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Stereochemical Studies. XVI.[1] Deaminative Acetolyses of L-Valine and L-Valine Benzyl Ester[2]

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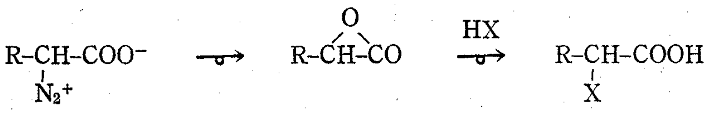
Detailed examinations were made of nitrous acid deaminations of L-valine and its benzyl ester in acetic acid. These showed that while the substitution product is the only detectable compound in the deamination of L-valine, various migration and elimination products are obtained along with the substitution product in the deamination of L-valine benzyl ester.

The reaction of aliphatic primary amines with nitrous acid produces a variety of products arising from substitution, migration, and elimination; because the activation energy required for decomposition of the aliphatic diazonium ion is rather small due to the great stability of the leaving nitrogen molecule. Therefore, the range of energies required for a number of competing reactions is compressed.[4] Also, the substitution reaction usually occurs with net inversion.[4] Highly specific examples in nitrous acid deamination are also known, *e.g.* in the field of α-amino acids.[5] Thus, although α-amino acid esters are reported to give substitution products with net inversion, α-amino acids are known to produce substitution products with retention,[5] probably because of the formation of an α-lactone intermediate by neighboring carboxylate group participation.[5,6]



$$\underset{N_2^+}{\text{R-CH-COO}^-} \longrightarrow \text{R-}\overset{O}{\text{CH-CO}} \xrightarrow{HX} \underset{X}{\text{R-CH-COOH}}$$

Detailed examination of nitrous acid deamination of the L-phenylalanine ethyl ester in acetic acid has shown that various migration and elimination products are also produced along with the corresponding substitution product.[7] Stereochemical results of the reaction suggested some participation by the neighboring phenyl group.[7,8] As we are interested in the nature of the diazonium ion (or its daughter carbonium ion) having a carboxyl group or an alkoxycarbonyl group at the reaction center, complete analyses of the reactions of aliphatic α-amino acid and its ester, L-valine and L-valine benzyl ester, were undertaken. Deamination of L-valine benzyl ester has been briefly reported, but not in detail.[9]

Deamination of L-valine benzyl ester was carried out with 1.2—1.3 molar equivalents of sodium nitrite in acetic acid. The mixture of neutral reaction products obtained was shown

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[1] Part XV: K. Koga, C.C. Wu, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 526 (1972).

[2] A preliminary report has been published as a communication: S. Yamada, M. Taniguchi, and K. Koga, *Tetrahedron Letters*, **1969**, 25.

[3] Location: *Hongo, Bunkyo-ku, Tokyo.*

[4] *a*) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957); *b*) L. Friedman, "Carbonium Ions," Vol. II, ed. by G.A. Olah and P. von R. Schleyer, Wiley-Interscience, New York, 1970, p. 655.

[5] *a*) A. Neuberger, "Advances in Protein Chemistry," Vol. IV, ed. by M.L. Anson and J.T. Edsall, Academic Press, New York, 1948, p. 327; *b*) P. Brewster, F. Hiron, E.D. Hughes, C.K. Ingold, and P.A.D.S. Rao, *Nature*, **166**, 179 (1950).

[6] E.S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt & Co., New York, 1959, p. 565.

[7] S. Yamada, T. Kitagawa, and K. Achiwa, *Tetrahedron Letters*, **1967**, 3007.

[8] *cf.* K. Koga, C.C. Wu, and S. Yamada, *Tetrahedron Letters*, **1971**, 2283, 2289.

[9] G. Losse and G. Bachmann, *Chem. Ber.*, **97**, 2671 (1964).

to be composed of twelve components by gas liquid chromatography (GLC) analysis (Fig. 1), and was chromatographed repeatedly on silica gel to give benzyl 3-hydroxyisovalerate (VIII), benzyl 2-acetoxyisovalerate (IX), and benzyl 3-acetoxyisovalerate (X) as pure forms. However, benzyl 2-methyl-3-butenate (III), benzyl 3-methyl-3-butenate (IV), and benzyl 3-methylcrotonate (VII) were isolated by preparative GLC. III ($[\alpha]^{23}_D$ −5.9° (benzene)) was proven to be formed with 21% net inversion by leading it to 2-methylbutanoic acid (XIII) of known configuration by catalytic hydrogenation. IX ($[\alpha]^{23}_D$ +6.6° (benzene)) was proven to be formed with 16% net inversion by comparison with an authentic sample. Although the isolation of benzyl angelate (V) and diastereoisomers of benzyl 3-acetoxy-2-methylbutyrate (XI and XII) was unsuccessful, these were identified with their corresponding authentic samples by GLC. The existence of benzyl tiglate, a *trans* isomer of V, could not be confirmed. Also the amounts of three compounds, I, II, and VI, were too small to be identified. The average ratio of the products is shown in Table I.

