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Amino Acids and Peptides. III.[1] A New Synthetic Approach to N-Acylated α-Amino Aldehydes from N-Acylated α-Amino Acids by Catalytic Reduction of Their Mixed Carbonic-Carboxylic Acid Anhydrides with Palladium-Charcoal

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Mixed carbonic-carboxylic acid anhydrides prepared from N-acylated α-amino acids and ethyl chloroformate in tetrahydrofuran were reduced to the corresponding N-acylated α-amino aldehydes with palladium-charcoal under hydrogen bubbling. The optimum conditions found for N-acetyl-L-alanine were applied to the conversion of several kinds of N-acylated α-amino acids to their corresponding aldehydes, as shown in Table II. It was found that considerable racemization occurred under the present reduction conditions.

Oxidation of some N-acylated β-amino alcohols with dimethylsulfoxide in the presence of dicyclohexylcarbodiimide and phosphoric acid was also studied.

The ready availability in recent years of optically active α-amino acids makes it highly desirable to have convenient routes from them to their corresponding β-amino alcohol and α-amino aldehyde derivatives that are expected to be promising synthetic intermediates. The present authors have already reported that β-amino alcohols and their N-acylated derivatives are obtained in high yields by reduction of their corresponding α-amino acid esters or their N-acylated derivatives with sodium borohydride.[3]

The preparative methods for aldehydes from their corresponding alcohols or carboxylic acid derivatives have been widely investigated.[4] Successful applications to the syntheses of α-amino aldehyde derivatives have been reported in the following cases: (a) reduction of α-amino acid esters with sodium amalgam in acidic media,[5] (b) electrolytic reduction of α-amino acids,[6] (c) lithium aluminum hydride reduction of N-tosylated α-aminoacyldimethylpyrazoles[7] and (d) Rosenmund reduction of N-phthalylamino acid chlorides.[8] However, these methods are not necessarily satisfactory, mainly because of the yields reported in the first three, and the necessity of using phthalyl residue to protect the amino group in the latter.

1) Part II: Y. Takeuchi, K. Koga, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **19**, 2603 (1971).
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4) S.R. Sandler and W. Karo, "Organic Functional Group Preparations," Academic Press, New York and London, 1968, Chapter 7.
5) *a*) C. Neuberg, *Ber.*, **41**, 956 (1908); *b*) E. Fischer, *ibid.*, **41**, 1019 (1908); *c*) E. Fischer and T. Kametaka, *Ann.*, **365**, 7 (1909); *d*) S. Akabori, *Nippon Kagaku Zasshi*, **52**, 844 (1931); *e*) *Idem*, *Ber.*, **66**, 151 (1933); *f*) E. Adams, *J. Biol. Chem.*, **217**, 317 (1955).
6) *a*) C. Neuberg, *Biochem. Z.*, **17**, 270 (1909); *b*) C. Neuberg, L. Scott, and S. Lachmann, *ibid.*, **24**, 152 (1910).
7) *a*) W. Ried and P. Pfänder, *Ann.*, **640**, 111 (1961); *b*) L. Birkofer and E. Frankus, *Ber.*, **94**, 216 (1961).
8) *a*) E. Mosettig, *Organic Reactions*, **4**, 362 (1950); *b*) K. Balenović, N. Bregant, D. Cerar, D. Fleš, and I. Jambrešić, *J. Org. Chem.*, **18**, 297 (1953); *c*) W.O. Foye and J.J. Hefferren, *J. Am. Pharm. Assoc.*, **43**, 124 (1954); *d*) K. Balenović, N. Bregant, T. Galijan, Z. Štefanac, and V. Škarić, *J. Org. Chem.*, **21**, 115 (1956); *e*) W.O. Foye and W.E. Lange, *J. Am. Pharm. Assoc.*, **45**, 742 (1956).

The present paper concerns a new synthetic approach to N-acylated α-amino aldehydes from their corresponding N-acylated α-amino acids and their derivatives.

Initially, we intended to oxidize easily accessible N-acylated β-amino alcohols[3] with dimethylsulfoxide (DMSO), a well known oxidation method of alcohols to the corresponding aldehydes under mild conditions.[9] Although oxidation in the presence of dicyclohexylcarbodiimide (DCCD) and phosphoric acid[10] gave the best results among the various reaction conditions reported,[11] the yields were not satisfactory as shown in Table I.

