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252. Hideo Seki, Kenji Koga, and Shun-ichi Yamada*1 : Chemistry of Amino Acids. III.*2 Reduction of Phenylalanine Ethyl Ester and Its Derivatives with Sodium Borohydride.*3

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Eleven kinds of ethyl 2-substituted-3-phenylpropionates (Ia~k) were reduced with sodium borohydride under a similar reaction condition and the effects of the α-substituents on the reduction were examined. Some esters (Ia~c, e, f, j, k) were hydrolyzed with alkali. The obtained data of hydrolysis rate constants were roughly parallel to those of ester reductions. These results may be explained by considering both inductive and steric effects of the α-substituents.

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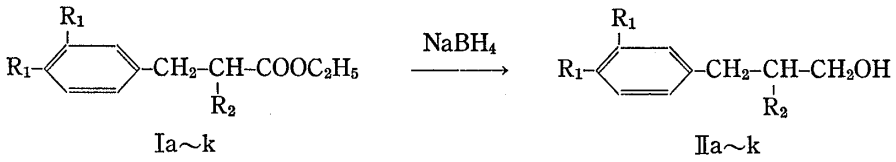
In the previous paper,[1] it was reported that optically active α-amino acid esters and their hydrochlorides could be reduced with sodium borohydride in anhydrous ethanol, in aqueous ethanol, or in water to give the corresponding optically active amino-alcohols in good yield. This fact seems to show that amino substituent at the α-position of ester group has some effect to promote the reduction, as Schenker[2] suggested already in the case of the reductions of hydroxy acid esters with sodium borohydride.

On the basis of this assumption, investigation as to the influence of substituents on the reaction time required for ester reductions and on the yield of the corresponding alcohols was carried out, changing the amino group of phenylalanine ethyl ester (Ib) to hydrogen (Ia), methylamino (Ic), benzylamino (Id), dimethylamino (Ie), acetamido (If and i), propionamido (Ig), pivalamido (Ih), hydroxy (Ij), and chloro (Ik) groups. These



Ia~k IIa~k

a : $R_1=R_2=H$
b : $R_1=H$, $R_2=NH_2$
c : $R_1=H$, $R_2=NHCH_3$
d : $R_1=H$, $R_2=NHCH_2C_6H_5$
e : $R_1=H$, $R_2=N(CH_3)_2$
f : $R_1=H$, $R_2=NHCOCH_3$
g : $R_1=H$, $R_2=NHCOC_2H_5$
h : $R_1=H$, $R_2=NHCOC(CH_3)_3$
i : $R_1=OCH_3$, $R_2=NHCOCH_3$
j : $R_1=H$, $R_2=OH$
k : $R_1=H$, $R_2=Cl$

esters (Ia~k) were reduced with 4 molar equivalents of sodium borohydride in the definite reaction conditions as shown in experimental part. The results are summarized in Table I.

Ethyl 3-phenylpropionate (Ia) was reduced to give 3-phenylpropanol (IIa) in 51% yield under reflux for 7.5 hr. in 50% aqueous ethanol, and phenylalanine ethyl ester (Ib) was already reported[1] to be reduced to 2-amino-3-phenylpropanol (IIb) in 84% yield

*1 Hongo, Tokyo (関 英男, 古賀憲司, 山田俊一).
*2 Part II : This Bulletin, **13**, 1001 (1965).
*3 Presented at the 85th Annual Meeting of Pharmaceutical Society of Japan, October, 1965, Tokushima.

1) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, S. Yamada : This Bulletin, **13**, 995 (1965).
2) E. Schenker : Angew. Chem., **73**, 81 (1961).

Table I. Reduction of Ethyl 2-Substituted-3-phenylpropionate (Ia~k) with 4 Molar Equivalents of $NaBH_4$

