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Chemistry of Diborane and Sodium Borohydride. VII.[1] Reduction of α-Amino Acid Amides with Sodium Borohydride

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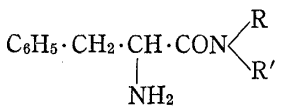
Tertiary amides of five amino acids and their derivatives were reduced with sodium borohydride in refluxing pyridine to the corresponding diamines in moderate yields. Effects of substituents at the α-position on α-substituted N,N-dimethylhydrocinnamamide were examined.

Sodium borohydride is a mild reducing agent, with the very useful characteristic of forming an aqueous solution. In our search for new properties of sodium borohydride in reactivities, we have been re-investigating the reduction of α-amino acid esters,[3a,b] carboxylic acids,[3c] tertiary amides,[3d,e] urea[3f] derivatives, and nitro[3g,h] and cyano[3g] groups to their corresponding alcohols and amines, also the nuclear reduction of pyridine derivatives[3i] and the dehydration of primary amides[3d,e] with sodium borohydride. Reports on the reductive cyclization of nitrile groups to imidazole rings[3j] and the decyanization of α-amino nitrile groups[3k] have most recently come from our laboratory.

Reduction of tertiary amides to the corresponding amines was first reported, by our group, [3d,e] to be successful with sodium borohydride in refluxing pyridine. Later, secondary amide was reported to be reduced to amine with sodium borohydride in refluxing triethylamine.[4] Recently Borch[5] reported a two-step reaction sequence utilizing sodium borohydride as the reducing agent for conversion of amides to the corresponding amines.

This paper deals with the reduction of several α-amino acid amides with sodium borohydride in order to extend our studies of the reaction reducing amides to the corresponding amines with sodium borohydride, and to exploit new utilization of amino acids.

Reactions of various types of DL-phenylalanine amides with sodium borohydride were investigated. The reduction of the primary amide (Ia) of phenylalanine with a large amount of sodium borohydride was carried out in refluxing pyridine, but no reduced amine was obtained and a considerable amount of starting amide (Ia) was recovered. This result was quite different from the dehydration of hydrocinnamamide to the corresponding nitrile[3e] under similar conditions.



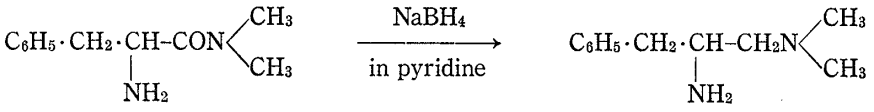
Ia: R=H, R′=H
IIa: R=CH_3, R′=H
IIIa: R=CH_3, R′=CH_3

Chart 1

1) Part VI: Y. Kikugawa, S. Ikegami and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 98 (1969).
2) Location: *Bunkyo-ku, Tokyo.*
3) *a*) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 995 (1965); *b*) H. Seki, K. Koga and S. Yamada, *ibid.*, **15**, 1948 (1967); *c*) K. Ishizumi, K. Koga and S. Yamada, *ibid.*, **16**, 492 (1968); *d*) S. Yamada, Y. Kikugawa and S. Ikegami, *ibid.*, **13**, 394 (1965); *e*) Y. Kikugawa, S. Ikegami and S. Yamada, *ibid.*, **17**, 98 (1969); *f*) Y. Kikugawa, S. Yamada, H. Nagashima and K. Kaji, *Tetrahedron Letters*, **1969**, 699; *g*) S. Yamada and Y. Kikugawa, *Chem. & Ind.*, **1967**, 1325; *h*) G. Ohtani, Y. Kikugawa and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 1840 (1968); *i*) S. Yamada and Y. Kikugawa, *Chem. & Ind.*, **1966**, 2169; *j*) S. Yamada, M. Kuramoto and Y. Kikugawa, *Tetrahedron Letters*, **1969**, 3101; *k*) S. Yamada and H. Akimoto, *Tetrahedron Letters*, **1969**, 3105.
4) K. Masuzawa, M. Kitagawa and H. Uchida, *Bull. Chem. Soc. Japan*, **40**, 244 (1967).
5) R.F. Borch, *Tetrahedron Letters*, **1968**, 61.

