COOC<u>H</u>$_3$). *Anal.* Calcd. for $C_7H_{12}O_5$: C, 47.72; H, 6.87. Found: C, 47.66; H, 6.97.

Methyl 2-Methyl-3-phenylpropionate (XVI)——a) Optically Pure (*S*)-(+)XVI: (*S*)-(+)-2-methyl-3-phenylpropionic acid (bp 138—140° (3 mmHg)), $\alpha_D^{19.5}$ +2.693° (l=0.1, neat), reported[14] α_D^{20} +2.51° (l=0.1, neat)), prepared by the reported method,[14] was esterified with CH_2N_2 in the usual manner to give (*S*)(+)XVI as a colorless liquid of bp 107—109° (14 mmHg), α_D^{20} +3.70° (l=0.1, neat), $[\alpha]_D^{20}$ +49.8° (c=2.042, MeOH), $[\alpha]_{350}^{20}$ +208° (c=2.042, MeOH). IR ν_{max}^{film} cm^{-1}: 1741 (ester). NMR (in CCl_4) τ: 8.93 (3H, d, J=

21) G. Melone, A. Vecchi, G. Pagani, and E. Testa, *J. Org. Chem.*, **25**, 859 (1960).
22) A. Michael and G. Tissot, *J. Prakt. Chem.*, **46**, 285 (1892).

6.6 Hz, -CH-C$\underline{H}_3$), 7.70—6.90 (3H, m, C_6H_5-C$\underline{H}_2$-CH-), 6.45 (3H, s, -COOC$\underline{H}_3$), 2.87 (5H, s, $C_6\underline{H}_5$-). *Anal.* Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.89; H, 7.92.

b) From (+)-X: A mixture of (+)-X (obtained from the deamination products of I described above) (300 mg) and 10% Pd-C (150 mg) in MeOH (50 ml) was shaken vigorously in an atomospheric pressure of H_2 for 3 days. The catalyst was filtered off, and the filtrate was evaporatd to dryness *in vacuo*. The residue was taken up in ether. The ethereal solution was washed with 10% Na_2CO_3, and sat. NaCl, dried over anhyd. Na_2SO_4, and evaporated to dryness to give (−)-XVI (140 mg) as a colorless liquid of $[\alpha]_D^{20}$ −30.5° (c=1.998, MeOH), $[\alpha]_{350}^{21}$ −132° (c=2, MeOH), corresponding to 63% R. This sample showed IR and NMR spectra identical with those of the sample prepared in a).

c) From (−)XI: (−)XI (obtained from the deamination products of I described above) was treated as in b) to give (−)-XVI as a colorless liquid of $[\alpha]_D^{20}$ −28.9° (c=1.522, MeOH), $[\alpha]_{350}^{33}$ −131° (c=1.5, MeOH), corresponding to 63% R. This sample showed IR and NMR spectra identical with those of the sample prepared in a).

Nitrous Acid Deamination of II in AcOH——$NaNO_2$ (0.785 g, 0.0108 mole) was added in portions during 6 hr at 20—22° to a solution of II (1.61 g, 0.009 mole) in AcOH (30 ml) then the whole was allowed to stand at room temperature overnight. The reaction mixture was evaporated *in vacuo*. The residue was mixed with H_2O, and extracted with ether. The ether layer was esterified with CH_2N_2 in the usual manner, from which the deamination products (1.31 g) were obtained as the neutral fraction. From the above H_2O layer, the starting material (II) (480 mg, 30%) was recovered. Gas chromatographic analysis of the deamination products using acenaphthene as an internal standard showed that the products (53% yield based on the unrecovered II) were composed of the following five compounds (values in parentheses are molar ratios of the products): V (3%), VI (4%), VII (3%), VIII (2%), and IX (88%).

Column chromatography of these deamination products on silica gel (50 g) with benzene afforded (+)-IX (500 mg) as a colorless liquid of bp 129—132° (5 mmHg), α_D^{20} +1.010 (l=0.1, neat), $[\alpha]_D^{20}$ +9.6° (c=2.144, benzene), $[\alpha]_{350}^{30}$ +51.3° (c=2.144, benzene), corresponding) to 27% R. The sample showed IR and NMR spectra identical with those described above. *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.09; H, 6.80.