Ester		Reaction condition			Yield (%)
No.	Substituent	Solvent	Temperature	Time[a]	
Ia	H	50% EtOH	reflux	7.5 hr.	51
Ia	H	50% EtOH	ice-cooling	3 days	55
Ib	$NH_2(HCl)$	50% EtOH	reflux	4.5 hr.	84[b]
Ib	$NH_2(HCl)$	abs. EtOH	reflux	15 hr.	80[b]
Ib	$NH_2(HCl)$	50% EtOH	ice-cooling	2 days	84[b]
Ic	$NHCH_3(HCl)$	50% EtOH	reflux	13.5 hr.	31
Id	$NHCH_2C_6H_5(HCl)$	50% EtOH	reflux	12.5 hr.	29
Ie	$N(CH_3)_2$	50% EtOH	reflux	20 hr.	29
If	$NHCOCH_3$	50% EtOH	room temp.	6 hr.	69
If	$NHCOCH_3$	50% EtOH	reflux	4 hr.	76
If	$NHCOCH_3$	abs. EtOH	reflux	9 hr.	83
Ig	$NHCOC_2H_5$	50% EtOH	reflux	5 hr.	75
Ih	$NHCOC(CH_3)_3$	50% EtOH	reflux	3 hr.	80
Ii	$NHCOCH_3$	50% EtOH	room temp.	7.5 hr.	62
Ij	OH	50% EtOH	reflux	1 hr.	74
Ij	OH	abs. EtOH	room temp.	2.5 hr.	98
Ik	Cl	abs. EtOH	room temp.	1.5 hr.	98.5

a) The reaction was monitored by thin-layer chromatography.
b) These data are quoted from the previous paper.[1]

under reflux for 4.5 hr. in the same solvent. These results indicate undoubtedly that the α-amino group of Ib facilitates the borohydride reduction of ester.

When the amino group of Ib was changed to mono- or di-alkylamino groups (Ic~e), a very long reaction time was necessary to complete the reduction in 50% aqueous ethanol and the yields of aminoalcohols (IIc~e) were about 30%. When these esters (Ic~e) were reduced in anhydrous ethanol, the reaction was not complete, in either case, after 30 hours' reflux.

In the case of N-acylphenylalanine ethyl esters (If~i), ester groups were reduced as readily as Ib was.

α-Hydroxyester (Ij) and α-chloroester (Ik) were reduced so readily that the corresponding alcohols (II j,k) were obtained almost quantitatively within 1~2 hr., even if the reductions were carried out in anhydrous ethanol at room temperature. On the contrary, it needs 15 and 9 hours' reflux respectively to complete the reductions of phenylalanine ethyl ester (Ib) and its N-acetyl derivative (If) in anhydrous ethanol.

These data indicate that the facility of ester reduction with sodium borohydride changes with the nature of the α-substituents of the ester group. In order to investigate the substituent effect more quantitatively, the present authors studied the alkaline hydrolysis of some esters whose reaction mechanism seems to resemble that of the borohydride reduction. According to Bender and Turnquest's method[3] with some modifications, seven kinds of esters presented in Table II were hydrolyzed in 50% aqueous ethanol at 25° with sodium hydroxide.

As shown in Table II, the second order rate constants of the esters whose α-substituents are hydrogen (Ia), amino (Ib), acetamido (If), hydroxy (Ij), and chloro (Ik), increase in this order. But when the substituents are methylamino (Ic) and dimethylamino (Ie) groups, the hydrolysis rates were low. These data are roughly parallel with those of reductions. Namely, the ester which has a high rate constant

3) M.L. Bender, B.W. Turnquest: J. Am. Chem. Soc., **77**, 4271 (1955).

Table II. Alkaline Hydrolysis of Ethyl 2-Substituted-3-phenylpropionate[a]

Ester No.	Substituent	Initial concentration (mole/liter) Ester	NaOH	10^2k[b]	k/k_{Ia}
Ia	H	0.0102	0.0103	1.36 ±0.18	1
Ib	NH_2	0.0101	0.0206	3.52 ±0.23	2.6
Ic	$NHCH_3$	0.0100	0.0203	0.559±0.024	0.41
Ie	$N(CH_3)_2$	0.0100	0.0203	0.504±0.030	0.37
If	$NHCOCH_3$	0.0100	0.0100	13.1 ±2.1	9.6
Ij	OH	0.0105	0.0105	15.8 ±1.2	12
Ik	Cl	0.0104	0.0105	45.1 ±5.8	33

a) The hydrolysis was carried out in 50% aq. EtOH (volume %) at 25.1 ± 0.1°.
b) k: second order rate constant (liter/mole. sec.).

