[Chem. Pharm. Bull.
17(1) 98—104 (1969)]

UDC 546.271.04: 542.942.1: 547.581.2.04

Chemistry of Diborane and Sodium Borohydride. VI.[1] The Reaction of Amides with Sodium Borohydride[2]

Yasuo Kikugawa, Shiro Ikegami
and Shun-ichi Yamada

Faculty of Pharmaceutical Sciences, University of Tokyo[3]

(Received May 11, 1968)

The reactions of primary, secondary and tertiary amides with sodium borohydride in refluxing pyridine were examined. Tertiary amides were reduced to the corresponding amines in moderate yield, in case of secondary amide no reaction occured and the starting amide was recovered, primary amides, on the contrary, were dehydrated to nitriles. Especially, when nicotinamide was used, the reduction of pyridine nucleus accompanied by dehydration occured to give 1,4,5,6-tetrahydronicotinonitrile.

Complex metal hydrides are the most available reducing agents for laboratory use. Especially sodium borohydride is expected to be used for industrial purpose because it can be employed in aqueous solvent and handled easily without any particular care, even though it cost a little expensive now.

We have been studying for the development of new reactions with readily available sodium borohydride, and the reductions of α-amino esters to amino alcohols[4a,4b] and carboxylic acids to alcohols,[4c] the nuclear reduction of pyridine derivatives[4d] and the reduction of cyano group to amine[4e] with sodium borohydride have been reported from our laboratory.

As a series of this work, this article reports an attempt to reduce various amides with sodium borohydride.

Since the amide group is generally highly resistant for the reduction, it is recognized that amides can not be reduced with sodium borohydride which is a mild reducing agent. However, when amides were refluxed with sodium borohydride in pyridine, tertiary amides, not primary and secondary amides, were found to be reduced to the corresponding amines under 10—20 hours' reflux. Solvents generally used for sodium borohydride reduction are water, alcohol, and tetrahydrofuran and it is very rare that pyridine was used in such a case. There are very few references[5] in which pyridine was used as a solvent for the selective reduction of steroidal carbonyl groups under mild reaction conditions at room temperature.

The fact that the combination of sodium borohydride and pyridine shows a strong reduction power might be considered to be due to the following advantages: 1) pyridine has a suitable boiling point for this reduction, 2) pyridine has a high electron-donating property,[6] and 3) pyridine dissolves sodium borohydride fairly well.

---

1) Part V: G. Otani, Y. Kikugawa and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 1840 (1968).

2) A part of this work was published before as a Communication to the Editor. S. Yamada, Y. Kikugawa and S. Ikegami, *Chem. Pharm. Bull.* (Tokyo), 13, 394 (1965).

3) Location: *Bunkyo-ku, Tokyo.*

4) *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.*, in press; *c*) K. Ishizumi, K. Koga and S. Yamada, *ibid.*, in press; *d*) S. Yamada and Y. Kikugawa, *Chem. Ind.* (London), **1966**, 2169; *e*) *Idem, ibid.*, **1967**, 1325.

5) *a*) O. Mancera, H.J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 1286 (1953); *b*) K. Adank, H.A. Pfenninger, W.G. Stoll and M. Viscontini, *Helv. Chim. Acta*, **46**, 1030 (1963); *c*) S.B. Kadin, *J. Org. Chem.*, 31, 620 (1966).

6) W. Gerrard, "The Organic Chemistry of Boron," Academic Press, London and New York, 1961 p. 136.

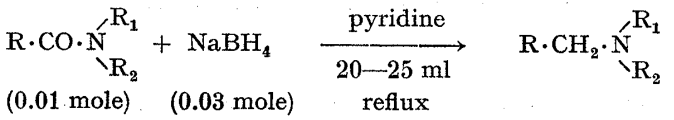
It is more interesting that when primary amides were treated with sodium borohydride in pyridine as above mentioned, dehydration of primary amides occured in stead of reduction and nitriles were found to be obtained in fairly yields. The dehydration of primary amides with lithium aluminum hydride under a certain condition has already been reported,[7] but this is the first one in case of sodium borohydride.[8] Generally speaking, acidic dehydrating agents such as phosphoryl chloride, thionyl chloride and toluenesulfonyl chloride in pyridine have been employed for the conversion of primary amides to nitriles, but it should be mentioned that dehydration with sodium borohydride, the basic reagent, is of great interest.