The reduction of phenylalanine N-monomethyl amide (IIa) was treated as above and the starting amide was, also, recovered quantitatively. However, the tertiary amide (IIIa) was reduced to the corresponding diamine (IIIb) under these conditions. This corresponded to our precious findings[3e] that only tertiary amides not secondary amides were reduced to amines. To find optimum reaction conditions, reactions with various molar ratios of IIIa and sodium borohydride were investigated. The use of 10 molar equivalents of sodium borohydride afforded the highest yield of diamine (IIIb) under refluxing in pyridine for 10 hr, as shown in Table I.

Table I. Reduction of DL-Phenylalanine Dimethylamide with Various Molar Ratios of Sodium Borohydride



IIIa IIIb

Molar ratio ($NaBH_4$/amide)	Reaction time (hr)	Yield of IIIb (%)
3	25	29
5	20	35
10	10	55

The reductions of the dialkyl amides of various types of amino acids such as phenylalanine, methionine, proline, tryptophan and threonine were carried out under these reduction conditions. The starting tertiary amides, IIIa, L-IIIa, IVa, Va, VIa and VIIa were prepared by the N-carboxy-α-amino acid anhydride method, IXa and Xa by the mixed anhydride method, and VIIIa by the reaction of 5-methyl-2-oxo-4-oxazolidinecarbonyl chloride, derived from L-threonine, with dimethylamine under the Schotten–Baumann reaction conditions.

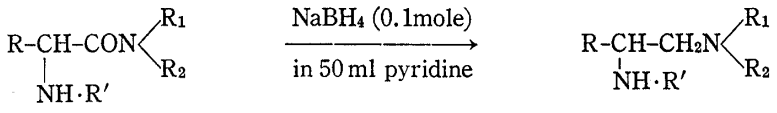
Table II shows representative results of the reduction reaction, all tertiary amides that were examined (runs, 3 to 11) were reduced to their tertiary amines in moderate yields. When amino acid amides, L-IIIa, L-VIIIa and L-Xa (runs, 4, 9 and 11), were optically active, the amines obtained (IIIb, VIIIb and Xb) were also optically active and showed a definite configuration, (*S*)-(+)-IIIb, (+) 5-(*R*)-methyl-4-(*R*)-dimethylaminomethyl-2-oxazolidinone (VIIIb) and (*S*)-(+)Xb according to the starting L-amino acids, even though it is not clear whether or not partial racemization occurred during this reduction. When a secondary and a tertiary amide co-existed in a molecule, such as VIa and IXa (runs, 7 and 10), the selective reduction took place only on a tertiary amide to give VIb and IXb, respectively.

In our previous paper,[3b] a substituent at the α-position of α-amino acid esters was found to influence the reduction rate of ester groups with sodium borohydride in aqueous alcohol. The facility of the reduction was of the following order; $-NH_2 > -H > -NH(CH_3) > -N(CH_3)_2$ at the α-substituent.

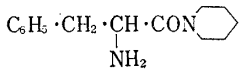
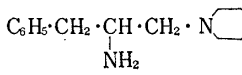
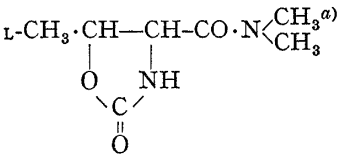
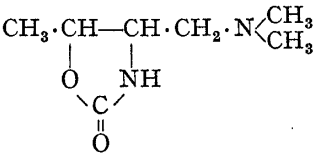
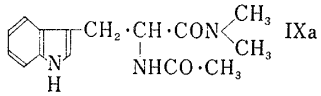
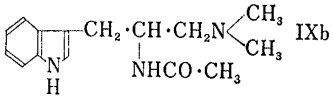
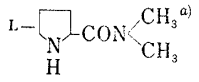
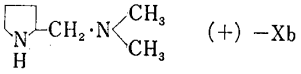
To examine whether or not similar neighboring participation takes place in this reduction of an amide, we investigated quantitative increase of the product and decrease of the starting material compared with reaction time, using gas chromatography. Reduction of amides was performed with 5 molar equivalents of sodium borohydride in refluxing pyridine. The results are shown in Fig. 1—4.