Table I. Yields of Aldehydes in the Oxidation of Alcohols with DMSO in the Presence of DCCD and H_3PO_4

Starting material	Reaction conditions		Yield (%)
	Temp.	Time (day)	
C_6H_5-CH_2-CH(-N(CO-C_6H_4-CO))-CH_2OH	room temperature	2	43[a]
C_6H_5-CH_2-CH($NHCOCH_3$)-CH_2OH	room temperature	1	25[a]
C_6H_5-CH_2-CH($NHCOC_6H_5$)-CH_2OH	room temperature	1	32[a]
CH_3-CH($NHCOC_6H_5$)-CH_2OH	room temperature	1	8[b]

a) yield by isolation *b*) yield by 2,4-dinitrophenylhydrazone

On the other hand, it has been reported from our laboratory that mixed carbonic-carboxylic acid anhydrides prepared from carboxylic acids and ethyl chloroformate are reducible with sodium borohydride to their corresponding alcohols in fair yields.[12] As acid chlorides having reactivities analogous with that of the mixed carbonic-carboxylic acid anhydrides are known to be reduced to their corresponding alcohols with sodium borohydride[13] and to their corresponding aldehydes under Rosenmund reduction conditions,[8] examinations were performed to find whether mixed carbonic-carboxylic acid anhydrides prepared from N-acylated α-amino acids and ethyl chloroformate were reduced to their corresponding N-acylated α-amino aldehydes under catalytic reduction conditions.

As shown in Chart 1, mixed carbonic-carboxylic acid anhydride (II) prepared from N-acetyl-L-alanine (I) and ethyl chloroformate under ice-cooling as described previously[12] was

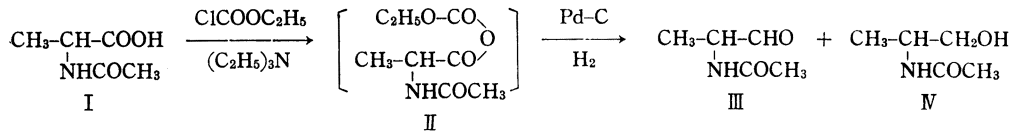

Chart 1

9) T. Sato, *Yuki Gosei Kagaku Shi*, **23**, 768 (1965).
10) *a*) K.E. Pfitzner and J.G. Moffatt, *J. Am. Chem. Soc.*, **85**, 3072 (1963); *b*) *Idem*, *ibid.*, **87**, 5661, 5670 (1965); *c*) A.H. Fenselau and J.G. Moffatt, *ibid.*, **88**, 1762 (1966).
11) *a*) N. Kornblum, W.J. Jones, and G.J. Anderson, *J. Am. Chem. Soc.*, **81**, 4113 (1959); *b*) T. Cohen and T. Tsuji, *J. Org. Chem.*, **26**, 1681 (1961); *c*) D.N. Jones and M.A. Saeed, *J. Chem. Soc.*, **1963**, 4657; *d*) C.R. Johnson and W.G. Phillips, *Tetrahedron Letters*, **1965**, 2101; *e*) J.D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4214 (1965).
12) K. Ishizumi, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 492 (1968).
13) S.W. Chaikin and W.G. Brown, *J. Am. Chem. Soc.*, **71**, 122 (1949).

stirred in tetrahydrofuran at 3—5° with 5% palladium-charcoal under hydrogen bubbling. It was found that the corresponding aldehyde (III) was actually produced with a small amount of the corresponding alcohol (IV). Although the generation of carbon dioxide was also observed, it was not useful as an indication of the formation of III because carbon dioxide could not be trapped quantitatively and the quantity of carbon dioxide trapped did not seem to parallel the quantity of III or IV in the reaction mixture. Therefore, the reaction was monitored by gas chromatography, as shown in Fig. 1.

From these findings, the catalytic reduction of II was further investigated to find the optimum reaction conditions.