The reduction of secondary amides, N-methylphenylpropionamide and N-methylbenzamide as model compounds, with sodium borohydride in refluxing pyridine was undertaken, and it was found that the starting material was recovered quantitatively in each case. However, it was recently reported that the cyclic secondary amide was reduced to the corresponding amine by refluxing with sodium borohydride for a long time in triethylamine.[9] Accordingly, the reducing power of sodium borohydride on various kinds of amides seems considerably to depend on the solvents used.

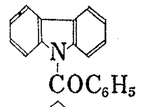
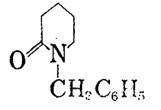
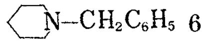
The Reaction of Tertiary Amides with Sodium Borohydride

N,N-Dimethylphenylpropionamide was reduced at various conditions to establish the most proper reduction condition and it was found that the reduction of tertiary amides was

Table I. The Reduction of Tertiary Amides with $NaBH_4$ in Pyridine



$$\underset{(0.01\ \text{mole})}{R\cdot CO\cdot N\begin{smallmatrix}R_1\\R_2\end{smallmatrix}} + \underset{(0.03\ \text{mole})}{NaBH_4} \xrightarrow[\text{20—25 ml reflux}]{\text{pyridine}} R\cdot CH_2\cdot N\begin{smallmatrix}R_1\\R_2\end{smallmatrix}$$

Numbers	Tertiary amides R	R₁	R₂	Reflux time (hr)	Recovery of starting material (%)	Amines yield (%)
1	$C_6H_5\cdot CH_2\cdot CH_2-$	CH_3	CH_3	20		51
2	$C_6H_5\cdot CH_2\cdot CH_2-$	$-(CH_2)_5-$		20		71
3	$C_6H_5\cdot CH_2\cdot CH_2-$	C_2H_5	C_2H_5	20	90	
4	$C_6H_5\cdot CH_2\cdot CH_2-$	CH_3	C_6H_5	20	71	
5	n-$C_7H_{15}-$	CH_3	CH_3	20		41
6	n-$C_7H_{15}-$	C_2H_5	C_2H_5	20	90	
7	C_6H_5-	CH_3	CH_3	10		30(25)[a]
8	C_6H_5-	$-(CH_2)_5-$		10		51
9	C_6H_5-	C_2H_5	C_2H_5	10		55
10	C_6H_5-	n-C_3H_7	n-C_3H_7	10		63
11	C_6H_5-	iso-C_3H_7	iso-C_3H_7	10	100	
12	C_6H_5-	CH_3	C_6H_5	10	80	
13				10		$C_6H_5CH_2OH$ 49
14				10		 66

a) Figures in parentheses shows the yield of benzyl alcohol.

---

[7] M.S. Newman and T. Fukunaga, *J. Am. Chem. Soc.*, **82**, 693 (1960).

[8] The dehydration of primary amide with sodium borohydride was first communicated by our group in 1965,[2] and the detailes were presented at the 86th Annual Meeting of Pharmaceutical Society of Japan, October 1966 at Sendai in Japan. Recently, dehydration of primary amide with sodium borohydride in diglyme was reported by other group (S.E. Ellzey, Jr., C.H. Mack and W.J. Connick, Jr. *J. Org. Chem.*, **32**, 846 (1967)).

[9] K. Masuzawa, M. Kitagawa, and H. Uchida, *Bull. Chem. Soc. Japan*, **40**, 244 (1967).

