

Reaction of *sec*-Amides with Metal Hydride. II.¹⁾ Reaction of Acid Chlorides with Sodium Acetanilidoborohydride

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Sodium acetanilidoborohydride prepared from acetanilide and sodium borohydride in α -picoline reduced acid chlorides to alcohols in dichloromethane. On the other hand, this reducing reagent prepared in pyridine did not reduce acid chlorides but reduced the pyridine ring to give acylpiperidines.

We found previously¹⁾ that sodium acetanilidoborohydride, prepared from sodium borohydride and acetanilide, was soluble in dichloromethane and other common organic solvents and showed a good ability to reduce carboxylic acid esters in α -picoline and aldehydes or ketones in dichloromethane.

In an attempted synthesis of the aldehyde from benzoyl chloride by the use of sodium acetanilidoborohydride prepared in pyridine, neither benzaldehyde nor benzyl alcohol was obtained, but N-benzoylpiperidine was unexpectedly obtained. Piperidine moiety was clearly derived from the pyridine, because pyridine was used as a solvent for the synthesis of anilidoborohydride.

On the other hand, sodium acetanilidoborohydride prepared in α -picoline showed normal reducing ability on acid chlorides in dichloromethane to give alcohols. The present investigation was undertaken to clarify the difference between pyridine and α -picoline as a solvent, and to establish the reduction method of acid chlorides to alcohols in aprotic solvents.

Reduction of Acid Chlorides

Generally, acid chlorides are thought to be easily reducible as are aldehydes and ketones with sodium borohydride or other reducing agents. However, aromatic acid chlorides require heating for reduction with sodium borohydride³⁾ in dioxane or with ammonium borohydrides⁴⁾ in benzene. Diborane, an acid-type reducing agent, reduces acid chlorides slowly or negligibly in diglyme at room temperature.⁵⁾

We synthesized sodium acetanilidoborohydride with sodium borohydride and acetanilide in α -picoline as described in the preceding report.¹⁾ Results of reduction of acid chlorides using anilidoborohydride are presented in Table I.

Acid chlorides were reduced to the corresponding alcohols in moderate yields at room temperature in dichloromethane containing isopropanol. When acid chlorides were reduced in dichloromethane only, the anilides were obtained as by-products in addition to alcohols. Hydride and nitrogen atom of acetanilidoborohydride (or unreacted acetanilide) attacked the acid chloride competitively to give an alcohol and an imide (A) which was hydrolysed to give an anilide (B) with the liberation of acetyl group as depicted in Chart 1.

The addition of 1 ml of isopropanol to dichloromethane prevented the formation of the anilide (B)⁶⁾ although the yield of alcohols was not improved. When the solvent was changed

1) Part I: Y. Kikugawa, *Chem. Pharm. Bull.* (Tokyo), **24**, 1059 (1976).

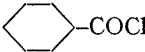
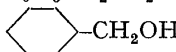

2) Location: 1-1 Keyakidai, Sakadomachi, Saitama. 350-02, Japan.

3) S.W. Chaikin and W.G. Brown, *J. Am. Chem. Soc.*, **71**, 122 (1949).

4) A.L. Tengzelins, *Fr. Patent*, **1**, 325, 439 [*c. A.*, **59**, 4820 (1963)].

5) H.C. Brown and B.C. Subba Rao, *J. Org. Chem.*, **22**, 1135 (1957).

TABLE I. Reaction of Acid Chlorides with Sodium Acetanilidoborohydride^{a)}
 in CH₂Cl₂ (25 ml) + Isopropanol (1 ml)

Compd. No.	Starting material	(mmol)	Compd. No.	Product	Yield ^{b)} (%)
I	C ₆ H ₅ COCl	2.1	VII	C ₆ H ₅ CH ₂ OH	70
I	C ₆ H ₅ COCl	3.0 ^{c)}	VII	C ₆ H ₅ CH ₂ OH	66
			VIII	C ₆ H ₅ CONHC ₆ H ₅	22
II	C ₆ H ₅ CH=CHCOCl	3.0	IX	C ₆ H ₅ CH=CHCH ₂ OH	58
			X	C ₆ H ₅ CH ₂ CH ₂ CH ₂ OH	trace
III		3.0 ^{c)}	XI		60
			XII		25
IV	CH ₃ (CH ₂) ₇ COCl	3.0	XIII	CH ₃ (CH ₂) ₇ CH ₂ OH	64
V	<i>o</i> -CH ₃ OC ₆ H ₄ COCl	3.0	XIV	<i>o</i> -CH ₃ OC ₆ H ₄ CH ₂ OH	65
VI	<i>p</i> -CH ₃ OC ₆ H ₄ COCl	3.0	XV	<i>p</i> -CH ₃ OC ₆ H ₄ CH ₂ OH	58 ^{d)}
VI	<i>p</i> -CH ₃ OC ₆ H ₄ COCl	3.0 ^{c)}	XV	<i>p</i> -CH ₃ OC ₆ H ₄ CH ₂ OH	57
			XVI	<i>p</i> -CH ₃ OC ₆ H ₄ CONHC ₆ H ₅	21