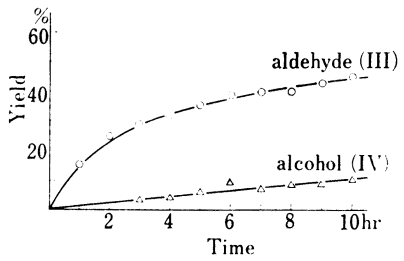

Fig. 1. Catalytic Reduction of II at 3—5°

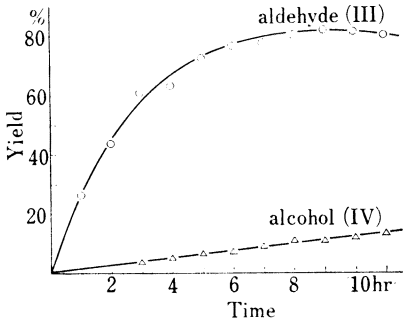

Fig. 2. Catalytic Reduction of II at 3—5° in the Presence of Acetic Acid

(1) Effect of Additives: During examination of the effects of various additives on the catalytic reduction of II at 3—5° with palladium-charcoal, it was found that the presence of a small amount of acetic acid in the reaction mixture extensively accelerated the rate of formation of the aldehyde (III) without affecting the rate of formation of the alcohol (IV), as shown in Fig. 2. Under this reaction condition, the aldehyde (III) was produced in 81% yield after 10 hr. However, it was found that the presence of an excess of triethylamine in the reaction mixture accelerated the rate of formation of the alcohol (IV), resulting in a high proportion of IV in the reaction products, as shown in Fig. 3.

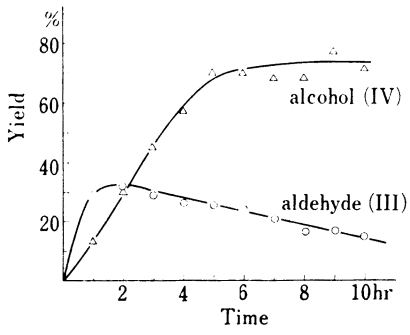

Fig. 3. Catalytic Reduction of II at 3—5° in the Presence of Triethylamine

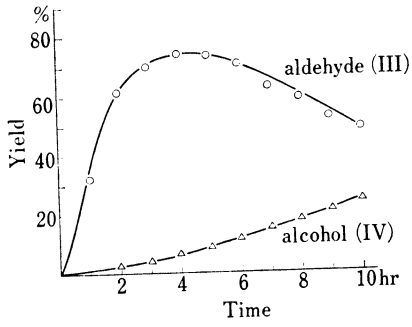

Fig. 4. Catalytic Reduction of II at 16.5—17.5° in the Presence of Acetic Acid

(2) Temperature: Catalytic reduction of II with palladium-charcoal in the presence of acetic acid at 16.5—17.5° proceeded faster than that at lower temperatures (at 3—5° and at −6——4°), but the maximum yield of II decreased somewhat, as shown in Fig. 4. Considering the stability of II, as well as practical easiness, it was concluded to be most appropriate to carry out the reaction under ice-cooling (at 3—5°).

(3) Catalyst: Catalytic reduction of II at 3—5° was examined with platinum oxide and Raney nickel (W_1 and W_2). It was found that the aldehyde (III) (2% yield) and the alcohol (IV) (19% yield) were produced with platinum oxide, while no reduction products were observed with Raney nickel.

From the above results, the most practical procedure for the catalytic reduction of II was found to use palladium-charcoal as a catalyst at 3—5° in the presence of acetic acid.

On the basis of this conclusion, several kinds of N-acylated α-amino acids were subjected to this catalytic reduction to their corresponding aldehydes. The general procedure is given in detail in the experimental, and results are shown in Table II. Yields of aldehydes from N-acetyl-L-phenylalanine (VI) and N-acetyl-L-isoleucine (VIII) were rather low. N-Acetyl-L-methionine (X) could not be changed to the corresponding aldehyde, probably because of the presence of poisonous sulfur in the molecule. However, N-acetyl-L-leucine (VII) and N-acetyl-L-valine (IX) were converted to their corresponding aldehydes in fair yields.

TABLE II. Yields of Aldehydes obtained by Catalytic Reduction

Starting material	Reaction conditions		Yield (%)
	Temp. (°C)	Time (hr)	
N-Acetyl-L-alanine (I)	3—5	10	81[a]
N-Benzoyl-L-alanine (V)	3—5	8	53[b]
N-Acetyl-L-phenylalanine (VI)	3—5	4	12[c]
	5—10	4	
N-Acetyl-L-leucine (VII)	3—5	10	77[b]
N-Acetyl-L-isoleucine (VIII)	3—5	11	35[b]
N-Acetyl-L-valine (IX)	3—5	8	70[b]
N-Acetyl-L-methionine (X)	3—5	10	0

a) yield by vpc *b*) yield by isolation *c*) yield by 2,4-dinitrophenylhydrazone

Two points must be mentioned about this reduction procedure. The first is that it is difficult to get completely reproducible results with different lots of catalyst. Therefore, selection of a catalyst of high activity is quite important for this reduction. The second is that considerable racemization was observed in products from this reduction. For example, the aldehyde (III) prepared from N-acetyl-L-alanine (I) was only 10% optically pure. Various degrees of racemization were also found in other aldehydes. Further research on this point will be reported in the future.