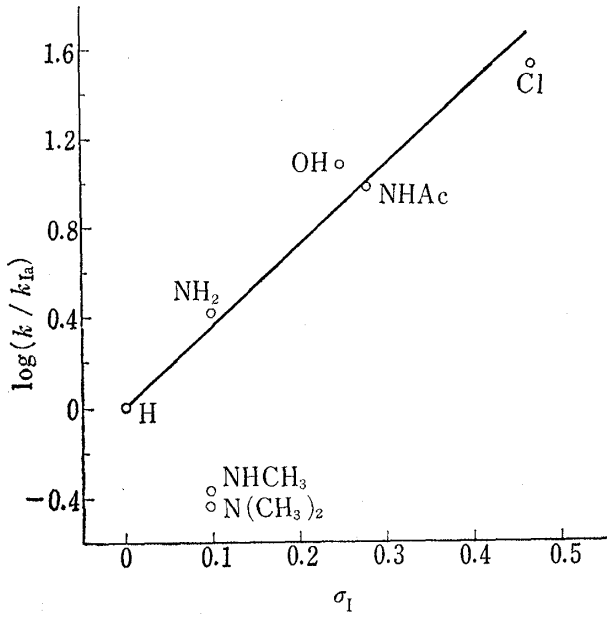


Fig. 1. Relationship between log (k/k_{Ia}) and the Taft's σ_I Constants of α-Substituents

can be reduced readily with sodium borohydride, but the ester which shows a low rate constant is not reduced so readily.

Logarithms of relative rate constants (k/k_{Ia}) were plotted against the Taft's σ_I constants[4] of α-substituents and shown in Fig. 1. These data may be explained as follows.

The magnitude of hydrolysis rate will be proportionate to that of electrophilicity of the ester carbonyl group and, in turn, to that of the inductive effect of the α-substituent. The greater the inductive effect, the faster the hydrolysis. In the case of the ester whose α-substituent is mono- or di-alkylamino group, hydrolysis is late because steric inhibition with the alkyl group would be more effective than its inductive effect.

Hydride ion (or borohydride ion) attacks the carbonyl group of the ester in reduction and hydroxide ion does also in alkaline hydrolysis. Since the mechanisms of both reactions seem to be similar, the reasoning mentioned above may be applied to the case of ester reduction. Namely, when the steric effect of the substituent is small, the ester reduction will become easier with the increase of the electron withdrawing property of the α-substituent.

But, when the reduction was carried out in 50% aqueous ethanol, hydrolysis of the ester occurred at the same time, so, the data of reductions were not always parallel to those of hydrolyses. For instance, though the hydrolysis rate of ethyl 2-acetamido-3-phenylpropionate (If) was larger than that of phenylalanine ethyl ester (Ib), the yield of alcohol did not increase in the former.

Since an amineborane type complex may be a reaction intermediate in the case of aminoester reduction, the effect of amine addition to the reaction medium was examined.

4) R.W. Taft Jr., I.C. Lewis: J. Am. Chem. Soc., **80**, 2436 (1958).

As shown in Table Ⅲ, several esters were reduced in the presence of ammonia or ethylamine, but the effect of amine addition was not obvious. This result may be obtained because of an acceleration of ester hydrolysis with the addition of an amine, an alkaline compound, in the aqueous medium, further investigations on this point will be reported in future.

Table Ⅲ. The Effect of Amine-addition on the Ester Reduction[a)]

Ester		Amine	Molar ratio (amine/ester)	Reaction		Yield (%)
No.	Substituent			Temp.	Time	
Ia	H			reflux	7.5 hr.	51
Ia	H			ice-cool	3 days	55
Ia	H	NH_3	2.7	room temp.	9 hr.	46
Ia	H	NH_3	1.2	ice-cool	3 days	45
Ia	H	$C_2H_5NH_2$	1.1	ice-cool	3 days	41
Id	$NHCH_2C_6H_5$			reflux	12.5 hr.	29
Id	$NHCH_2C_6H_5$	NH_3	2.6	room temp.	5 days	35
If	$NHCOCH_3$			room temp.	6 hr.	69
If	$NHCOCH_3$	NH_3	3.9	room temp.	6 hr.	68
Ii	$NHCOCH_3$ (3,4-dimethoxy)			room temp.	7.5 hr.	62
Ii	$NHCOCH_3$ (3,4-dimethoxy)	NH_3	1.2	room temp.	7.5 hr.	87

a) The reduction of ester was carried out with 4 molar equivalents of $NaBH_4$ in 50% aq. EtOH, and monitored by thin-layer chromatography.

Experimental*4

Materials——All esters were prepared by the esterification of the corresponding acids with abs. EtOH and $SOCl_2$ in the similar manner described previously.[5)] $NaBH_4$ was obtained from Kawaken Fine Chemicals Co., Ltd. and used without any purification.