The starting amide (IIIa) containing a primary amino group at the α-position was clearly more readily reduced than was XIa having no substituent at the α-position (Fig. 1 and 2). As compared with Va and XIIa, most of the starting amide, IIIa, disappeared in an hour even though the quantitative relationship between starting amide and the amine produced

TABLE II. Reduction of Various Amino Acid Amides with Sodium Borohydride in Pyridine



(0.01 mole) Ia–Xa Ib–Xb

Run No.	Starting amides[a]	Reflux time (hr)	Amines obtained	Yield (%)
1	$C_6H_5\cdot CH_2\cdot CH(NH_2)\cdot CONH_2$ Ia	15	——	62[b]
2	$C_6H_5\cdot CH_2\cdot CH(NH_2)\cdot CONH\cdot CH_3$ IIa	20	——	98[b]
3	$C_6H_5\cdot CH_2\cdot CH(NH_2)\cdot CON(CH_3)_2$ IIIa	10	$C_6H_5\cdot CH_2\cdot CH(NH_2)\cdot CH_2N(CH_3)_2$ IIIb	55
4	L-IIIa	10	(+)-IIIb	45
5	 IVa	10	 IVb	62
6	$C_6H_5\cdot CH_2\cdot CH(NH\cdot CH_3)\cdot CON(CH_3)_2$ Va	10	$C_6H_5\cdot CH_2\cdot CH(NH\cdot CH_3)\cdot CH_2N(CH_3)_2$ Vb	45
7	$C_6H_5\cdot CH_2\cdot CH(NH\cdot CO\cdot CH_3)\cdot CON(CH_3)_2$ VIa	10	$C_6H_5\cdot CH_2\cdot CH(NH\cdot COCH_3)\cdot CH_2N(CH_3)_2$ VIb	52
8	$CH_3\cdot S\cdot CH_2\cdot CH_2\cdot CH(NH_2)\cdot CO\cdot N(CH_3)_2$ VIIa	10	$CH_3\cdot S\cdot CH_2\cdot CH_2\cdot CH(NH_2)\cdot CH_2\cdot N(CH_3)_2$ VIIb	56
9	 VIIIa		 (+)-VIIIb	47
10	 IXa	12	 IXb	61
11	 Xa	10	 (+)-Xb	30

a) Small capital letter prefix indicates the absolute configuration of amino acids, no prefix indicates racemic forms.
b) Recovered percentages of starting amides.

showed some contradiction (Fig. 2). With Va, 30% of the starting amide remained after 3 hr, (Fig. 3). The reduction did not almost proceed in 3 hr with XIIa (Fig. 4.). Thus, the following order was observed for facility in reducing amides IIIa, Va, XIa and XIIIa, depending on the substituents; $-NH_2 > -NH\cdot CH_3 > H \approx -N(CH_3)_2$. This tendency is similar to that for α-amino acid esters in sodium borohydride reduction.

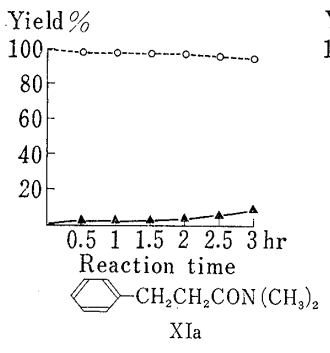


Fig. 1

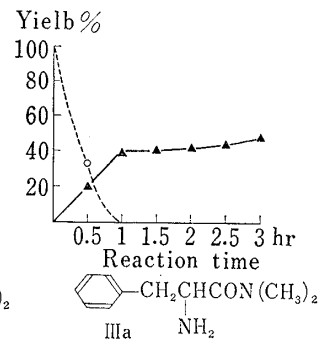


Fig. 2

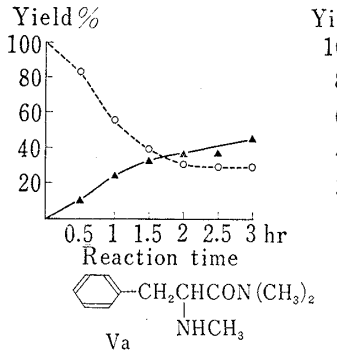


Fig. 3

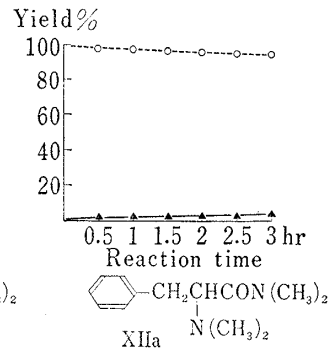


Fig. 4

Fig. 1—4. Relationships between Increase of Products and Decrease of Starting Amides with Reaction Time

---○---○---: starting amide —▲—▲—: reduced diamine

Experimental[6]

Materials——Sodium borohydride was purchased from Kawaken Fine Chemicals Co., Ltd., and used without further purification. Pyridine was purified according to a method given in a previous paper.[3e] Starting materials were prepared as follows.