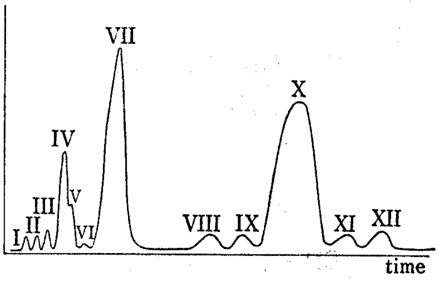
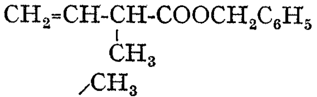
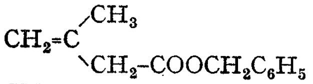
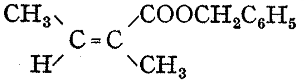
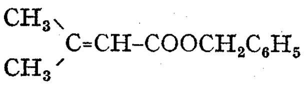
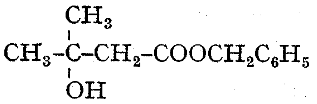
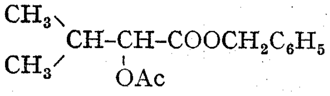
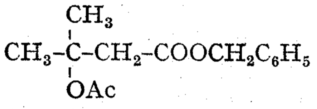
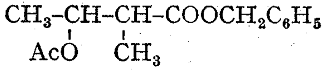


Fig. 1. Gas Chromatogram of Deamination Products of L-Valine Benzyl Ester

TABLE I. Deamination Products of L-Valine Benzyl Ester

No.	Structure	Product ratio (%)
I	unidentified	
II	unidentified	
III	 $CH_2{=}CH{-}\underset{\underset{\textstyle CH_3}{\vert}}{CH}{-}COOCH_2C_6H_5$	1—2
IV	 $CH_2{=}C\left<\begin{matrix}CH_3\\CH_2{-}COOCH_2C_6H_5\end{matrix}\right.$	5—6
V	 $\begin{matrix}CH_3 & & COOCH_2C_6H_5\\ & C{=}C & \\ H & & CH_3\end{matrix}$	0—1
VI	unidentified	
VII	 $\left.\begin{matrix}CH_3\\CH_3\end{matrix}\right>C{=}CH{-}COOCH_2C_6H_5$	22
VIII	 $CH_3{-}\overset{\overset{\textstyle CH_3}{\vert}}{\underset{\underset{\textstyle OH}{\vert}}{C}}{-}CH_2{-}COOCH_2C_6H_5$	5—6
IX	 $\left.\begin{matrix}CH_3\\CH_3\end{matrix}\right>CH{-}\underset{\underset{\textstyle OAc}{\vert}}{CH}{-}COOCH_2C_6H_5$	2—3
X	 $CH_3{-}\overset{\overset{\textstyle CH_3}{\vert}}{\underset{\underset{\textstyle OAc}{\vert}}{C}}{-}CH_2{-}COOCH_2C_6H_5$	55
XI XII	 $CH_3{-}\underset{\underset{\textstyle AcO}{\vert}}{CH}{-}\underset{\underset{\textstyle CH_3}{\vert}}{CH}{-}COOCH_2C_6H_5$	6—7

Processes which form products in the present deamination reaction may be explained as shown in Chart 1. It is certain that three conformations (XIV, XV, and XVI) are suggested for the diazonium ion from L-valine benzyl ester. It is highly characteristic that large amounts of migration and elimination products of tertiary β-hydrogen (IV, VII, VIII, and X, totalling 87—89% of the products) were obtained. Considering the concerted mecha-