Ethyl DL-2-Methylamino-3-phenylpropionate Hydrochloride (Ic-HCl)——DL-2-Methylamino-3-phenylpropionic acid (m.p. 227° (decomp.)) was prepared by the method of Quitt, *et al.*[6)] and esterified with abs. EtOH and $SOCl_2$ by refluxing for 6.5 hr. On evaporation of the solvent, crystals were obtained and recrystallized from EtOH–ether to yield white small needles in 84% yield. m.p. 151~151.5° (decomp.). Several more recrystallizations raised the melting point to 152~152.5° (decomp.). IR ν_{max}^{KBr} cm^{-1} : 1740 (ester). *Anal.* Calcd. for $C_{12}H_{18}O_2NCl$: C, 59.13; H, 7.44; N, 5.75. Found : C, 59.10; H, 7.35; N, 5.64.

Ethyl DL-2-Benzylamino-3-phenylpropionate Hydrochloride (Id-HCl)——DL-2-Benzylamino-3-phenylpropionic acid (m.p. 213.5° (decomp.)) was prepared by the method of Quitt, *et al.*[6)] and esterified as above by refluxing for 4 hr. The obtained solid (m.p. 120~130°, yield 94%) was recrystallized from acetone–ether to give colorless needles of m.p. 140.5~141.5°. IR ν_{max}^{KBr} cm^{-1} : 1741 (ester). *Anal.* Calcd. for $C_{18}H_{22}O_2NCl$: C, 67.60; H, 6.93; N, 4.38. Found : C, 67.74; H, 6.94; N, 4.24.

Ethyl DL-2-Propionamido-3-phenylpropionate (Ig)——DL-2-Propionamido-3-phenylpropionic acid (m.p. 132~133°) was prepared from DL-phenylalanine and propionyl chloride by the Schotten–Baumann method, and esterified as above. Colorless needles were obtained by recrystallization of the product from benzene–hexane, m.p. 49.5~50.5°, yield 83%. IR ν_{max}^{KBr} cm^{-1} : 3318 (NH), 1736 (ester), 1649, 1547 (amide). *Anal.* Calcd. for $C_{14}H_{19}O_3N$: C, 67.45; H, 7.68; N, 5.62. Found : C, 67.72; H, 7.68; N, 5.63.

DL-2-Pivalamido-3-phenylpropionic Acid——To an ice-cooled solution of DL-phenylalanine (10 g., 60.5 mmole) in 10% aq. NaOH (60 ml.) was added dropwise an ether solution of pivaloyl chloride (8.0 g., 66.3 mmole), and the mixture was stirred for 3.5 hr. with ice-cooling, made acidic with conc. HCl and extracted with ether. The ether solution was washed with water, dried over Na_2SO_4, and evaporated to give a pale brown oil which solidified after 2 days' cooling. The solid (m.p. 138~139°) was recrystallized from aq. EtOH to give colorless needles of m.p. 139.5~140.5° (14.0 g., 93%). IR ν_{max}^{KBr} cm^{-1} : 3378 (NH), 1737 (COOH), 1622, 1534 (amide).

*4 All melting points and boiling points are not corrected. IR spectra were measured with a Koken DS-402-G spectrophotometer.

5) S. Yamada, K. Koga, H. Matsuo : This Bulletin, **11**, 1140 (1963).
6) P. Quitt, J. Hellerbach, K. Vogler : Helv. Chim. Acta, **46**, 327 (1963).

Ethyl DL-2-Pivalamido-3-phenylpropionate (Ih)——The obtained acid was esterified as above by refluxing for 3 hr. The reagents being evaporated, the remaining solid (m.p. 60~63°) was recrystallized from hexane to afford white needles, m.p. 68~70° (yield, 96%). IR ν_{max}^{KBr} cm^{-1} : 3333 (NH), 1740 (ester), 1635, 1533 (amide). Further recrystallization from hexane raised the melting point to 70~71°. *Anal.* Calcd. for $C_{16}H_{23}O_3N$: C, 69.28; H, 8.36; N, 5.05. Found : C, 69.46; H, 8.27; N, 5.16.

Ethyl DL-2-Acetamido-3-(3,4-dimethoxyphenyl)propionate (Ii)——DL-2-Acetamido-3-(3,4-dimethoxyphenyl)propionic acid was esterified as above by refluxing for 4.5 hr. On evaporation of EtOH, a brown solid remained (yield, 82%) and was recrystallized from EtOH to give white needles of m.p. 116~118°. IR ν_{max}^{KBr} cm^{-1} : 3315 (NH), 1749 (ester), 1638, 1560 (amide). *Anal.* Calcd. for $C_{15}H_{21}O_5N$: C, 61.00; H, 7.17; N, 4.74. Found : C, 60.90; H, 7.20; N, 4.88.