DL-Phenylalanine Amide (Ia)——Compound Ia was prepared in a manner similar to that described by Koenings, *et al.*[7] Colorless prisms, mp 137.5—138.5° recrystallized from EtOAc (Reported mp 138—139°).

DL-Phenylalanine Methylamide (IIa)——Compound IIa was prepared by reacting N-carboxy-DL-phenylalanine anhydride[8] with methylamine as reported previously,[8] bp_3 165°. Picrate: yellow needles, mp 215—216° recrystallized from EtOH. *Anal.* Calcd. for $C_{16}H_{17}O_8N_5$: C, 47.17; H, 4.21; N, 17.19. Found: C, 47.53; H, 4.54; N, 16.66.

DL-Phenylalanine Dimethylamide (IIIa)——Compound IIIa was prepared in a manner similar to that described by Hanby, *et al*,[8] bp_5 150—152°. Picrate: yellow needles, mp 212—213° recrystallized from EtOH. *Anal.* Calcd. for $C_{17}H_{19}O_8N_5$: C, 48.45; H, 4.55; N, 16.62. Found: C, 48.81; H, 4.82; N, 16.56.

L-Phenylalanine Dimethylamide (L-IIIa)——Compound L-IIIa was prepared in the same way as IIIa, bp_3 148—150°. $[\alpha]_D^{13}$ +104.11° (c=0.972, EtOH). Picrate: yellow needles, mp 167.5—169° recrystallized from EtOH. *Anal.* Calcd. for $C_{17}H_{19}O_8N_5$: C, 48.45; H, 4.55; N, 16.62. Found: C, 48.74; H, 4.64; N, 16.32.

DL-Phenylalanine Piperidine Amide (IVa)——Compound IVa was prepared from N-carboxy-DL-phenylalanine anhydride and piperidine in the same as IIIa, $bp_{0.07}$ 140—149°. Picrate: yellow needles, mp 232° recrystallized from EtOH. *Anal.* Calcd. for $C_{20}H_{23}O_8N_5$: C, 52.06; H, 5.02; N, 15.18. Found: C, 52.47; H, 5.26; N, 15.19.

N-Methyl-DL-phenylalanine Dimethylamide (Va)——Method A: A mixture of benzaldehyde (15.9 g, 0.15 mole), DL-phenylalanine dimethylamide (IIIa) (9.6 g, 0.05 mole), *p*-toluenesulfonic acid (trace), and benzene (60 ml) was refluxed for 10 hr using a Dean–Stark apparatus. Excess benzaldehyde was removed *in vacuo* producing a yellow crystalline residue, which was washed with petroleum ether. A solution of sodium borohydride (1.9 g, 0.05 mole) in MeOH (10 ml) was added dropwise to a cold solution of above crude Schiff base (7.0 g, 0.025 mole) in MeOH (20 ml) and the mixture was stirred for 2 hr under ice–cooling. Solvent was removed *in vacuo* and the residue was treated with water and extracted with ether. The ether layer was washed with satd. NaCl solution, dried over anhyd. Na_2SO_4, and distilled, to give N-benzyl-DL-phenylalanine dimethylamide, bp_4 195—196°, later solidified, prisms mp 50—52° recrstallized from benzene–*n*-hexane, 4.9 g (70%). *Anal.* Calcd. for $C_{18}H_{22}ON_2$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.56; H, 7.94; N, 9.70. A mixture of N-benzyl-DL-phenylalanine dimethylamide (9.0 g, 0.03 mole) with 98% formic acid (4.5 ml, 0.09 mole) and 37% formaldehyde (2.5 ml, 0.036 mole) was refluxed for 3 hr. The mixture was evaporated to dryness under reduced pressure. The oily residue was extracted with ether. The ether layer was washed with 10% NaOH and satd. NaCl solution, dried over anhyd. Na_2SO_4 and evaporated to afford white crystals, N-benzyl-N-methyl-DL-phenylalanine dimethylamide. Colorless prisms mp 65—66° recrystallized from *n*-hexane, 7.2 g (80%). *Anal.* Calcd. for $C_{19}N_{24}ON_2$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.12; H, 8.22; N, 9.73. Catalytic debenzylation of N-benzyl-N-methyl-DL-phenylalanine dimethylamide (6.0 g, 0.02 mole) in AcOH (40 ml) with 5% Pd–C (3.0 g) was carried out. The work up afforded N-methyl-DL-phenylalanine dimethylamide, bp_2 133°, 2.0 g (50%) as usual. Picrate: yellow needles mp 204° recrys-