Experimental[14]

Oxidation of Alcohols with DMSO in the Presence of DCCD and H_3PO_4

Oxidation of N-Phthalyl-DL-phenylalaninol——A solution of H_3PO_4 (0.45 g, 4.6 mmoles) in DMSO (5 ml) was added to a solution of N-phthalyl-DL-phenylalaninol[15] (2.0 g, 7.1 mmoles) and DCCD (4.65 g, 22.8 mmoles) in DMSO (10 ml) and benzene (10 ml), then the whole was allowed to stand at room temperature for 2 days. A solution of oxalic acid (2.9 g) in MeOH (3 ml) was added to the reddish-brown colored reaction mixture and the whole was stirred at room temperature for 3 hr. Precipitates were filtered off, and were washed with AcOEt. The filtrate and the washings were combined, washed with satd. aq. $NaHCO_3$, H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness to give a reddish-brown oil (2.12 g). This was

14) All melting and boiling points are uncorrected. IR spectra were measured with a Koken DS-402G spectrometer and NMR spectra were measured with a JNM 3H-60 spectrometer operating at 60 mHz using TMS as an internal standard. Gas chromatographic data were obtained with a Yanagimoto GCG-3D gas chromatograph using columns packed with 15% Carbowax 20M on Diasolid L (60—80 mesh, 2 meter).

15) S. Yamada, K. Koga, and H. Matsuo, *Chem. Pharm. Bull.* (Tokyo), **11**, 1140 (1963).

chromatographed on silica gel with $CHCl_3$ to give 2-phthalimido-3-phenylpropionaldehyde (850 mg, 43%) as an oil.

2,4-Dinitrophenylhydrazone: Yellow prisms of mp 209—210° from EtOH–EtOAc. IR ν_{max}^{KBr} cm^{-1}: 3312 (NH), 1778, 1720 (imide), 1619 (C=N), 1515, 1333 (NO_2). *Anal.* Calcd. for $C_{23}H_{17}O_6N_5$: C, 60.13; H, 3.73; N, 15.25. Found: C, 60.11; H, 3.98; N, 15.42.

Oxidation of N-Acetyl-L-phenylalaninol——A solution of N-acetyl-L-phenylalaninol (prepared according to the reported method,[3] mp 96—99°, $[\alpha]_D^{12.5}$ −15.0° (c=1.056, EtOH)) (3.0 g, 15.5 mmoles) and DCCD (9.5 g, 46.5 mmoles) in DMSO (10 ml) and benzene (10 ml) was mixed with a solution of H_3PO_4 (0.82 g, 8.4 mmoles) in DMSO (5 ml) under ice-cooling and the whole was allowed to stand at room temperature for 1 day. The work up as above gave a brown syrup. This was chromatographed on silica gel with 3% EtOH in $CHCl_3$ to give 2-acetamido-3-phenylpropionaldehyde (750 mg, 25% yield) as an oil. NMR (in $CDCl_3$) τ: 8.01 (3H, singlet, -COC**H**$_3$), 2.78 (5H, singlet, C$_6$**H**$_5$-), 0.38 (1H, singlet, -C**H**O). $[\alpha]_D^{21}$ −8.4° (c= 1.053, EtOH).

2,4-Dinitrophenylhydrazone: Yellowish-orange needles of mp 200—201° from EtOH. $[\alpha]_D^{27}$ +2.4° (c= 0.497, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3298 (NH), 1656, 1547 (amide), 1619 (C=N), 1513, 1331 (NO_2). *Anal.* Calcd. for $C_{17}H_{17}O_5N_5$: C, 54.98; H, 4.61; N, 18.86. Found: C, 54.79; H, 4.48; N, 18.99.