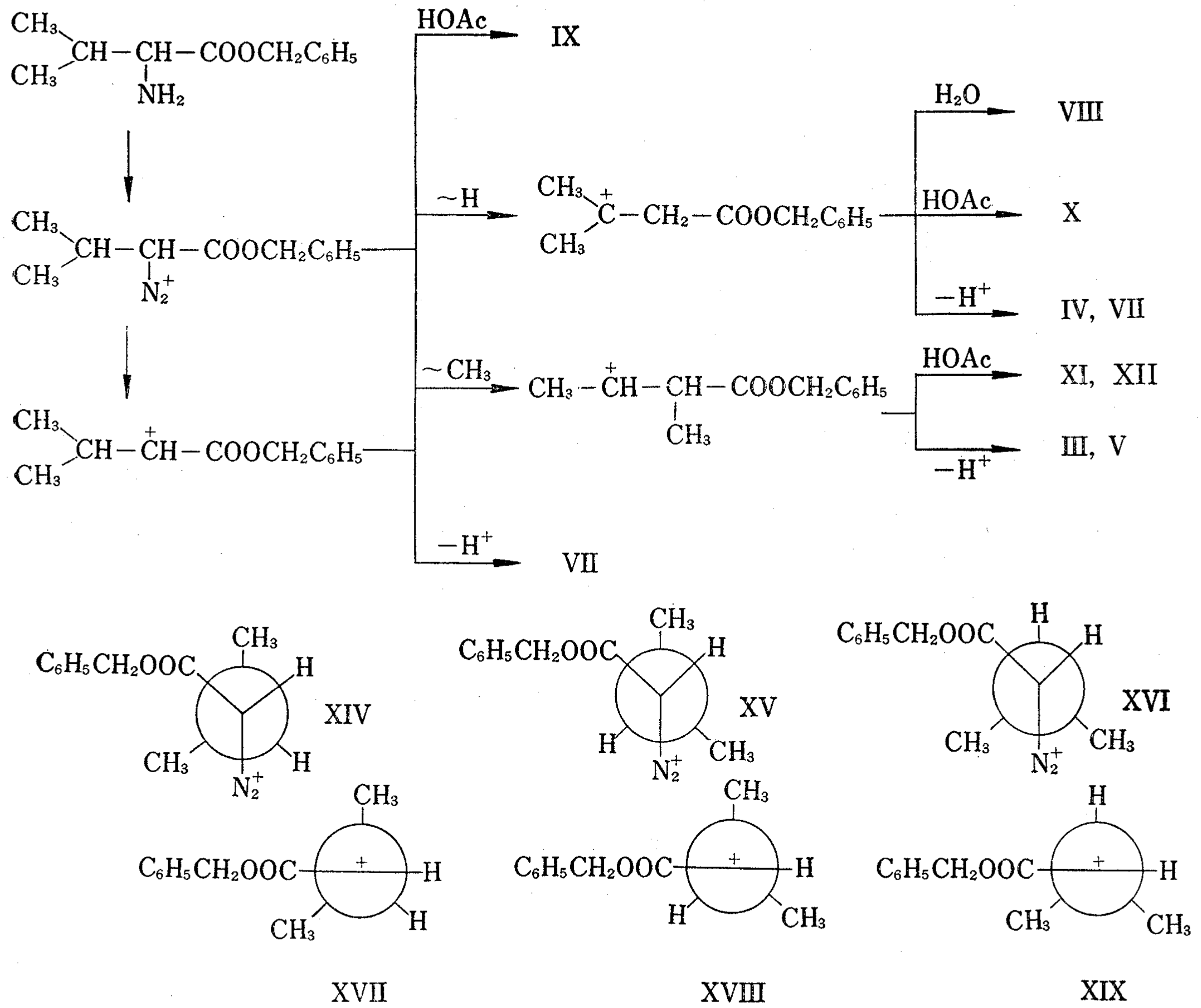


Chart 1

nism with the loss of nitrogen, they must be formed only from conformation XVI, which seems impossible to such a large extent. Therefore, open carbonium ions would participate in forming these products. Thus, the initially formed open carbonium ions XVII and XVIII, by loss of nitrogen from XIV and XV, rotate to give XIX, which undergoes hydrogen migration and elimination. This mechanism seems also to be demonstrated by formation of V, which can not be produced by the concerted mechanism. As stated above, however, III and IX were proven to be formed with net inversion. Thus, it seems reasonable that both the concerted diazonium ion mechanism and the open carbonium ion mechanism participate in the deaminative acetolysis of L-valine benzyl ester.

Although deamination of L-valine has already been reported,[9,10] we reinvestigated the reaction under the conditions described above, and the reaction product was led to benzyl ester with phenyldiazomethane. As reported,[10] the unrearranged substitution product was produced as almost the only product by GLC analysis, with at least 94% net retention.