6) All melting and boiling points are uncorrected.
7) E. Koenings and B. Mylo, *Chem. Ber.*, **41**, 4439 (1908).
8) W.E. Hanby, S.G. Waley and J. Watson, *J. Chem. Soc.*, **1950**, 3009.

tallized from EtOH. *Anal.* Calcd. for $C_{18}H_{21}O_8N_5$: C, 49.65; H, 4.86; N, 16.09. Found: C, 49.94; H, 4.91; N, 16.31.

Method B: N-Benzylidene-DL-phenylalanine dimethylamide was prepared in a manner similar to that described in method A. A mixture of Schiff base (28 g, 0.1 mole) and methyl iodide (36 g, 0.26 ml) was heated under reflux for 15 hr. After excess methyl iodide was removed *in vacuo*, 90% aqueous EtOH (100 ml) was added to the residue, and the mixture was refluxed for 1 hr. After evaporation of EtOH, the residue was made basic with 10% NaOH, and extracted with ether. The ether layer was washed with satd. NaCl solution, dried over anhyd. Na_2SO_4, then evaporated to afford a pale yellow oil, bp_2 128—131°, 10 g (73%). Picrate: yellow needles mp 204° recrystallized from EtOH. The mixed mp of the product, compared with the authentic sample from method A, showed no depression.

N-Acetyl-DL-phenylalanine Dimethylamide (VIa)——Compound IIIa was acetylated with acetic anhydride–pyridine. Colorless prisms mp 99—100° were recrystallized from ether–*n*-hexane. *Anal.* Calcd. for $C_{13}H_{18}O_2N_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.71; H, 7.74; N, 12.00.

DL-Methionine Dimethylamide (VIIa)——Compound VIIa was prepared from N-carboxy-DL-methionine anhydride[9] and dimethylamine, pale yellow oil, bp_5 142—145°. Picrate: yellow needles mp 138—141° recrystallized from EtOH. *Anal.* Calcd for $C_{13}H_{19}O_8N_5S$: C, 38.51; H, 4.72; N, 17.28. Found: C, 38.20; H, 5.08; N, 17.35.

N,N-Dimethyl-L-5-methyl-2-oxo-4-oxazolidinecarboxamide (VIIIa)——The corresponding carboxylic acid was prepared from L-threonine in a manner similar to that described in the literature.[10] A mixture of carboxylic acid (6.0 g, 0.042 mole), thionyl chloride (15 ml, 0.21 mole) and anhyd. benzene (15 ml) was refluxed for 2.5 hr. After evaporation to dryness, the residual syrup was dissolved in anhyd. tetrahydrofuran (30 ml), to which a solution of dimethylamine (12 g, 0.27 mole) in anhyd. tetrahydrofuran (60 ml) was slowly added under ice cooling. The precipitated mixture of amide and dimethylamine hydrochloride was filtered. Recrystallization from EtOH gave colorless prisms mp 156—157°, 6.0 g (80%). $[\alpha]_D^{14}$ +98.0° (c=1.00, EtOH). *Anal.* Calcd. for $C_7H_{12}O_3N_2$: C, 48.83; H, 7.03; N, 16.27. Found: C, 48.68; H, 6.94; N, 16.12.