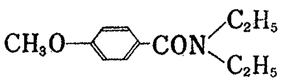
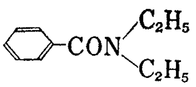
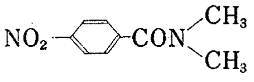
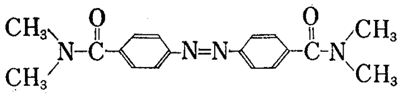
best effected by using 0.03 mole of sodium borohydride for 0.01 mole of tertiary amide and refluxing for about 20 hrs in 20—25 ml pyridine, and in case of aromatic tertiary amides, 10 hours' reflux was enough for the complete reduction of amides. However, in case of benzoylcarbazole, the corresponding reduced amine was not obtained and benzyl alcohol was obtained in 49% yield. When N-benzylpiperidone was submitted to this reduction, lactam group was smoothly reduced in 66% yield.

One of the characteristics of this reduction is to show a large steric requirement of substituents R_1, and R_2 on nitrogen atom. N,N-Dimethyl amides were reduced to the amines but N,N-diethyl amides were not reduced in case of tertiary aliphatic amides, on the other hand, aromatic amides from dimethyl to di-*n*-propyl derivatives were reduced to the corresponding amines respectively and isopropyl derivative failed to be reduced and the starting material was recovered. It may be due to the relatively mild reduction potential of sodium borohydride and the bulkiness of borohydride ion BH_4^-.

It was reported[10] that N-methyl-N-phenyl amides were reduced to the corresponding aldehydes with lithium aluminum hydride, but no aldehyde and no amine were obtained in the case of N-methyl-N-phenylbenzamide with sodium borohydride in refluxing pyridine.

Aromatic tertiary amides have a tendency to be reduced more easily than aliphatic ones, accordingly shorter reflux time was necessary for the formers than the latters. These differences may be attributable to the electronic effect of phenyl group. Therefore, the reduction of aromatic tertiary amides bearing various kinds of substituents at para position was undertaken to find out this electronic effect in this reduction. The results are shown in the Table II.

Table II. The Reduction of *p*-Substituted Aromatic Tertiary Amides with $NaBH_4$

Numbers	Tertiary amides	Reflux time (hr)	Recovery of starting material (%)	Amines yield (%)
15		5	85	a small amount
		6	65	11
		10	20	44
		15	20	46
16		6	25	28
		10	—	55
17		1—2		quantitatively

When methoxyl group is introduced at the *para* position of phenyl nuclei, the elctropositivity of carbonyl group of the amide should be weakened and the facility of the reduction of amide group might be thought to become difficult. The results were in accordance with this assumption as shown in the Table II. However, when nitro group is introduced at the *para* position, the reduction of nitro group occured first to give azo compound prior to the reduction of tertiary amide group. From above results, it was found to be difficult to say exactly whether this reduction depends on the electronic effect, but we suppose that the electronic effect is perceived in such a kind of reduction.

The detailed reduction mechanism of this reduction is obscure at present stage, but since the combination of sodium borohydride and pyridine can reduce the tertiary amides, this reduction mechanism may be due to the reducing factors different from ordinary hydride

---

[10] F. Weygand, G. Ebenhardt, H. Linden, F. Schaber and I. Eigen, *Angew. Chem.*, **65**, 525 (1953).

reduction of sodium borohydride. Under this consideration, the following reaction process might be assumed in the non hydroxylic solvent, especially in pyridine.

Pyridine borane was synthesized by separate route¹¹⁾ and the reduction of tertiary amides with pyridine boran was tried on the same reaction condition as with sodium borohydride in refluxing pyridine but only the starting material was recovered.

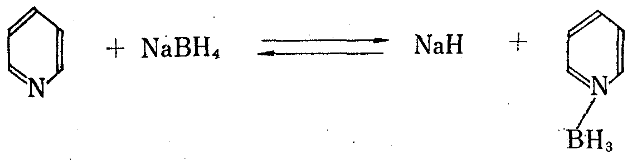


Chart 1

The Reaction of Primary Amide with Sodium Borohydride

The facility of amides with hydride ion is under the following order¹²⁾
tertiary amide>secondary amide>primary amide.

By the present reagent, sodium borohydride in pyridine, under the same reaction conditions that the tertiary amides were reduced, primary amides were not reduced but dehydrated to give nitriles as shown in the Table III.