Deamination of 3-methyl-2-butylamine was reported to give a different pattern of products[11] from that of deaminations of L-valine and its benzyl ester. While the carboxyl

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[10] *a*) E. Fischer and H. Scheibler, *Ber.*, **41**, 2891 (1908); *b*) C.G. Baker and A. Meister, *J. Am. Chem. Soc.*, **73**, 1336 (1951); *c*) M. Winitz, L. Bloch-Frankenthal, N. Izumiya, S.M. Birnbaum, C.G. Baker, and J.P. Greenstein, *J. Am. Chem. Soc.*, **78**, 2423 (1956); *d*) Pl.A. Plattner, K. Vogler, R.O. Studer, P. Quitt, and W. Keller-Schierlein, *Helv. Chim. Acta*, **46**, 927 (1963).

[11] *a*) M.S. Silver, *J. Org. Chem.*, **28**, 1686 (1963); *b*) M.S. Silver and A.G. Meek, *Tetrahedron Letters*, **1971**, 3579.

group attached to the reaction center is thought to hold the configuration in deamination by nucleophilic participation, there is as yet no clear explanation of the difference between the ester group and the methyl group. Studies on properties of carbonium ions adjacent to the carboxylic acid derivatives will be reported in the future.

Experimental[12)]

Nitrous Acid Deamination of L-Valine Benzyl Ester——$NaNO_2$ (8.3 g, 0.12 mole) was added in portions for 5.5 hr at 20—28° to a stirred solution of L-valine benzyl ester (prepared *via* its *p*-toluenesulfonate by the reported method[13)] as a liquid of bp 134—138.5° (4 mmHg), $[\alpha]_D^{27}$ +12.1° (c=1.740, dioxane)) (20.5 g, 0.099 mole) in AcOH (300 ml), and the whole was allowed to stand at room temperature overnight (negative in KI-starch test). The solvent was evaporated *in vacuo* to give a residue, which was shaken vigorously with a mixture of H_2O (25 ml) and benzene (250 ml). The benzene layer was washed successively with 10% aq. Na_2CO_3, H_2O, 10% aq. HCl, sat. aq. NaCl, then dried over anhyd. Na_2SO_4. Evaporation of the benzene *in vacuo* afforded a mixture of reaction products (20.5 g) as an orange-colored liquid, which was shown to be composed of at least twelve compounds by GLC analysis, as shown in Fig. 1 and Table I (4.5 m. 3—5% Carbowax 20M on Diasolid L at a column temperature of 176°). The GLC response ratio of the products was determined with the authentic samples described below.

Separation of a Mixture of Reaction Products——Separation of a mixture of reaction products was carried out by repeated chromatographies on silica gel with hexane, benzene, chloroform or a mixture of them as the eluting solvent or by preparative GLC using columns containing 20% Carbowax 20M on chromosorb WAW. Six compounds (III, IV, VII, VIII, IX, and X) were isolated in pure forms as described below.

Benzyl 2-Methyl-3-butenate (III)——a) Isolation from Reaction Products: This compound was isolated from reaction products by column chromatography, distillation, and preparative GLC as a colorless liquid of $[\alpha]_D^{23}$ −5.9° (c=5.310, benzene), corresponding to 21% (R) configuration. This sample was identified with the sample prepared in b) by GLC, IR, and NMR.

b) Synthesis: A mixture of 2-methyl-3-butenoic acid[14)] (0.45 g, 4.5 mmoles) and powdered KOH (0.25 g, *ca.* 4.5 mmoles) in EtOH (1 ml) was evaporated *in vacuo* to dryness. The residue was mixed with benzyl bromide (0.75 g, 4.4 mmoles) in DMF (10 ml), and the whole was stirred at room temperature for 2 hr. After addition of H_2O (10 ml), the reaction mixture was extracted with ether. The ethereal solution was washed successively with sat. aq. $NaHCO_3$, H_2O, 10% aq. HCl, H_2O, then dried over anhyd. Na_2SO_4. Evaporation of the solvent left a residue (0.70 g), which was purified by column chromatography on silica gel followed by distillation to give III (0.34 g, 39% yield) as a colorless liquid of bp 102° (7 mmHg). IR ν_{max}^{film} cm^{-1}: 1740 (ester), 1640 (double bond). NMR (in CCl_4) τ: 2.75 (5H, s, $C_6\underline{H}_5$-), 3.8—4.4 (1H, m, =C$\underline{H}$-), 4.7—5.1 (2H, m, C$\underline{H}_2$=), 4.95 (2H, s, -OC$\underline{H}_2C_6H_5$), 6.90 (1H, m, -C$\underline{H}(CH_3)$-), 8.75 (3H, d, J=7 Hz, C$\underline{H}_3$-CH-). *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.90; H, 7.43.