a) Anilidoborohydride was synthesized in α -picoline and the anilidoborohydride formed were estimated to be about 9.0 mmol from its NMR spectrum.

b) Yields were based on the starting material used.

c) CH₂Cl₂ alone was used as a solvent. Isopropanol was not added to the reaction mixture.

d) VI reacted with CH₃OH in CH₂Cl₂ to give methyl *p*-anisate (20%) as a by product. Reagent grade CH₂Cl₂ contains about 0.2% CH₃OH.

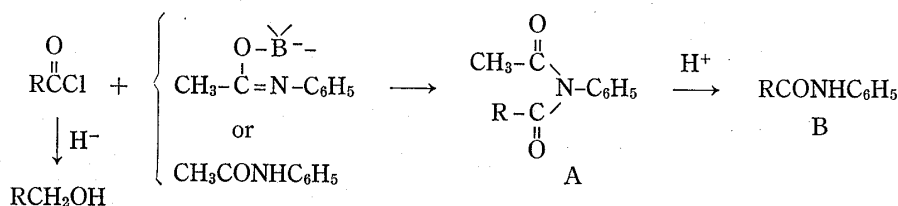


Chart 1

from dichloromethane to acetonitrile, almost the same results were obtained (the yield of alcohols was raised slightly). The present method provides a mild reduction of acid chlorides in aprotic solvents.

Formation of N-Acylpiperidine

Sodium acetanilidoborohydride synthesized in pyridine did not reduce acid chlorides, but unexpectedly reduced pyridine ring to form acylpiperidines as a final product. The yield of benzoylpiperidine (XVIII) was poor when benzoyl chloride was added to the dichloromethane solution containing anilidoborohydride. As the reduction of substituted pyridine ring with sodium borohydride proceeded smoothly by the addition of a proton source,⁷⁾ 1 ml of isopropanol was added to the reaction solvent before the addition of benzoyl chloride. The yield of XVIII was improved (20%→80%) as expected.

In the reaction of *para*-substituted acid chloride (VI), the corresponding piperidine (XXII) was obtained, while the *ortho*-substituted compound (V) was mainly converted to the alcohol (XIV), which indicated the presence of a considerable steric requirement in this reaction. In the case of IV, the alcohol (XIII) was obtained, which was compatible with the report⁸⁾ that an aliphatic acid chloride was more reducible than aromatic one with borohydrides.

In order to clarify the origin of piperidine moiety of the acylpiperidines, the preparation of sodium acetanilidoborohydride in pyridine was examined in detail. After about equimolar

6) A trace of isopropyl esters was detected from NMR spectra.

7) Y. Kikugawa, S. Ikegami, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 101 (1969).

8) S.W. Chaikin and W.G. Brown, *J. Am. Chem. Soc.*, **71**, 124 (1949).

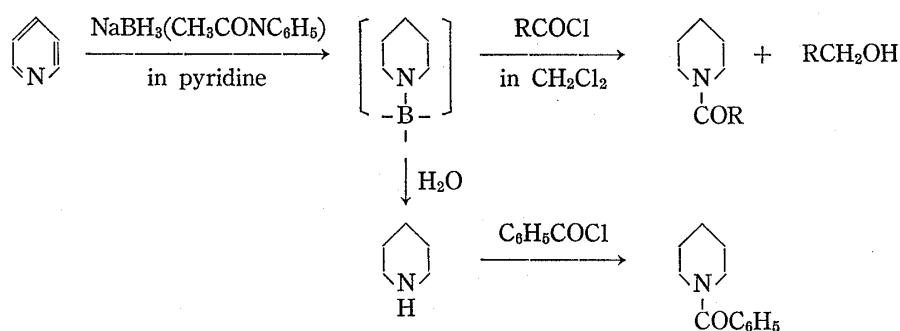


TABLE II. Reaction of Acid Chlorides with Sodium Acetanilidoborohydride^{a)} in CH_2Cl_2 (25 ml) + iso-PrOH (1 ml)