Oxidation of N-Benzoyl-L-phenylalaninol——A solution of N-benzoyl-L-phenylalaninol (mp 169—170°, $[\alpha]_D^{20.5}$ − 88.0° (c=0.582, EtOH), reported[16] mp 169°) (2.0 g, 7.8 mmoles) and DCCD (8.0 g, 39.2 mmoles) in DMSO (10 ml) and benzene (15 ml) was mixed with a solution of H_3PO_4 (0.4 g, 4.0 mmoles) in DMSO (7.5 ml) and the whole was allowed to stand at room temperature for 1 day. The work up as above gave a reddish-brown solid (3.12 g), from which 2-benzamido-3-phenylpropionaldehyde (630 mg, 32%) was obtained by chromatography on silica gel. Recrystallizations from benzene gave colorless fine needles of mp 143—144°, $[\alpha]_D^{26.5}$ −106.8° (c=0.249, EtOH). IR ν_{max}^{KBr} cm^{-1}: 3367 (NH), 1741 (CHO), 1630, 1541 (amide). NMR (in $CDCl_3$) τ: 6.72 (2H, doublet, J=7 Hz, C$_6$H$_5$-C**H**$_2$-), 5.15 (1H, multiplet, -CH$_2$-C**H**(NH-)CHO), 2.2—2.9 (11H, C$_6$**H**$_5$- and N**H**COC$_6$**H**$_5$), 0.33 (1H, singlet, -C**H**O). *Anal.* Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.70; H, 6.23; N, 5.72.

2,4-Dinitrophenylhydrazone: Yellow fine needles of mp 210.5° from AcOEt. IR ν_{max}^{KBr} cm^{-1}: 3410 (NH), 1653 (amide), 1619 (C=N), 1523, 1337 (NO_2). *Anal.* Calcd. for $C_{22}H_{19}O_5N_5$: C, 60.96; H, 4.42; N, 16.16. Found: C, 60.98; H, 4.57; N, 16.05.

Oxidation of N-Benzoyl-L-alaninol——A solution of N-benzoyl-L-alaninol (mp 131.5—132.5°, $[\alpha]_D^{29}$ −4.6° (c=1.011, EtOH), reported[17] mp 131.5—132.5°, $[\alpha]_D^{25}$ −2.9° (c=7.4, 96% EtOH)) (1.0 g, 5.6 mmoles) and DCCD (4.6 g, 22.5 mmoles) in DMSO (15 ml) was mixed with a solution of H_3PO_4 (0.27 g, 2.8 mmoles) in DMSO (10 ml) and the whole was allowed to stand at room temperature for 1 day. The work up as above gave a orange solid, which was chromatographed on silica gel. The eluate was reacted with 2,4-dinitrophenylhydrazine to give 150 mg (8%) of 2,4-dinitrophenylhydrazone of 2-benzamidopropionaldehyde as yellow fine needles of mp 179—180°, $[\alpha]_D^{33}$ +13.0° (c=0.278, EtOH). IR ν_{max}^{KBr} cm^{-1}: 3303 (NH), 1627, 1535 (amide), 1618 (C=N), 1510, 1324 (NO_2). *Anal.* Calcd. for $C_{16}H_{15}O_5N_5$: C, 53.78; H, 4.23; N, 19.60. Found: C, 53.91; H, 4.43; N, 19.81.

Catalytic Reduction of Mixed Carbonic-Carboxylic Acid Anhydrides

General Procedure——A solution of ethyl chloroformate (2.39 g, 22 mmoles) in dehyd. THF (30 ml) was added dropwise to a solution of N-acylated α-amino acid (20 mmoles) and Et_3N (2.23 g, 22 mmoles) in dehyd. THF (80 ml) under ice-cooling. The colorless precipitates were filtered off, washed with dehyd. THF (50 ml) and the filtrate and the washings were combined. AcOH (2.0 ml) and 5% Pd-C (dry)[18] (50% of the theoretical weight of the mixed anhydride) were added to this solution. A stream of H_2 was passed through the stirred reaction mixture under ice-cooling for several hr. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue obtained was worked up as follows.

Reduction of N-Acetyl-L-alanine (I)——a) Isolation of 2-Acetamidopropionaldehyde (III): The reaction was carried out from I (mp 126—127°, $[\alpha]_D^{16}$ −69.7° (c=0.601, H_2O)) (2.62 g, 20 mmoles) according to the general procedure for 7 hr. The residue (4.1 g) obtained on evaporation of THF solution was chromatographed on silica gel (150 g) with 2% EtOH in $CHCl_3$ to give III (1.32 g, 58% yield) as an oil of bp 110° (7 mmHg), $[\alpha]_D^{21}$ −4.4° (c=0.690, EtOH). IR $\nu_{max}^{liq.}$ cm^{-1}: 3310 (NH), 1745 (CHO), 1665, 1555 (amide). NMR (in $CDCl_3$) τ: 8.66 (3H, doublet, J=7 Hz, C**H**$_3$-CH(NH-)-), 7.95 (3H, singlet, -COC**H**$_3$), 5.61 (1H, multiplet, J=7 Hz, CH$_3$-C**H**(NH-)-CHO), 2.94 (1H, broad, N**H**), 0.50 (1H, singlet, C**H**O).