Benzyl 3-Methyl-3-butenate (IV)——a) Isolation from Reaction Products: This compound was isolated from reaction products by column chromatography followed by preparative GLC, as a colorless liquid of bp 106—107° (5 mmHg), and was identified with the sample prepared in b). IR ν_{max}^{film} cm^{-1}: 1742 (ester), 1650 (double bond). NMR (in CCl_4) τ: 2.79 (5H, s, $-C_6\underline{H}_5$), 5.01 (2H, s, -OC$\underline{H}_2C_6H_5$), 5.23 (2H, m, C$\underline{H}_2$=), 7.07 (2H, broad s, -C$\underline{H}_2$-), 8.28 (3H, broad s, C$\underline{H}_3$-).

b) Synthesis: A solution of VIII (12.0 g) and conc. H_2SO_4 (5 drops) in benzene (40 ml) was refluxed for 4 hr with a Dean-Stark apparatus. After cooling, the solution was mixed with H_2O (50 ml) and ether (200 ml). The organic layer was separated, washed with 10% aq. Na_2CO_3, H_2O, then dried over anhyd. Na_2SO_4. Evaporation of the solvent left an oil, which was shown to be a mixture of IV and VII. Separation by preparative GLC afforded IV as a colorless liquid of bp 87.5—89° (2 mmHg). *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.46; H, 7.47.

Benzyl Angelate (V)——This compound was synthesized from angelic acid[15)] in a manner similar to the synthesis of III, described above, as a colorless liquid of bp 117° (7 mmHg) in 33% yield. IR ν_{max}^{film} cm^{-1}: 1715 (ester), 1648 (double bond). NMR (in CCl_4) τ: 2.75 (5H, s, $-C_6\underline{H}_5$), 4.00 (1H, m, -C$\underline{H}$=), 4.90 (2H,

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12) All melting and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO DS-402G spectrometer. Nuclear magnetic resonance (NMR) spectra were measured with a JEOL JNM-3H-60 spectrometer operating at 60 MHz using tetramethylsilane as an internal standard. Optical rotations were measured with a Yanaco OR-50 Automatic Polarimeter. Separation of compounds by preparative GLC was carried out with a Perkin-Elmer F-21 Gaschromatograph. Spectral measurements and microanalyses were performed by members of the Central Analysis Room of this faculty.

13) L. Zervas, M. Winitz, and J.P. Greenstein, *J. Org. Chem.*, **22**, 1515 (1957).

14) J.F. Lane, J.D. Roberts, and W.G. Young, *J. Am. Chem. Soc.*, **66**, 543 (1944).

15) R.E. Buckles and G.V. Mock, *J. Org. Chem.*, **15**, 680 (1950).

s, -OC$\underline{H}_2$C$_6$H$_5$), 8.05 (3H, m, C$\underline{H}_3$-), 8.10 (3H, s, C$\underline{H}_3$-). *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.63; H, 7.27. This compound was shown to be present in the deamination mixture by GLC and NMR.

Benzyl Tiglate——A solution of tiglic acid[15] (1.5 g, 15 mmoles), benzyl alcohol (7.0 g, 65 mmoles), and conc. H_2SO_4 (0.3 ml) in benzene (50 ml) was refluxed for 5 hr with a Dean-Stark apparatus. After cooling, the solution was mixed with benzene (100 ml) and H_2O (10 ml). The benzene layer was separated, washed with 10% aq. Na_2CO_3, H_2O, then dried over anhyd. Na_2SO_4. Evaporation of the solvent left an oil, which was purified by column chromatography on silica gel to give benzyl tiglate (1.0 g, 35% yield) as a colorless liquid of 134° (9 mmHg). IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1715 (ester), 1650 (double bond). NMR (in CCl_4) τ: 2.75 (5H, s, -C$_6\underline{H}_5$), 3.20 (1H, m, -C$\underline{H}$=), 4.90 (2H, s, -OC$\underline{H}_2$C$_6$H$_5$), 8.15 (3H, s, C$\underline{H}_3$-), 8.25 (3H, m, C$\underline{H}_3$-). *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.81; H, 7.31. The existence of this compound in the deamination mixture could not be confirmed by GLC and NMR.