Compd. No.	Starting material	(mmol)	Compd. No.	Product	Yield ^{b)} (%)
I	$\text{C}_6\text{H}_5\text{COCl}$	1.5	XVIII	$\text{C}_6\text{H}_5\text{CON}(\text{CH}_2)_5$	80
II	$\text{C}_6\text{H}_5\text{CH}=\text{CHCOCl}$	2.2	XIX	$\text{C}_6\text{H}_5\text{CH}=\text{CHCON}(\text{CH}_2)_5$	56
			IX	$\text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2\text{OH}$	trace
IV	$\text{CH}_3(\text{CH}_2)_7\text{COCl}$	2.0	XX	$\text{CH}_3(\text{CH}_2)_7\text{CON}(\text{CH}_2)_5$	<i>ca</i> 55 ^{c)}
			XIII	$\text{CH}_3(\text{CH}_2)_7\text{CH}_2\text{OH}$	
V	<i>o</i> - $\text{CH}_3\text{OC}_6\text{H}_4\text{COCl}$	2.0	XXI	<i>o</i> - $\text{CH}_3\text{OC}_6\text{H}_4\text{CON}(\text{CH}_2)_5$	<i>ca</i> 75 ^{d)}
			XIV	<i>o</i> - $\text{CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{OH}$	
VI	<i>p</i> - $\text{CH}_3\text{OC}_6\text{H}_4\text{COCl}$	2.0	XXII	<i>p</i> - $\text{CH}_3\text{OC}_6\text{H}_4\text{CON}(\text{CH}_2)_5$	67
			XV	<i>p</i> - $\text{CH}_3\text{OC}_6\text{H}_4\text{CH}_2\text{OH}$	trace
XVII	<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$	2.6	XXIII	<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{N}(\text{CH}_2)_5$	86

a) Anilidoborohydride was synthesized in pyridine and the anilidoborohydride formed was estimated to be about 7.5 mmol from its NMR spectrum.

b) Yields were based on the starting material used.

c) Approximate ratio (XX:XIII=75:25) was calculated from the gas chromatographic analysis.

d) NMR spectrum of the products showed the preferential formation of the alcohol (XIV) (XXI:XIV=33:67).

hydrogen to acetanilide was evolved, color of the pyridine solution changed from colorless to orange during additional 0.5–1 hr of heating. After the removal of pyridine, dichloromethane was added to the residue. Insoluble materials were filtered and the dichloromethane was evaporated. The nuclear magnetic resonance (NMR) spectrum of the residue (crude sodium acetanilidoborohydride) showed new peaks⁹⁾ due to the methylene absorptions of piperidine moiety at δ 1.4–1.6 (broad) and 2.5–3.4 (broad).¹⁰⁾

Evidently, this piperidine, whose nitrogen atom should be fixed with the boron atom and not to be evaporated under a reduced pressure, reacted with acid chlorides to give acylpiperidines, although the reason why pyridine was reduced to piperidine but not α -picoline has not been solved as yet.¹¹⁾ The free piperidine liberated from the residue by the addition of water was trapped as benzoylpiperidine by the Schotten-Baumann reaction. It is of particular interest that unsubstituted pyridine was reduced with anilidoborohydride, while

9) Post-treatment of the reaction mixture before the change of color resulted in the absence of methylene absorptions in the NMR spectrum. In this case acylpiperidines were not obtained.

10) The NMR spectrum of authentic piperidine shows the absorptions of the methylene group adjacent to ring nitrogen, and of other methylene groups at δ 2.5–3.0 (4H, m) and 1.3–1.7 (6H, m).

11) Anilidoborohydride prepared in pyridine was only effective to reduce pyridine and an equimolar pyridine mixed with α -picoline solvent was found not to react with anilidoborohydride. In the case of α -picoline, anilidoborohydride could not reduce α -picoline even when heating was prolonged for several hours. Therefore, anilidoborohydride prepared in α -picoline becomes a good reagent for the reduction of various functional groups.

pyridine has never been reduced with other borohydride derivatives.¹²⁾ Further studies on the reduction of heteroaromatic rings with anilidoborohydrides are now in progress.