Table III. The Dehydration of Primary Amides with $NaBH_4$

$$\underset{(0.01\ \text{mole})}{R\cdot CO\cdot NH_2} + \underset{(0.03\ \text{mole})}{NaBH_4} \xrightarrow[\substack{20\text{—}25\ \text{ml}\\ \text{reflux}}]{\text{pyridine}} R\text{–}C\equiv N$$

Numbers	Primary amides R	Reflux time (hr)	Nitrile yield (%)
18	$n\text{-}C_7H_{15}\text{–}$	20	37
19	$C_6H_5\cdot CH_2\cdot CH_2\text{–}$	20	56
20	$C_6H_5\cdot CH{=}CH\text{–}$	(5)[a)]	Trace
21	$C_6H_5\text{–}$	(5)	Trace
22	$p\text{-}CH_3O\text{–}C_6H_4\text{–}$	(5)	27
23	$3,4\text{-}CH_2\langle^{O}_{O}\rangle C_6H_3\text{–}$	(5)	9

a) Bath temperature was kept at 100—110°.

This dehydration reaction took place in moderate yield in the case of aliphatic acid amides, such as octanamide and phenypropionamide, but in the case of aromatic amides such as cinnamamide, benzamide, *p*-methoxybenzamide and 3,4-methylenedioxybenzamide the reaction mixtures generally turned to brown and black and only a small amount of nitriles were obtained.

However, when nicotinamide was used as a aromatic primary amide, 1,4,5,6-tetrahydronicotinonitrile was obtained in 20% yields under the similar reduction conditions as above, with sodium borohydride in pyridine. In the course of this reduction, when a small amount of ethanol was added to the reaction mixture, the yield raised to 42%.

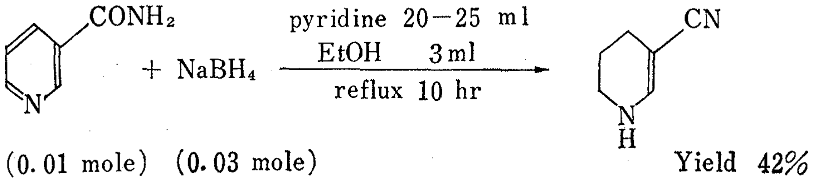


Chart 2

---

11) M.D. Taylor, L.R. Grant, and C.A. Sands, *J. Am. Chem. Soc.*, **77**, 1506 (1955).
12) V.M. Micovic and M.L.J. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

This result shows that the dehydration of primary amide accompanied by the reduction of pyridine nucleus took place at the same time with sodium borohydride in pyridine. Neither reduction nor dehydration reaction of nicotinamide with sodium borohydride in alcohol occurred and the starting material was recovered. From these facts, the following matter will be concluded: 1) Pyridine is necessary for the dehydration of primary amides. 2) In alcohol, no reaction occurs, but the addition of alcohol in pyridine, that is, the addition of hydroxylic solvent, promotes the reduction of pyridine nucleus.

Recently the reduction of nicotinamide with sodium borohydride in diglyme was reported separately to give 1,4,5,6-tetrahydronicotinonitrile **in** poor yield by S.E. Ellzey, *et al.*[8,13]

Experimental[14]

Materials——Sodium borohydride was purchased from Kawaken Fine Chemicals Co., Ltd. and used without further purification.

Benzamide and nicotinamide were obtained from commercial sources and purified before use.

Benzoylcarbazole and benzylpiperidone were prepared in the similar manner described in the literatures,[15—17] other amides were prepared by Schotten–Baumann Reactions.

Purification of Pyridine——Commercially available pyridine (1 liter) was refluxed with KOH (250 g) for 5 hours, and allowed to stand at room temperature overnight, and then distilled after addition of more KOH (150 g).