Benzyl 3-Methylcrotonate (VII)——a) Isolation from Reaction Products: This compound was isolated from reaction products by column chromatography followed by preparative GLC as a colorless liquid of bp 109—117° (5 mmHg), and was identified with the sample prepared in b). IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1723 (ester), 1650 (double bond). NMR (in CCl_4) τ: 2.75 (5H, s, -C$_6\underline{H}_5$), 4.35 (1H, m, =C$\underline{H}$-), 4.95 (2H, s, -OC$\underline{H}_2$C$_6$H$_5$), 7.85 (3H, d, J=1 Hz, C$\underline{H}_3$-), 8.15 (3H, d, J=1 Hz, C$\underline{H}_3$-).

b) Synthesis: This compound was obtained from VIII as a mixture with IV, as described above. It was purified by preparative GLC to a colorless liquid of bp 95—97° (2 mmHg). *Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.82; H, 7.36.

Benzyl 3-Hydroxyisovalerate (VIII)——a) Isolation from Reaction Products: This compound was isolated from reaction products by column chromatography as a liquid of bp 85° (3 mmHg). It was identified with the sample prepared in b). IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3440 (hydroxy), 1735 (ester). NMR (in CCl_4) τ: 2.80 (5H, s, -C$_6\underline{H}_5$), 4.95 (2H, s, -OC$\underline{H}_2$C$_6$H$_5$), 6.80 (1H, broad, -O$\underline{H}$), 7.60 (2H, s, -C$\underline{H}_2$-), 8.80 (6H, s, C$\underline{H}_3$-).

b) Synthesis: This compound was prepared from benzyl bromoacetate and acetone under the Reformatsky reaction condition as a colorless liquid of bp 121—124° (2 mmHg) in 61% yield. *Anal.* Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.04; H, 7.66.

Benzyl 2-Acetoxyisovalerate (IX)——a) Isolation from Reaction Products: This compound was isolated from reaction products by column chromatography as a colorless liquid of bp 116—122° (3.5 mmHg), and was identified with the sample prepared in b) by GLC, IR, and NMR. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1745 (ester), 1232 (acetoxy). NMR (in CCl_4) τ: 2.75 (5H, s, -C$_6\underline{H}_5$), 4.90 (2H, s, -OC$\underline{H}_2$C$_6$H$_5$), 5.25 (1H, d, J=3.5 Hz, -C$\underline{H}$(OAc)-), 7.6—7.8 (1H, m, -C$\underline{H}$-CH(OAc)-), 7.96 (3H, s, -OCOC$\underline{H}_3$), *ca.* 9.0 (6H, four peaks, (C$\underline{H}_3$)$_2$CH-). $[\alpha]_D^{29}$ +6.6° (c=2.342, benzene), corresponding to 16% (R) configuration.

b) Synthesis: A solution of benzyl (S)-2-hydroxyisovalerate ($[\alpha]_D^{23}$ −16.1° (c=2.02, EtOH), reported[9] $[\alpha]_D^{20}$ −16.3° (c=2.1, EtOH)) (1.0 g, 4.8 mmoles) and Ac_2O (1.1 g, 10.8 mmoles) in pyridine (10 ml) was heated at 90° for 2 hr, after which it was evaporated *in vacuo* to dryness. The residue was mixed with H_2O (20 ml), and the whole was extracted with ether. The ethereal solution was washed successively with sat. aq. $NaHCO_3$, H_2O, 10% aq. HCl, H_2O, then dried over anhyd. Na_2SO_4. Evaporation of the ether left a yellow oil, which was purified by column chromatography to give optically pure (S)-IX (0.9 g, 75% yield) as a colorless liquid of bp 143° (7 mmHg). $[\alpha]_D^{20}$ −42.1° (c=2.156, benzene). *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.04; H, 7.17.

Benzyl 3-Acetoxyisovalerate (X)——a) Isolation from Reaction Products: This compound was isolated from reaction products by column chromatography as a colorless liquid of bp 130—133° (4.5 mmHg), and was identified with the sample prepared in b). IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1740 (ester), 1245 (acetoxy). NMR (in CCl_4) τ: 2.70 (5H, s, -C$_6\underline{H}_5$), 4.95 (2H, s, -OC$\underline{H}_2$C$_6$H$_5$), 7.15 (2H, s, -C$\underline{H}_2$-), 8.20 (3H, s, -OCOC$\underline{H}_3$), 8.55 (6H, s, (C$\underline{H}_3$)$_2$C(OAc)-).

b) Synthesis: A solution of VIII (2.2 g, 9.6 mmoles) and Ac_2O (2.0 g, 19.6 mmoles) in pyridine (20 ml) was heated at 95° for 6 hr. Ac_2O (2.0 g, 19.6 mmoles) was added to the solution, then the whole was refluxed for 2.5 hr. Ac_2O (5.0 g, 49 mmoles) was added to this solution, and the reaction mixture was further refluxed for 6 hr. The residue obtained on evaporating the mixture to dryness *in vacuo* was mixed with H_2O (20 ml), then the whole was extracted with ether. The ethereal solution was washed successively with sat. aq. $NaHCO_3$, H_2O, 10% aq. HCl, H_2O, then dried over anhyd. Na_2SO_4. Evaporation of the ether left an oil, which was purified by column chromatography to a colorless liquid of bp 132—133.5° (4 mmHg). *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.24; H, 7.27.