Ethyl DL-2-Hydroxy-3-phenylpropionate (Ij)——DL-2-Hydroxy-3-phenylpropionic acid (m.p. 95~96°) was prepared by the method of Suwa[7] in the yield of 49% from DL-phenylalanine and esterified with EtOH and $SOCl_2$ by refluxing for 6.5 hr. The ester was obtained as a colorless oil of $b.p_{18}$ 156~157° (yield, 80%). (reported[8] : $b.p_{16}$ 148~152°). IR ν_{max}^{Cap} cm^{-1} : 3474 (OH), 1742 (ester). *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found : C, 67.89; H, 7.17.

Ethyl DL-2-Chloro-3-phenylpropionate (Ik)——DL-2-Chloro-3-phenylpropionic acid ($b.p_7$ 157~160°) was prepared according to the method of Kanao[9] in the yield of 61%, esterified as above by refluxing for 6 hr., and treated as usual to give a pale yellow oil in 89% yield, which was distilled to give a pale yellow oil ($b.p_7$ 127~134°). This oil was not pure, because 3 spots were observed on its thin-layer chromatogram and its IR-spectrum shows OH stretching (3430 cm^{-1}) and C=C stretching bands (1635 cm^{-1}). So this ester (5.8 g.) was chromatographed on silica gel (180 g.) and eluted with benzene. The early fractions were concentrated and distilled to give a pale yellow oil (5.1 g., $b.p_5$ 118~119°) (reported[9] : $b.p_{13}$ 134~134.5°). IR ν_{max}^{Cap} cm^{-1} : 1747 (ester). No absorption band depending on O-H or C=C was observed. *Anal.* Calcd. for $C_{11}H_{13}O_2Cl$: C, 62.12; H, 6.16. Found : C, 61.92; H, 6.18.

Reduction——All reductions were carried out in a similar manner using $NaBH_4$ in 50% aq. EtOH or abs. EtOH, and monitored by thin-layer chromatography.

3-Phenylpropanol (IIa)——A solution of ethyl 3-phenylpropionate (Ia) ($b.p_3$ 91~93°, 4.0 g., 28.1 mmole) in 50% aq. EtOH (50 ml.) was added dropwise to a solution of $NaBH_4$ (3.4 g., 112 mmole) in 50% aq. EtOH (50 ml.). The mixture was refluxed for 7.5 hr., concentrated *in vacuo* to remove EtOH, and extracted with ether. The ether layer was washed with water, dried over Na_2SO_4, and concentrated to give 1.55 g. (51%) of a pale yellow oil. Distillation *in vacuo* gave a colorless oil of $b.p_4$ 99~100° (reported[10] : $b.p_7$ 105~107°). IR ν_{max}^{Cap} cm^{-1} : 3360, 1058, 1030 (OH).

p-Nitrobenzoate : pale yellow rods from EtOH, m.p. 47~48°. IR ν_{max}^{KBr} cm^{-1} : 1729 (ester), 1518, 1353 (NO_2). *Anal.* Calcd. for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30; N, 4.91. Found : C, 67.72; H, 5.36; N, 4.94.

When the reduction was carried out in an ice-cooling bath under stirring for 3 days, the alcohol (IIa) was obtained in 55% yield. When ammonia or ethylamine (2.7~1.1 molar equivalents) was added to the reaction mixture, the reaction time was 9 hr. at room temperature or 3 days at a low temperature with ice-cooling and the yield of IIa was 46~41%.

DL-2-Methylamino-3-phenylpropanol (IIc)——To a solution of $NaBH_4$ (0.95 g., 25.1 mmole) in 50% aq. EtOH (15 ml.) was added dropwise a solution of Ic-HCl (1.50 g., 6.2 mmole) in 50% aq. EtOH (25 ml.). After the mixture was refluxed for 13.5 hr., it was concentrated *in vacuo* to a volume of 20 ml. and extracted with ether. The ether solution was treated as usual to give a yellow oil (320 mg., 31%).

Neutral oxalate : white needles from aq. EtOH, m.p. 214.5° (decomp.). IR ν_{max}^{KBr} cm^{-1} : 1609 (COO^-), 1074 (OH). *Anal.* Calcd. for $C_{22}H_{32}O_6N_2$: C, 62.84; H, 7.67; N, 6.66. Found : C, 62.93; H, 7.70; N, 6.62.