General Procedure for the Reduction of Tertiary Amides——To a solution of $NaBH_4$ (0.03 mole) in pyridine (20—30 ml), was added tertiary amide (0.01 mole) and the whole was refluxed for 10 or 20 hours.The solvent was removed under reduced pressure and the residue was acidified with 10% HCl. This solution was refluxed for 10—30 minutes. After cooling, the reaction mixture was extracted with ether and then made alkaline with 10% aq. NaOH and NaOH pellets. The oil separated was extracted with ether, which was washed with satd. NaCl and dried over Na_2SO_4. Ether was removed and the residue was purified by distillation.

General Procedure for Dehydration of Primary Amides——1) Dehydration of Benzamide, Anisamide, Piperonylamide and Cinnamamide: To a solution of $NaBH_4$(0.03 mole) in pyridine (20—25 ml) was added primary amide (0.01 mole) and the reaction temperature was maintained at 100—110° for 5 hours. The color of the solution was changed to blownish black. Under reduced pressure the solvent was removed and water was added to the residue. The aqueous layer was extracted with ether which was dried over Na_2SO_4. Ether was removed and the residue was purified with silica gel chromatography to give the corresponding nitrile.

2) Dehydration of Octanamide and Phenylpropionamide: To a solution of $NaBH_4$ (0.03 mole) in pyridine (20—25 ml) was added primary amide and the whole was refluxed for 20 hr. Pyridine was removed under reduced pressure and the residue was weakly acidified with 10% HCl, and heated on an oil bath to keep the temperature at 100—110° for 10 minutes. After cooling, the mixture was extracted with ether which was washed with satd. NaCl and dried over Na_2SO_4. Ether was removed and the residue was distilled to give a pure product.

3) Preparation of 1,4,5,6-Tetrahydronicotinonitrile: To a solution of $NaBH_4$ (1.4 g) in pyridine (30 ml), was added nicotinamide (1.5 g, mp 128—129.5°), the whole was refluxed for 10 hr. When reflux was continued for first 4 hr, C_2H_5OH (3 ml) was added dropwise to the reaction mixture for 10—15 minutes. After the reaction ended, pyridine was removed under N_2 atmosphere and H_2O (20 ml) was added to the residue. The aqueous layer was extracted with ether which was washed with satd. NaCl and dried over Na_2SO_4. Ether was distilled off and the residue was distilled to give 1,4,5,6-tetrahydronicotinonitrile as a slightly yellow oil (560 mg, 42.2%) bp 140° (3.5 mmHg), NMR (CCl_4)τ: 4.23 (1H broad, $>$N–H), 2.96 (1H, doublet, J=6 cps,

---

[13] In Ellzey's paper, the reduction of nicotinamide with sodium borohydride in diglyme was described as an example of dehydration of primary amides.

[14] All melting points and boiling points were uncorrected. NMR spectra were taken on Model J.N.M. 3H 60 spectrometer with Me_4Si as the internal standard. IR spectra measurements were performed with a Spectrometer, Model DS-402. Japan Spectroscopic Co., Ltd. The measurement of UV spectra was carried out with a Cary Model 11 recording spectrophotometer.

[15] O. Fischer, *Chem. Ber.*, 32, 1302 (1899).

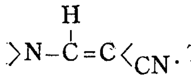
[16] S. Sugasawa and T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 587 (1958).

[17] T.S. Stevens and S.H. Tucker, *J. Chem. Soc.*, **123**, 2146 (1923).