Benzyl 2-Methylacetoacetate——A mixture of ethyl 2-methylacetoacetate[16] (22.5 g, 0.156 mole) and benzyl alcohol (22.5 g, 0.208 mole) was heated at 175° for 1 hr to remove EtOH. The residue was distilled to give a liquid (19.0 g) of bp 125—155° (13 mmHg). The fore-runner (bp of up to 125° (13 mmHg)) was treated as above to give a liquid (7.0 g) of bp 140—155° (13 mmHg). The two distillates were combined and distilled to give benzyl 2-methylacetoacetate (24.3 g, 76% yield) as a liquid of bp 145—148° (9 mmHg). NMR (in CCl_4) τ: 2.73 (5H, s, C$_6\underline{H}_5$-), 4.90 (2H, s, -OC$\underline{H}_2$C$_6$H$_5$), 6.55 (1H, q, J=6.5 Hz, -C$\underline{H}$(CH$_3$)-), 7.92

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[16] M.I. Kabachnik, S.T. Ioffe, E.M. Popov, and K.V. Vatsuro, *Tetrahedron*, **12**, 76 (1961).

(3H, s, $C\underline{H}_3$-CO-), 8.75 (3H, d, $J=6.5$ Hz, -CH($C\underline{H}_3$)-). *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.96; H, 6.72.

Benzyl 3-Hydroxy-2-methylbutyrate——A solution of $NaBH_4$ (0.50 g, 13.2 mmole) in diglyme (16 ml) was added to a stirred solution of benzyl 2-methylacetoacetate (7.00 g, 34.0 mmoles) in diglyme (18 ml) at 8—14°, then the whole was stirred at room temperature for 1 hr. Ether (150 ml) and H_2O (40 ml) were added to this solution. The ethereal layer was separated, then the aqueous layer was extracted with ether. The combined ethereal solution was washed successively with H_2O, 10% aq. HCl, H_2O, then dried over anhyd. Na_2SO_4. Evaporation of the solvent and distillation of the residue afforded an oil of bp 95—150° (5 mmHg), which was purified by column chromatography to give benzyl 3-hydroxy-2-methylbutyrate (2.9 g, 41% yield) as a colorless liquid of bp 87—130° (3 mmHg). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1}: 3440 (hydroxy), 1733 (ester). *Anal.* Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.41; H, 7.73.

A Mixture of Diastereomeric Benzyl 3-Acetoxy-2-methylbutyrate (XI and XII)——The solution of benzyl 3-hydroxy-2-methylbutyrate obtained above (2.1 g, 10 mmoles) and Ac_2O (4.0 g, 39 mmoles) in pyridine (15 ml) was warmed at 80° for 4 hr. The residue obtained on evaporating the mixture to dryness *in vacuo* was shaken with a mixture of ether (80 ml) and H_2O (20 ml). The ethereal layer was separated, washed successively with sat. aq. $NaHCO_3$, H_2O, 10% aq. HCl, H_2O, then dried over anhyd. Na_2SO_4. Evaporation of the solvent left a residue, which was purified by column chromatography to give a colorless liquid (1.9 g, 75% yield) of bp 142° (4 mmHg). IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1}: 1745 (ester), 1240 (acetoxy). NMR (in CCl_4) τ: 2.75 (5H, s, $C_6\underline{H}_5$-), 4.95 (2H, s, -$OC\underline{H}_2C_6H_5$), 4.8—5.1 (1H, m, -C$\underline{H}$(OAc)-), 7.3—7.6 (1H, m, -C$\underline{H}$(CH_3)-), 8.15, 8.20 (3H, s, -$OCOC\underline{H}_3$), 8.7—9.0 (6H, m, $C\underline{H}_3$-). *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.42; H, 7.45. This sample was shown by GLC and NMR to be a mixture of diastereomers found in reaction products.