N-Acetyl-DL-tryptophan Dimethylamide (IXa)——Ethyl chloroformate (10.3 g, 0.095 mole) was added under stirring at 0° to a mixture of N-carbobenzyloxy-DL-tryptophan[11] (32 g, 0.095 mole) and triethylamine (9.6 g, 0.095 mole) in dimethylformamide (200 ml). The mixture was then allowed to stand for 40 min at the same temperature. A solution of dimethylamine (8.6 g, 0.19 mole) in tetrahydrofuran (40 ml) was slowly added with stirring over a period of 10 min to the mixture between 0° to 10°. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residual pale brown syrup was dissolved in chloroform and the chloroform layer was washed with 10% Na_2CO_3, 5% HCl, and satd. NaCl solution. Evaporation of chloroform gave N-carbobenzyloxy-DL-tryptophan dimethylamide. Colorless prisms mp 119—120° recrystallized from EtOH, 17.0 g (47%). *Anal.* Calcd. for $C_{21}H_{23}O_3N_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 68.95; H, 6.36; N, 11.32.

Catalytic decarbobenzyloxylation of N-carbobenzyloxy-DL-tryptophan dimethylamide (16.0 g, 0.04 mole) in EtOH (300 ml) with 5% Pd–C (4.0 g) was carried out. The DL-tryptophan dimethylamide produced was acetylated as usual with acetic anhydride–pyridine. Colorless prisms mp 190—195° recrystallized from acetone. *Anal.* Calcd. for $C_{15}H_{19}O_2N_3$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.83; H, 6.94; N, 15.38.

L-Proline Dimethylamide (Xa)——Compound Xa was prepared by the mixed anhydride method in the same manner as IXa from N-carbobenzyloxy-L-proline which is described in the literature.[12] Colorless oil, bp_2 92—94°, 30% yield from L-proline. $[\alpha]_D^{14}$ −103.6° (c=1.07, EtOH). Picrate: yellow needles mp 154—156° recrystallized from MeOH. *Anal.* Calcd. for $C_{13}H_{17}O_8N_5$: C, 42.05; H, 4.62; N, 18.86. Found: C, 42.50; H, 4.58; N, 19.14.

General Procedure for the Reduction of Amides with Sodium Borohydride——A mixture of the starting amides (0.01 mole) and sodium borohydride (0.1 mole) in pyridine (50 ml) was refluxed from 8 to 20 hr. Solvent was removed under reduced pressure, and the residue was treated as follows.

A: The residue was acidified with 10% HCl and this solution was refluxed for 10 minutes. After cooling, the reaction mixture was extracted with ether, then made alkaline with 10% NaOH and NaOH pellets. The oil which separated was extracted with ether. The ether layer was washed with satd. NaCl solution and dried over Na_2SO_4. Ether was removed and the residue was purified by distillation.

B: Water was added to the residue and extracted with ether. The ether layer was washed with satd. NaCl solution and dried over Na_2SO_4. Ether was removed and the residue was purified by distillation in VIb and VIIIb or by alumina chromatography in IXb.

Physical constants for the amines obtained are shown in Table III.

9) A.C. Fathing, *J. Chem. Soc.*, **1950**, 3213.
10) T. Kaneko and T. Inui, *Nippon Kagaku Zasshi*, **82**, 1075 (1961).
11) E.L. Smith, *J. Biol. Chem.*, **175**, 45 (1948).
12) A. Berger, J. Kurtz and E. Katchalski, *J. Amer. Chem. Soc.*, **76**, 5552 (1954).