2,4-Dinitrophenylhydrazone: Yellow fine needles of mp 199—200° (decomp.) from EtOH. IR ν_{max}^{KBr} cm^{-1}: 3301 (NH), 1645, 1555 (amide), 1620 (C=N), 1518, 1328 (NO_2). *Anal.* Calcd. for $C_{11}H_{13}O_5N_5$: C, 44.74; H, 4.44; N, 23.72. Found: C, 45.13; H, 4.46; N, 23.52.

Reduction of the aldehyde (III) obtained above with $NaBH_4$ in EtOH in the usual manner afforded N-acetyl-L-alaninol (IV) of $[\alpha]_D^{25}$ −3.3° (c=1.010, EtOH), corresponding to be 10% optically pure based on the value below for the optically pure sample.

16) J.H. Hunt and D. McHale, *J. Chem. Soc.*, **1957**, 2073.
17) A. Kjaer and B.W. Christensen, *Acta Chem. Scand.*, **15**, 1477 (1961).
18) Purchased from Nippon Engelhard Co., Ltd.

b) Changes in Product Composition during Reduction: A solution of the mixed anhydride (II) was prepared from I (1.31 g, 10 mmoles) according to the general procedure. AcOH (1.0 ml), 5% Pd-C (dry) (1.0 g) and diphenyl ether (1.0 g) were added to this solution, and the reaction was carried out according to the general procedure. At hourly intervals, the product composition in the reaction mixture was monitored by gas chromatography using diphenyl ether as an internal standard. Results are shown in Fig. 2.

c) Changes in Product Composition during Reduction in the Absence of AcOH: The reaction was carried out as in b), except that AcOH was not added. Results are shown in Fig. 1.

d) Changes in Product Composition during Reduction in the Presence of Excess Et_3N: The reaction was carried out as in b), except that Et_3N (1.0 g, 10 mmoles) was added instead of AcOH to the reaction mixture. Results are shown in Fig. 3.

e) Reduction at 16.5—17.5°: The reaction was carried out from I (1.31 g, 10 mmoles) as in the general procedure, except that the reaction temperature was maintained at 16.5—17.5° and that diphenyl ether (602 mg) was added to the reaction mixture. Products were monitored by gas chromatography using diphenyl ether as an internal standard. Results are shown in Fig. 4.

f) Reduction at −6——4°: The reaction was carried out as in e), except that the temperature was maintained at −6——4°. Results were almost similar with those in b).

g) Reduction with Platinum Catalyst: The reaction was carried out as in b), except that PtO_2 (1.0 g) was used instead of 5% Pd-C (dry). Gas chromatographic analyses showed that yields of the aldehyde (III) and the alcohol (IV) were 2 and 19%, respectively, after 10 hr.

h) Reduction with Raney Ni: The reaction was carried out as in c), except that 4 ml of Raney Ni (W_1, wet) or 3 ml of Raney Ni (W_2, wet) was used instead of 5% Pd-C (dry). Reduction products were found to be absent in the reaction mixture.

Reduction of N-Benzoyl-L-alanine (V)——The reaction was carried out from V (mp 148.5—149°, $[\alpha]_D^{28.5}$ +33.5° (c=1.126, 1N NaOH)) (1.93 g, 10 mmoles) for 8 hr according to the general procedure to give an oily residue (1.60 g). This was chromatographed on silica gel (50 g) with CH_2Cl_2 to give 2-benzamidopropionaldehyde (0.94 g, 53%) as an oil. $[\alpha]_D^{28}$ −0.63° (c=1.109, EtOH). IR $\nu_{max}^{liq.}$ cm^{-1}: 3270 (NH), 1730 (CHO), 1635, 1530 (amide).

2,4-Dinitrophenylhydrazone: Yellow fine needles of mp 178.5—179° from EtOH. *Anal.* Calcd. for $C_{16}H_{15}O_5N_5$: C, 53.78; H, 4.23; N, 19.60. Found: C, 53.86; H, 4.25; N, 19.55.