2-Methylbutanoic Acid (XIII)——a) Synthesis of (S)(+)-XIII: (S)(+)-XIII was prepared from commercial (S)(−)-2-methylbutanol (bp 126—128.5°, $[\alpha]_D^{23}$ −5.1° (neat)) according to the reported method,[17] as a colorless liquid of bp 88—89° (27 mmHg) in 49% yield. Optical rotation of this compound, α_D^{26} +1.521° ($l=0.1$, neat), $[\alpha]_D^{26}$ +16.3° (neat), $[\alpha]_D^{27}$ +18.0° ($c=1.934$, ether), corresponds to 85% in optical purity based on the reported[17] value of $[\alpha]_D$ +19.2° (neat). *Anal.* Calcd. for $C_5H_{10}O_2$: C, 58.80; H, 9.87. Found: C, 58.76; H, 9.86.

b) Preparation from Substance III Isolated from the Reaction Mixture: A mixture of III ($[\alpha]_D^{23}$ −5.9° ($c=5.310$, benzene)) (0.52 g) and 5% Pd-C (0.20 g) in ether (20 ml) was shaken vigorously under an atmospheric pressure of H_2 until absorption of H_2 ceased. The catalyst was filtered off, then the filtrate was evaporated under atmospheric pressure to leave an oil (0.20 g), which was purified by column chromatography on silica gel with ether to a colorless liquid of $[\alpha]_D^{23}$ −4.4° ($c=1.590$, ether), corresponding to 21% (R) configuration. This was identified by IR and NMR with the sample prepared in a).

Nitrous Acid Deamination of L-Valine——$NaNO_2$ (4.8 g, 69.6 mmoles) was added in portions for 4.5 hr at 30—35° to a stirred solution of L-valine (7.0 g, 59.8 mmoles) in AcOH (72 ml), then the whole was allowed to stand at room temperature overnight. The solvent was evaporated *in vacuo* to give a residue, which was shaken vigorously with a mixture of ether (120 ml), H_2O (10 ml), and conc. HCl (6 ml). After washing the the mixture with H_2O, the ether layer was extracted with 10% aq. Na_2CO_3. Aqueous extracts were combined and acidified with conc. HCl, then extracted with ether. The ether layer was washed with sat. aq. NaCl, then dried over anhyd. Na_2SO_4. Evaporation of the solvent gave a yellow oil (10.1 g). Quantitative analysis of this sample by GLC using acenaphthene as an internal standard showed that the yield of 2-acetoxyisovaleric acid was 64%.

a) Purification of the Reaction Product: Purification of the crude reaction product by distillation and column chromatography on silica gel afforded 2-acetoxyisovaleric acid as a colorless liquid of bp 110—111° (4 mmHg), $[\alpha]_D^{26}$ −23.6° ($c=6.774$, EtOH), corresponding to 97% (S) configuration.[10d] *Anal.* Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.28; H, 7.60.

b) Esterification of the Reaction Product with Phenyldiazomethane: A solution of phenyldiazomethane in ether[18] was added to a solution of the crude reaction product (1.5 g) in ether until the orange color persisted. After the addition of excess HCOOH, the reaction mixture was washed with 10% aq. Na_2CO_3, H_2O, then dried over anhyd. Na_2SO_4. Evaporation of the solvent gave an oil (3.4 g). Gas chromatographic comparisons of this oil with the sample obtained by reacting phenyldiazomethane with AcOH showed that IX is the sole product. Purification of this oil by column chromatography on silica gel afforded IX as a colorless liquid of bp 134° (5 mmHg), $[\alpha]_D^{20}$ −39.7° ($c=2.114$, benzene), corresponding to 94% (S) configuration. IR and NMR spectra of this sample were superimposable on those of the sample described above. *Anal.* Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.01; H, 7.32.

Control Experiment——$NaNO_2$ (0.03 g, 0.43 mmoles) was added in portions at room temperature to a solution of IV (0.10 g, 0.40 mmoles) in AcOH (10 ml), then the mixture was allowed to stand at room tem-

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17) F.L. Weisenborn, J.W. Bolger, D.B. Rosen, L.T. Mann, Jr., L. Johnson, and H.L. Holmes, *J. Am. Chem. Soc.*, **76**, 1792 (1954).

18) C.G. Overberger and J.-P. Anselme, *J. Org. Chem.*, **28**, 592 (1963).

perature overnight. The solvent was evaporated *in vacuo* to give a residue, which was shaken with a mixture of H_2O and benzene. The benzene layer was washed successively with 10% aq. Na_2CO_3, H_2O, 10% aq. HCl, sat. aq. NaCl, then dried over anhyd. Na_2SO_4. Evaporation of the benzene *in vacuo* afforded a yellow oil (0.13 g), which was shown by GLC analysis to be only IV with few impurities. The same experiments were carried out for other compounds. All identified compounds in the deamination reaction mixture were unchanged under the reaction conditions and work up.