Table III. Physical Constants of Obtained Amines

Compound No.	bp(°C)/mmHg or (mp °C)	Derivatives mp(°C)	Procedure	Molecular formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIb	95— 98/3	219—221 (2HCl)[a]	A	$C_{11}H_{20}N_2Cl_2$	52.59	8.03	11.15	52.71	8.02	11.43
L-IIIb	88— 90/4[c]	161—162 (2 pic.)[b]	A	$C_{23}H_{24}O_{14}N_8$	43.40	3.80	17.61	43.59	3.93	17.43
IVb	107—109/2	238 (2HCl)	A	$C_{14}H_{24}N_2Cl_2$	57.73	8.31	9.62	57.95	8.10	9.71
Vb	110—112/7.5	213—215 (2 pic.)	A	$C_{24}H_{26}O_{14}N_8$	44.31	4.03	17.23	44.60	4.05	17.27
VIb	(69— 70)		B	$C_{13}H_{20}ON_2$	70.87	9.15	12.72	71.15	9.16	13.14
VIIb	73— 76/3	194—196 (2 pic.)	A	$C_{19}H_{24}O_{14}N_8S$	36.77	3.90	18.06	37.34	4.00	18.36
VIIIb	128—130/1[d]	180—182 (2 pic.)	B	$C_{13}H_{17}O_9N_5$	40.31	4.43	18.08	40.84	4.61	17.78
IXb	(127—128)		B	$C_{15}H_{21}ON_3$	69.46	8.16	16.21	69.66	8.29	15.87
Xb	133—135/760[e]	212—213 (2 pic.)	A	$C_{19}H_{22}O_{14}N_8$	38.91	3.78	19.11	39.09	4.03	19.66

a) 2HCl: Dihydrochloride *b*) 2 pic: Dipicrate *c*) $[\alpha]_D^{18}$ +14.7° (*c*=1.167, EtOH)
d) $[\alpha]_D^{14}$ +34.9° (*c*=1.005, EtOH) *e*) $[\alpha]_D^{16}$ +2.7° (*c*=0.817, EtOH)

Gas Chromatography——Gas chromatography was carried out with a Yanagimoto GCG-3. Column: 5% SE-30 on Diasolid L, 3 m. Carrier gas: He. Flow rate: 60 ml/min. Column temperature 200°. Quantitative estimation of starting materials (amides) and products (amines) was made by the internal standard method using acenaphthene. Peak areas on the chromatogram were measured by the half width procedure. Authentic samples of starting amide N,N-dimethyl-3-phenylpropanamide XIa, and reduced amine N,N-dimethyl-3-phenylpropylamine were prepared in manner similar to that described previously by Yamada, *et al.*[3e] The other starting amide N,N-dimethyl-DL-phenylalanine dimethylamide XIIa, and reduced diamine N,N,N′,N′-tetramethyl-3-phenyl-1,2-propanediamine XIIb were synthesized as follows.

N,N-Dimethylamino-DL-phenylalanine Dimethylamide (XIIa)——A mixture of L-phenylalanine dimethylamide (11.0 g, 0.057 mole), 98% formic acid (13.5 ml, 0.27 mole) and 37% formaldehyde (12.5 ml, 0.18 mole) was refluxed for 8 hr. The mixture was evaporated to dryness under reduced pressure. The oily residue was extracted with ether. The ether layer was washed with 10% NaOH and satd. NaCl solution, dried over anhyd. Na_2SO_4, and evaporated to afford white crystals 3.5 g (30%). Colorless prisms mp 68—69° recrystallized from *n*-hexane. *Anal.* Calcd. for $C_{13}H_{20}ON_2$: C, 70.79; H, 9.10; N, 12.42. Found: C, 70.87; H, 9.15; N, 12.72.

N,N,N′,N′-Tetramethyl-3-phenyl-1,2-propanediamine (XIIb)——Reduction with $LiAlH_4$: To a cold solution of XIIa (2.20 g, 0.01 mole) in ether (40 ml) was added 0.76 g (0.02 mole) of lithium aluminum hydride. This mixture was refluxed for 10 hr. Excess lithium aluminum hydride was decomposed by adding water (0.9 ml), 15% NaOH (0.9 ml) and water (2.6 ml). The solid was filtered, and thoroughly washed with ether. The combined filtrate and washings were washed with satd. NaCl solution, dried over anhyd. Na_2SO_4, and evaporated to afford a pale yellow oil, bp_{10} 119—120°, 1.76 g (85%). Dipicrate: yellow needles mp 181—183° recrystallized from EtOH. *Anal.* Calcd. for $C_{25}H_{28}O_{14}N_8$: C, 45.18; H, 4.25; N, 16.86. Found: C, 45.40; H, 4.30; N, 17.23.

Reduction with $NaBH_4$: In sodium borohydride reduction of XIIa, which was carried out as in the general procedure mentioned above, a small amount of diamine was obtained. This compound was identical with an authentic sample based on its infrared spectrum and gas chromatography. The mixed mp of the picrate compared with the authentic sample showed no depression.

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