Reduction of N-Acetyl-L-phenylalanine (VI)——To a mixed anhydride solution prepared from VI (mp 167.5—168°, $[\alpha]_D^{12}$+48.6° (c=1.036, EtOH)) (2.07 g, 10 mmoles) according to the general procedure were added 5% Pd-C (dry) (2.0 g) and AcOH (0.5 ml). A stream of H_2 was passed through this stirred reaction mixture for 4 hr at 3—5°, followed by 4 hr at 5—10°. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo* to give a residue (3.1 g). The residue was taken up in AcOEt, and the AcOEt solution was washed with satd. aq. $NaHCO_3$, H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to give a pale yellow oil. Column chromatography of this oil on silica gel (50 g) with $CHCl_3$ afforded a pale yellow oil (1.21 g). This oil (140 mg) afforded 50 mg (12%) of 2,4-dinitrophenylhydrazone of 2-acetamido-3-phenylpropionaldehyde as brown leaflets of mp 195.5°, after recrystallization from EtOH. This sample was shown to be identical with the sample described above by the mixed melting point test.

Reduction of N-Acetyl-L-leucine (VII)——The reduction was carried out from VII (mp 184—185°, $[\alpha]_D^{28}$−23.5° (c=0.953, EtOH)) (3.46 g, 20 mmoles) for 10 hr according to the general procedure. The residue obtained on evaporation of the solvent was taken up in AcOEt. This solution was washed with satd. aq. $NaHCO_3$, H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness to give 2-acetamido-4-methylvaleraldehyde (2.42 g, 77%) as an oil. $[\alpha]_D^{28}$−3.5° (c=1.192, EtOH). IR $\nu_{max}^{liq.}$ cm^{-1}: 3277 (NH), 1740 (CHO), 1655, 1540 (amide). NMR (in CCl_4) τ: 9.08 (6H, $(CH_3)_2CH$-), 8.54 (2H, doublet of doublets, J=8.5 and 15 Hz, $-CH_2-$), 8.02 (3H, singlet, $-COCH_3$), 5.72 (1H, multiplet, $-CH(NH-)-$), 4.8 (1H, broad, NH), 0.54 (1H, singlet, CHO).

2,4-Dinitrophenylhydrazone: Yellowish-brown small needles of mp 178.5—179.5° from benzene–hexane. IR ν_{max}^{KBr} cm^{-1}: 3308 (NH), 1654, 1544 (amide), 1619 (C=N), 1511, 1328 (NO_2). *Anal.* Calcd. for $C_{14}H_{19}O_5N_5$: C, 49.84; H, 5.68; N, 20.76. Found: C, 50.52; H, 5.85; N, 20.38.

Reduction of this aldehyde with $NaBH_4$ in EtOH in the usual manner afforded N-acetyl-leucinol of $[\alpha]_D^{34}$−2.0° (c=1.097, EtOH), corresponding to be 5% optically pure based on the value for the optically pure sample below.

Reduction of N-Acetyl-L-isoleucine (VIII)——Reduction was carried out from VIII (mp 149.5—150.5° $[\alpha]_D^{28}$+14.2° (c=1.047, EtOH)) (3.46 g, 20 mmoles) for 11 hr according to the general procedure. The residue obtained on evaporation of the solvent was taken up in AcOEt. The AcOEt solution was washed with satd. aq. $NaHCO_3$, H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness to give an oil (3.98 g), which was subjected to column chromatography on silica gel (110 g). A syrup eluted with 5% EtOH in CH_2Cl_2 was distilled to give 2-acetamido-3-methylvaleraldehyde (1.1 g, 35%) as an oil of bp 118° (7 mmHg), $[\alpha]_D^{36}$ −7.1° (c=1.086, EtOH). IR $\nu_{max}^{liq.}$ cm^{-1}: 3298 (NH), 1739 (CHO), 1656, 1545 (amide). NMR (in CCl_4) τ: 9.10 (3H, triplet, J=6 Hz, CH_3-CH_2-), 9.05 (3H, doublet, J=6 Hz, CH_3-CH), 8.01 (3H, singlet, $-COCH_3$), 5.56 (1H, multiplet, $-CH(NH-)$), 2.43 (1H, broad, NH), 0.53 (1H, singlet, CHO).