DL-2-Benzylamino-3-phenylpropanol (IId)——To a solution of $NaBH_4$ (0.95 g., 25.1 mmole) in 50% aq. EtOH (15 ml.) was added a solution of Id-HCl (2.0 g., 6.3 mmole) in the same solvent (40 ml.). The mixture was refluxed for 12.5 hr. and concentrated. The residual solution was shaken with $CHCl_3$, the $CHCl_3$ layer was separated, washed with water, dried, and evaporated to give a solid of m.p. 64~67° (430 mg., 29%). Recrystallization from benzene-hexane gave white needles, m.p. 67.5~68.5° (reported[11] : m.p. 69~71°). IR ν_{max}^{KBr} cm^{-1} : 3322, 1060 (OH). *Anal.* Calcd. for $C_{16}H_{19}ON$: C, 79.63; H, 7.94; N, 5.80. Found : C, 79.81; H, 7.80; N, 5.97.

From the aqueous layer, the acid corresponding to the ester (Id) was obtained in 70% yield.

When the reduction was carried out in the presence of ammonia (2.6 molar equivalents) at room temperature, five days were necessary to complete the reaction and the yield of IId was 35%.

DL-2-Dimethylamino-3-phenylpropanol (IIe)——To a solution of 1.5 g. (39.6 mmole) of $NaBH_4$ in 50% aq. EtOH (25 ml.) was added dropwise a solution of ethyl DL-2-dimethylamino-3-phenylpropionate (Ie) ($b.p_{11}$

7) A. Suwa : Z. Physiol. Chem., **72**, 113 (1911).
8) H. Gault, R. Weick : Bull. soc. chim. France, [4], **31**, 1000 (1922).
9) S. Kanao : Yakugaku Zasshi, **58**, 256 (1938).
10) J.B. Conant, W.R. Kirner : J. Am. Chem. Soc., **46**, 232 (1924).
11) A. Stoll, J. Peyer, A. Hofmann : Helv. Chim. Acta, **26**, 929 (1943).

137～138°, 2.1 g., 9.65 mmole) in 50% aq. EtOH (45 ml.). After being refluxed for 20 hr., the reaction mixture was treated as above to afford 500 mg. (29%) of a pale yellow oil. Distillation under reduced pressure gave a colorless oil of b.p_7 115～120° (reported[12] : b.p_{14} 151°).

Methiodide : colorless needles from water, m.p. 200～201° (reported[12] : m.p. 200°). IR ν_{max}^{KBr} cm^{-1}: 3370, 1057 (OH). *Anal.* Calcd. for $C_{12}H_{20}ONI$: C, 44.87; H, 6.28; N, 4.36. Found : C, 44.93; H, 6.19; N, 4.26.

From the aqueous layer, hydrolyzed acid of Ie was recovered in 61% yield.

DL-N-{(α-Hydroxymethyl)phenethyl}acetamide (IIf)——A solution of ethyl DL-2-acetamido-3-phenylpropionate (If) (m.p. 67～68°, 1.5 g., 6.4 mmole) in 50% aq. EtOH (45 ml.) was added dropwise to a solution of $NaBH_4$ (0.98 g., 26.9 mmole) in 50% aq. EtOH (15 ml.). The mixture was refluxed for 4 hr. and treated as above to yield a pale yellow syrup (930 mg., 76%) which crystallized on standing, and was recrystallized from benzene to give white needles, m.p. 93.5～94.5°. IR ν_{max}^{KBr} cm^{-1} : 3312 (NH, OH), 1641, 1569 (amide), 1049 (OH). *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found : C, 68.41; H, 7.76; N, 7.31.

When the reduction was carried out at room temperature for 6 hr., the yield of alcohol (IIf) was 69%. The addition of ammonia (3.9 molar equivalents) did not raise the yield (68%) under the same reaction condition.

DL-N-{(α-Hydroxymethyl)phenethyl}propionamide (IIg)——To a solution of $NaBH_4$ (1.25 g., 33.0 mmole) in 50% aq. EtOH (20 ml.) was added dropwise a solution of Ig (2.0 g., 8.0 mmole) in 50% aq. EtOH (50 ml.), and the mixture was refluxed for 5 hr., concentrated, and extracted with $CHCl_3$. On evaporation of $CHCl_3$, a viscous oil (1.25 g., 75%) was obtained and crystallized when cooled with hexane, m.p. 63～66°. Recrystallization from ether-hexane raised the melting point to 66～67.5°. IR ν_{max}^{KBr} cm^{-1} : 3339 (NH, OH), 1641, 1552 (amide), 1034 (OH). *Anal.* Calcd. for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.76. Found : C, 69.67; H, 8.12; N, 6.84.