Experimental

All melting points are uncorrected. The following instruments were used for obtaining the physical data. Infrared (IR) spectra, Shimadzu IR-400; NMR spectra (tetramethylsilane as an internal standard), Hitachi R-20; gas chromatography, Shimadzu GC-4BM. Column chromatography was carried out on silica gel (Merck, Art. 7734) using benzene: acetone (6: 1) for elution.

Materials—NaBH₄ and reagent grade pyridine, α -picoline, CH₂Cl₂ and CH₃CN were purchased from Wako Chemical Industries Ltd., Tokyo. The starting materials I, II, and XVII, and the authentic alcohols VII, IX—XI, and XIII—XV, were purchased from Tokyo Kasei Kogyo Co. The starting materials III (bp 46—47°/6 Torr), IV (bp 72—74°/5 Torr), V (bp 116—117°/5 Torr), and VI (bp 109—110°/3.5 Torr) were synthesized from the corresponding acids with SOCl₂ and purified by distillation. All the authentic acylpiperidines were synthesized from the corresponding acid chlorides with piperidine and gave satisfactory spectral data. XVIII (bp 154°/8 Torr, reported¹³⁾ bp 170—171°/14 Torr), XIX (mp 121—122°, from EtOH, reported¹⁴⁾ mp 122°), XX (bp 134—135°/4 Torr, reported¹⁵⁾ bp 184—187°/13 Torr), XXI (bp 165°/5 Torr),¹⁶⁾ XXII (bp 163—164°/3 Torr, reported¹⁴⁾ bp 210°/16 Torr), XXIII (mp 96—97°, from EtOH, reported¹⁷⁾ mp 98—99°). The anilides, acetanilide and VIII, were purchased from Tokyo Kasei Kogyo Co., and XII (mp 148°, from benzene, reported¹⁸⁾ mp 145°) and XVI (mp 172—173°, from benzene-acetone, reported¹⁹⁾ mp 168°) were synthesized from the acid chlorides with aniline.

General Procedure for Reduction of Acid Chlorides—A mixture of NaBH₄ (15 mmol, 570 mg) and acetanilide (10 mmol, 1.35 g) in α -picoline (10 ml) was maintained at 100° for about 90 min. After about 0.01 mol H₂ had evolved, α -picoline was distilled off *in vacuo* (70°/30 Torr). To the residue was added CH₂Cl₂ (25—30 ml) and insoluble materials that appeared were removed by filtration. The starting acid chloride (3.0 mmol, see Table I) was added with stirring after the addition of iso-PrOH (1 ml). After 30-min stirring, CH₂Cl₂ was evaporated *in vacuo*. To the residue was added 10% HCl with cooling, the aq. layer was extracted with CHCl₃, and the combined CHCl₃ was dried over anhyd. Na₂SO₄. After evaporation of CHCl₃, the solidified residue was washed with cold benzene. Acetanilide was collected by filtration and the filtrate was distilled off *in vacuo*. The residual oil was purified by column chromatography. Identity of alcohols was established by the comparison of spectral data and/or the retention time of the authentic samples in gas chromatographic analysis.²⁰⁾

General Procedure for Formation of Acylpiperidines—The same procedure was carried out except for the replacement of α -picoline with pyridine. Mixed melting point measurement was used for the identification of XIX and XXIII.

Detection of Piperidine as N-Benzoylpiperidine—A mixture of acetanilide (10 mmol, 1.35 g) and NaBH₄ (15 mmol, 570 mg) in pyridine (10 ml) was heated at 100—110° for 190 min. After the color of the solution was changed from colorless to orange, the solvent was evaporated *in vacuo*. To the residue was added CH₂Cl₂ (20 ml) and insoluble materials that appeared were removed by filtration. To the filtrate was added 1 ml of iso-PrOH, the solution was stirred for 30 min²¹⁾, and 10% HCl (25 ml) was added to the solution with cooling. CH₂Cl₂ layer was separated, washed with H₂O (10 ml), and the combined aq. layer was made alkaline (pH 13) with KOH (8 g) under cooling. Then BzCl (5 mmol, 700 mg) in ether (20 ml) was added to the solution under