2,4-Dinitrophenylhydrazone: Yellow needles of mp 178° from benzene–hexane. IR ν_{max}^{KBr} cm^{-1}: 3284 (NH), 1654, 1539 (amide), 1618 (C=N), 1507, 1333 (NO_2). *Anal.* Calcd. for $C_{14}H_{19}O_5N_5$: C, 49.84; H, 5.68; N, 20.76. Found: C, 49.83; H, 5.85; N, 20.97.

Reduction of N-Acetyl-L-valine (IX)——The reduction was carried out from IX (mp 165—166°, $[\alpha]_D^{22.5}$ −20.1° (c=0.492, H_2O)) (3.18 g, 20 mmoles) for 8 hr according to the general procedure. The residue obtained on evaporation of the solvent was taken up in AcOEt and the AcOEt solution was washed with satd. aq. $NaHCO_3$, H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the solvent *in vacuo* gave a yellow oil (3.25 g), which was chromatographed on silica gel with 2—4% EtOH in CH_2Cl_2 to give 2-acetamidoisovaleraldehyde (2.1 g, 70%), bp 101—102° (2 mmHg), $[\alpha]_D^{21}$ +1.0° (c=0.964, EtOH). IR $\nu_{max}^{liq.}$ cm^{-1}: 3288 (NH), 1735 (CHO), 1656, 1539 (amide). NMR (in CCl_4) τ: 9.04 (3H, doublet, J=7 Hz, CH_3-CH), 8.99 (3H, doublet, J=7 Hz, CH_3-CH), 8.00 (3H, singlet, -$COCH_3$), 5.56 (1H, multiplet, -CH(NH-)), 3.1 (1H, broad, NH), 0.45 (1H, singlet, -CHO).

2,4-Dinitrophenylhydrazone: Orange needles of mp 200° from benzene–EtOH. IR ν_{max}^{KBr} cm^{-1}: 3318 (NH), 1656, 1550 (amide), 1617 (C=N), 1516, 1333 (NO_2). *Anal.* Calcd. for $C_{13}H_{17}O_5N_5$: C, 48.29; H, 5.30; N, 21.66. Found: C, 48.62; H, 5.83; N, 21.69.

Reduction of this aldehyde with $NaBH_4$ in EtOH in the usual manner afforded N-acetyl-valinol of mp 58—66°, $[\alpha]_D^{21}$ −23.3° (c=0.537, EtOH), corresponding to be 75% optically pure based on the value for the optically pure sample below.

Reduction of N-Acetyl-L-methionine (X)——The reduction was carried out from X (mp 103—104°, $[\alpha]_D^{23}$ −21.5° (c=1.207, H_2O)) (3.83 g, 20 mmoles) for 10 hr according to the general procedure. It was found that no reduction products were present in the reaction mixture.

N-Acetyl-L-alaninol——The reduction of N-acetyl-L-alanine methyl ester (bp 138—141° (3 mmHg), $[\alpha]_D^{24}$ −93.4° (c=1.642, H_2O)) with $NaBH_4$ in aq. EtOH, according to the reported procedure,[3] afforded N-acetyl-L-alaninol, bp 144—147° (5 mmHg), mp 52—57°, $[\alpha]_D^{24.5}$ −31.6° (c=1.026, EtOH). *Anal.* Calcd. for $C_5H_{11}O_2N$: N, 11.96. Found: N, 11.66.

N-Acetyl-L-leucinol——The reduction of N-acetyl-L-leucine ethyl ester (bp 121—122° (2 mmHg), $[\alpha]_D^{29}$ −40.7° (c=1.094, EtOH)) with $NaBH_4$ in aq. EtOH[3] gave N-acetyl-L-leucinol of bp 148—150° (3 mmHg), $[\alpha]_D^{28}$ −40.6° (c=0.950, EtOH) in 51% yield.

O-Benzoate: mp 62—63° from petr. ether. *Anal.* Calcd. for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.41; H, 7.95; N, 5.41.

N-Acetyl-L-valinol——The reduction of N-acetyl-L-valine ethyl ester (bp 117—120° (3 mmHg), $[\alpha]_D^{28}$ −51.2° (c=0.598, H_2O)) with $NaBH_4$, in the reported manner,[3] afforded N-acetyl-L-valinol of mp 76—77°, $[\alpha]_D^{26}$ −29.8° (c=1.002, EtOH) in 85% yield. *Anal.* Calcd. for $C_7H_{15}O_2N$: N, 9.65. Found: N, 9.43.