DL-N-(α-Hydroxymethyl)phenethyl-pivalamide (IIh)——A solution of Ih (2.0 g., 7.2 mmole) in 50% aq. EtOH (100 ml.) was added to a solution of $NaBH_4$ (1.1 g., 29.1 mmole) in 50% aq. EtOH (15 ml.). The mixed solution was refluxed for 3 hr. and worked up as above to afford a pale brown oil (1.36 g., 80%). Recrystallization from benzene-hexane (1:9) gave white needles, m.p. 66～67°. IR ν_{max}^{KBr} cm^{-1} : 3280 (NH, OH), 1621, 1535 (amide), 1052 (OH). *Anal.* Calcd. for $C_{14}H_{21}O_2N$: C, 71.45; H, 9.00; N, 5.95. Found : C, 71.70; H, 9.05; N, 5.87.

DL-N-{(α-Hydroxymethyl-3,4-dimethoxy)phenethyl}acetamide (IIi)——A solution of Ii (2.0 g., 6.77 m mole) in 50% aq. EtOH (55 ml.) was added to a solution of $NaBH_4$ (1.03 g., 27.2 mmole) in the same solvent (20 ml.). The mixture was stirred at room temperature for 7.5 hr. and concentrated *in vacuo* to remove EtOH. After the excess $NaBH_4$ was decomposed with 10% HCl, the aqueous solution was made alkaline with satd. $NaHCO_3$ solution. From this solution, the product was extracted with $CHCl_3$ and treated as usual to give a syrup (1.11 g.) whose IR spectrum shows a small C=O band (1740 cm^{-1}) of ester. Then this syrup was hydrolyzed by refluxing for 6 hr. with 10% HCl (10 ml.) and EtOH (3 ml.). The reaction mixture was treated as usual to give DL-2-amino-3-(3,4-dimethoxyphenyl)propanol (0.89 g., 62% from the starting ester) as a brown solid (m.p. 57～61°). Recrystallization from CH_2Cl_2-hexane gave white needles of m.p. 85～86° (reported[13] : m.p. 63～64.5°). IR ν_{max}^{KBr} cm^{-1} : 3377, 3320 (NH_2), 3485, 3206, 1061, 1025 (OH). *Anal.* Calcd. for $C_{11}H_{17}O_3N$: C, 62.54; H, 8.11; N, 6.63. Found : C, 62.63; H, 8.05; N, 6.46.

When the reduction was carried out in the presence of ammonia (1.2 molar equivalents) under stirring for 7.5 hr. at room temperature, IIi was obtained in 87% yield. Recrystallization from AcOEt gave colorless fine needles of m.p. 93～94°. IR ν_{max}^{KBr} cm^{-1} : 3296, 3221 (NH, OH), 1635, 1523 (amide), 1048, 1030 (OH), *Anal.* Calcd. for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56; N, 5.53. Found : C, 61.27; H, 7.40; N, 5.25.

DL-3-Phenyl-1,2-propanediol (IIj)——To a solution of $NaBH_4$ (1.6 g., 42.3 mmole) in EtOH (80 ml.) was added a solution of Ij (2.0 g., 10.3 mmole) in EtOH (15 ml.). The EtOH solution was stirred for 2.5 hr. at room temperature and concentrated to dryness. The residue was decomposed with 10% HCl, made alkaline with 10% Na_2CO_3 solution and extracted with $CHCl_3$. After the usual treatment, a pale yellow oil (1.54 g., 98%) was obtained from the $CHCl_3$ layer. Distillation of this substance *in vacuo* gave a colorless viscous oil of b.p_6 143～145° (reported[14] : b.p_6 147～149°). IR ν_{max}^{Cap} cm^{-1} : 3340, 1090, 1070, 1031 (OH).

When the reduction was carried out in 50% aq. EtOH by refluxing for 1 hr., the alcohol (IIj) was obtained in 74% yield.

Dibenzoate : colorless needles from EtOH, m.p. 74～75° (reported[15] : m.p. 74～75°). IR ν_{max}^{KBr} cm^{-1} : 1733, 1715 (ester). *Anal.* Calcd. for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59. Found : C, 76.80; H, 5.80.