- 12) Pyridine having an electron-withdrawing group at the meta position was reported to be reduced to a dihydropyridine derivative [Y. Kikugawa, M. Kuramoto, I. Saito, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 1914 (1973)].
- 13) Y. Kikugawa, S. Ikegami, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 103 (1969).
- 14) D. Vorlander and P. Herrmann, *Liebigs Ann. Chem.*, **320**, 91 (1902).
- 15) M. Asano and T. Kanematsu, *Yakugaku Zasshi*, **46**, 375 (1926).
- 16) XXI has not been listed in literature to our knowledge. Spectral data of XXI are as follows: IR ν_{\max}^{Carb} cm⁻¹: 2925 (CH₂), 1630—1610 (C=O); NMR (CDCl₃) δ : 1.5—1.7 (6H, br., (CH₂)₃), 3.05—3.22 (2H, m, CH₂), 3.65—3.75 (2H, m, CH₂), 3.78 (3H, s, OCH₃), 6.78—7.30 (4H, m, aromatic).
- 17) H. Staudinger and H. Schneider, *Ber.*, **56**, 704 (1923).
- 18) M. Regitz and J. Rüter, *Chem. Ber.*, **101**, 1269 (1968).
- 19) R. Jaunin and G. Séchaud, *Helv. Chim. Acta.*, **39**, 1261 (1956).
- 20) Temperature of the glass column (1.5 m \times 3 mm, i. d.), packed with 10% SE-30 on Chromosorb W (60—80 mesh) and injection chamber were kept at 130° and 150° (for alcohols) or 200° (for acylpiperidines) and 220°, respectively. N₂ was used as a carrier gas at the flow rate of 70 ml/min. Mixed melting point measurement was used for the identification of VIII, XII, and XVI.
- 21) Sometimes the presence of a small amount of dihydropyridine was detected by NMR spectra [P.T. Lansbury and J.O. Peterson, *J. Am. Chem. Soc.*, **85**, 2236 (1963)]. Complete reduction of dihydropyridine to piperidine was carried out.

vigorous stirring. After 1.5-hr stirring, the aq. layer was extracted with ether (25 ml) which was washed with sat. NaCl and dried over anhyd. Na₂SO₄. After evaporation of ether, the residual oil was purified by column chromatography (SiO₂, hexane: AcOEt=7:3 for elution) to give benzoylpiperidine (440 mg, 23% from acetanilide) which was identified by comparison of spectral data with the authentic sample and by gas chromatographic analysis.

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Hydrolysis of Bis(*p*-hydroxyphenyl)pyridyl-2-methane Disulfate. I. Presence of Arylsulfatase and Laxative Activity

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The laxative action of bis (*p*-hydroxyphenyl)pyridyl-2-methane disulfate is considered to be dependent on the formation of the free phenolic compound, bis(*p*-hydroxyphenyl)pyridyl-2-methane by hydrolysis. Therefore, the activity of the parent compound as a laxative must be governed by arylsulfatase activity in the human intestine. When examinations of human feces were made, arylsulfatase activity in the intestine was detected, and about 98% of the samples were shown to be positive.

Validity of the fecal arylsulfatase test in the test population might be supported by the liquefaction test of rat feces with the injection of the parent compound into duodenum.

It is well known that many naturally occurring and synthetic phenolic compounds are used in medicinals for their laxative properties. In addition, it has been hypothesized that the free phenolic group is essential for the laxative action.²⁻⁵⁾ Pala, *et al.*⁶⁾ described bis(*p*-hydroxyphenyl)pyridyl-2-methane disulfate (I) as a new laxative but asserted that no phenolic groups were released when it was administered to rats. The study did not mention arylsulfatases which have been detected in intestines, microorganisms of intestinal flora and other tissues.

According to Ferlemann, *et al.*,⁵⁾ bisacodyl (III) (Fig. 1), whose structure is similar to that of I, is decomposed by either fecal homogenates or freshly collected fluid from the small intestine of the rat. It was found that the hydrolytic activity of the homogenates and fluids could be abolished by heating.

In contrast to the manner in which bisacodyl is hydrolyzed, the hydrolysis of the disulfate compound (I) can be attributed to microorganisms of the intestinal flora.⁷⁾ Scheline⁸⁾ described

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8) R.R. Scheline, *J. Pharm. Sci.*, **57**, 2021 (1968).