Table IV. Physical Constants of the Compounds

Numbers[a]	Starting materials bp °C/mmHg or mp °C	Products bp °C/mmHg or mp °C (lit.)	Derivatives mp °C (lit.)[b]	Analysis (%)					
				Calcd.			Found		
				C	H	N	C	H	N
1	144—145/7	104—105/15[c] (215—220)	pic. 98.5—99[c] (99)	42.86	2.62	18.18	43.24	2.95	18.40
2	191—192/10	135—135.5/8.5 (272—274)[d]	pic. 101—101.5 (99—100)[d]	55.55	5.59	12.96	55.71	5.79	13.15
3	156—157.5/9								
4	168—169/3.5								
5	106—106.5/9	87/24 (191/760)[e]	pic. 70—71 (72)[e]	49.73	6.78	14.50	49.38	6.67	14.87
6	120—130/10								
7	139—140/17	77—80/22 (177.8—178.2/766)[f]	pic. 93—94 (96)[g]	49.45	4.43	15.38	49.55	4.49	15.56
8	170—171/14	117—118.5/16 (115/13)[h]	HCl[i] 178.5—179.0 (178)[j]	68.08	8.51	6.62	68.14	8.51	6.76
9	136—137/10	89/15 (211—212)[k]	pic. 120 (120)[l]	52.04	5.14	14.28	52.29	5.39	14.18
10	136—137/4	120—122/20 (235—243)[m]	pic. 119—120.5 (121)[n]	54.28	5.75	13.33	54.15	5.86	13.04
11	63—66								
12	150/5								
13	98—99	87—89/8 (206.5)[o]							
14	147—151/3	128—131/20 (115/13)[h]	pic. 178—179 (178—179)[p]	53.46	4.99	13.86	53.48	5.05	13.95
15	40—41	123—125/14 (102—103/1)[q]	pic. ~103	51.18	5.26	13.27	51.18	5.26	13.04
16	=(9)								
17	98	239—240		66.23	6.79	17.17	66.52	6.74	16.92
18	103—104	120—130/100 (198—200)[r]							
19	98—100	122—125/13 (170/15)[s]							
20	145—147								
21	125—126								
22	162.5—164.0	58.5—59.5 (61—62)[t]		72.16	5.30	10.52	72.05	5.45	10.60
23	163—164	93—93.5 (90—91)[u]		65.30	3.43	9.52	65.11	3.44	9.52

a) the numbers correspond to the compound listed in Table I, and III
b) pic.=picrate
c) C. Mannich and G. Heilmer, *Chem. Ber.*, **55**, 361 (1921)
d) A. Pollard and R. Robins on, *J. Chem. Soc.*, **1927**, 2780
e) H.T. Clarke, *J. Chem, Soc.*, **103**, 1698 (1913)
f) H. Emde, *Chem. Ber.*, **42**, 2593 (1909)
g) J.V. Brown, M. Kühn and O. Goll, *Chem. Ber.*, **59**, 2335 (1926)
h) J. King, *J. Chem. Soc.*, **1951**, 900
i) HCl =HCl salt
j) F. Haase and R. Wolffenstein, *Chem. Ber.*, **37**, 3232 (1904)
k) V. Meyer, *Chem. Ber.*, **10**, 310 (1877)
l) B. Flürschein and E.L. Holmes, *J. Chem. Soc.*, **1926**, 1568
m) J.V. Brown and R. Schwarz, *Chem. Ber.*, **35**, 1281 (1902)
n) J.V. Brown and R. Schwarz, *Chem. Ber.*, **35**, 1282 (1902)
o) H. Kopp, *Ann.*, **94**, 313 (1855)
p) K. Kindler, *Archiv der Pharmazie*, **1927**, 403
q) *C.A.* **55**, 14466 g (1961); A.L. Mndzhoyan, A.A. Aroyan and T.R. Ovsepyan, *Izvest. Akad. Nauk Armyan. S.S.R., Khim. Nauki* **13**, 275 (1960)
r) A.W. Hofmann, *Chem. Ber.*, **17**, 1410 (1884)
s) K. Klarmann, *J. Am. Chem. Soc.*, **48**, 2363 (1926)
t) B. Bottcher and F. Bauer, *Ann.*, **568**, 227 (1950)
u) W.J. Gensler and J.E. Stouffer, *J. Org. Chem.*, **23**, 910 (1958)



$>N-\overset{H}{\overset{|}{C}}=C<_{CN}$. This doublet was changed to singlet, when N–H was deuterated.). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2180 (strong, C≡N), 1630 (strong, C=C), UV $\lambda_{max}^{ethanol}$ mμ (ε): 265 (14600), benzoate mp 103—104° recrystallized from iso-PrOH. *Anal.* Calcd. for $C_{13}H_{12}ON_2$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.82; H, 5.59; N, 13.43.

Acknowledgement The authers are grateful to the members of the Central Analysis Room of this Faculty microanalyses and other physical measurements.