DL-2-Chloro-3-phenylpropanol (IIk)——A solution of Ik (3.23 g., 15.2 mmole) in EtOH (30 ml.) was added to a solution of $NaBH_4$ (2.3 g., 60.8 mmole) in EtOH (100 ml.). The solution was stirred for 1.5 hr. at room temperature and worked up as above. A pale yellow oil (2.55 g., 98.5%) was obtained and distilled under reduced pressure, b.p_7 122～124°. IR ν_{max}^{Cap} cm^{-1} : 3374, 1074, 1040, 1025 (OH). *Anal.* Calcd. for $C_9H_{11}OCl$: C, 63.35; H, 6.50. Found : C, 62.67; H, 6.27.

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p-Nitrobenzoate : faint yellow needles from EtOH, m.p. 53.5~54.5°. IR ν_{max}^{KBr} cm^{-1} : 1734 (ester), 1524, 1347 (NO_2). *Anal.* Calcd. for $C_{16}H_{14}O_4NCl$: C, 60.11; H, 4.41; N, 4.38. Found : C, 60.06; H, 4.61; N, 4.39.

Alkaline Hydrolyses——Hydrolyses were carried out by the method of Bender and Turnquest[3] with some modifications as follows. Equal quantities (20 ml.) of approximately 0.02*N* solutions of ester and NaOH in 50% aq. EtOH (by volume) which had attained thermal equilibrium (25.1±0.1°) were mixed. Two milliliter samples were removed after appropriate amounts of time and pipetted into a known excess of dilute HCl (0.03*N* HCl, 5 ml.). Titration of this mixture was effected to a phenolphthalein end-point using 0.01*N* NaOH solution. In the case of aminoesters, the initial concentration of NaOH was two times that of aminoester. See Table II, and Fig. 2 and 3 for representative experiments.

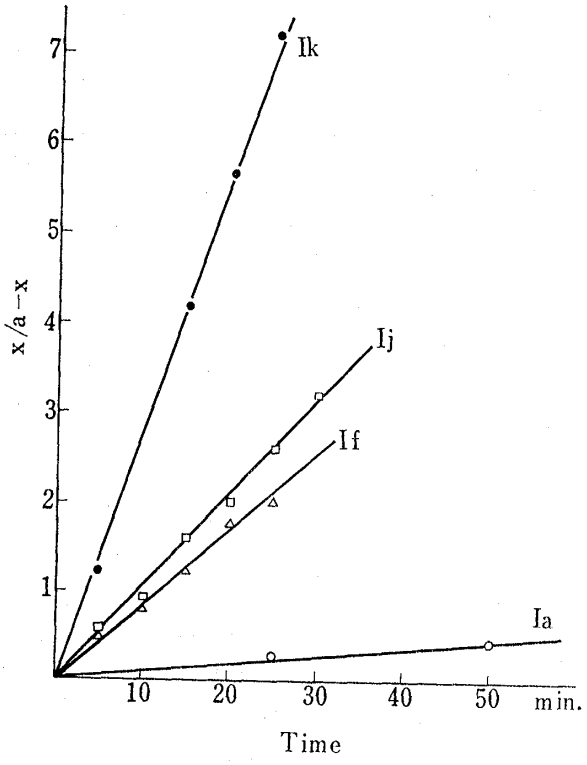

Fig. 2. Alkaline Hydrolysis of $C_6H_5CH_2CH(R)$-$COOC_2H_5$

Ia : R=H If : R=$NHCOCH_3$
Ij : R=OH Ik : R=Cl

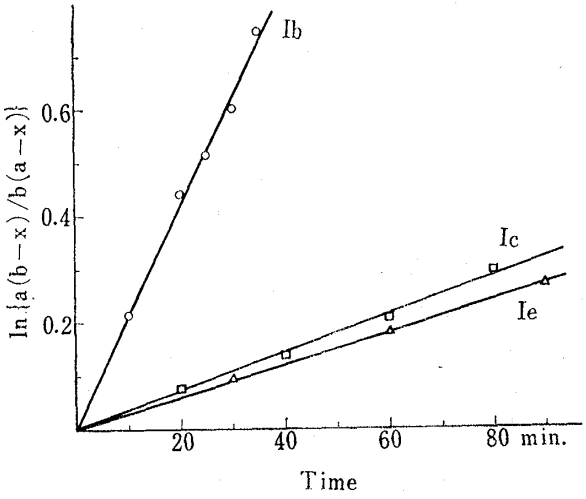

Fig. 3. Alkaline Hydrolysis of $C_6H_5CH_2CH(R)$-$COOC_2H_5$

Ib : R=NH_2
Ic : R=$NHCH_3$
Ie : R=$N(CN_3)_2$

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