Notes

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Reduction of Heterocyclic Compounds. II.[1] Reduction of Heterocyclic Compounds with Sodium Borohydride–Transition Metal Salt Systems

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The reduction of heterocyclic compounds with the sodium borohydride–transition metal salt system was investigated. Among transition metal salts examined in this system, the sodium borohydride–nickelous chloride system was found to exhibit the strongest reducing activity. Quinoline, isoquinoline, quinoxaline and their derivatives were reduced with this system to give the corresponding tetrahydro derivatives.

Keywords——reduction; sodium borohydride–nickelous chloride system; sodium borohydride; transition metal salt; 1,2,3,4-tetrahydroquinoline; 1,2,3,4-tetrahydroisoquinoline; 1,2,3,4-tetrahydroquinoxaline

Sodium borohydride ($NaBH_4$) is a relatively mild reducing agent which is practically specific for the carbonyl group in aldehydes and ketones. However, some interesting studies have been made on the reduction of heterocyclic compounds with $NaBH_4$. For example, Yamada *et al.* reported that the heterocyclic ring of 3-substituted (with an electron-withdrawing substituent) pyridines, quinolines and 4-substituted isoquinolines could be reduced by $NaBH_4$ to provide the corresponding dihydro and tetrahydro derivatives in a polar solvent.[2a–e] Gribble *et al.*[3] and Rao *et al.*[4] achieved the reduction of heterocyclic compounds by treatment with $NaBH_4$ in the presence of a carboxylic acid. Interestingly, McQuillin *et al.* reported the reduction of heterocyclic compounds with 1,2,6-trispyridine-rhodium trichloride–$NaBH_4$.[5]

In the previous paper, we reported that quinoline, isoquinoline and quinoxaline derivatives were reduced to the corresponding 1,2,3,4-tetrahydro derivatives by treatment with diborane. However, alkyl-substituted quinoline and isoquinoline homologs were not reduced by diborane in satisfactory yields. In the past decade, $NaBH_4$–transition metal salt systems have revolutionized the reduction of functional groups,[6a–i] so we next investigated the applicability of such systems. In the present paper, we wish to report the reduction of heterocyclic compounds with $NaBH_4$–transition metal salt systems. Firstly, in order to compare the reducing ability of various transition metal salts, we examined the reduction of quinaldine (**1**) with $NaBH_4$–transition metal salt systems, such as $NaBH_4$–cobaltous chloride ($CoCl_2$), $NaBH_4$–nickelous chloride ($NiCl_2$), $NaBH_4$–cupric chloride ($CuCl_2$) and $NaBH_4$–chromic chloride ($CrCl_3$). Thus, $NaBH_4$ (4 mol eq) was added to a solution of **1** and a transition metal salt in methanol at room temperature, followed by purification to give the reaction product. Ultraviolet (UV) spectra of the reaction products obtained with $NaBH_4$–$CoCl_2$ and $NaBH_4$–$NiCl_2$ exhibited characteristic bands at 248 and 300 nm due to 1,2,3,4-tetrahydroquinaldine (**2**), and the characteristic bands of **1** were absent. On the other hand, characteristic bands of **2** were not prominent after the reactions using $CuCl_2$ and $CrCl_3$ as shown in Fig. 1.

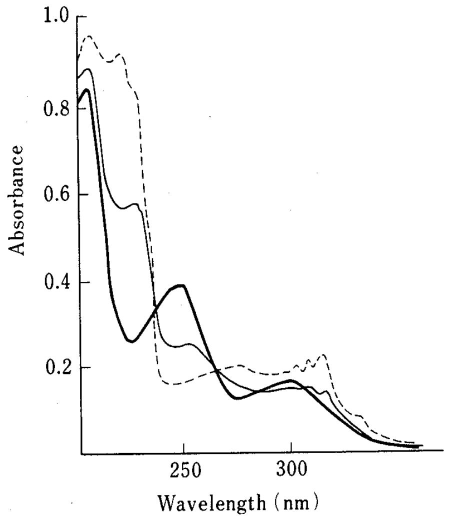


Fig. 1. UV Spectra of Quinaldine (**1**) in Various $NaBH_4$–Transition Metal Salt Systems

------, $NaBH_4:CrCl_3:\mathbf{1}=4:1:1$ (mol).
——, $NaBH_4:CuCl_2:\mathbf{1}=4:1:1$ (mol).
——, $NaBH_4:CoCl_2:\mathbf{1}=4:1:1$ (mol); $NaBH_4:NiCl_2:\mathbf{1}=4:1:1$ (mol).

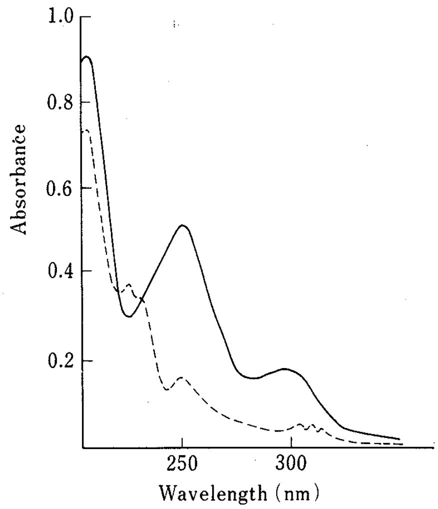


Fig. 2. UV Spectra of Quinaldine (**1**) in the $NaBH_4$–$NiCl_2$ and $NaBH_4$–$CoCl_2$ Systems

——, $NaBH_4:NiCl_2:\mathbf{1}=4:0.5:1$ (mol).
------, $NaBH_4:CoCl_2:\mathbf{1}=4:0.5:1$ (mol).

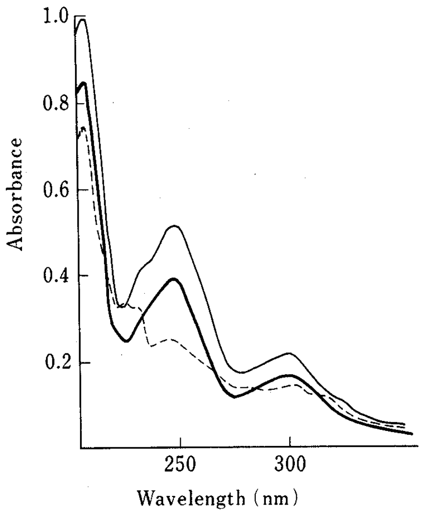


Fig. 3. UV Spectra of Quinaldine (**1**) in the $NaBH_4$–$NiCl_2$ System

------, $NaBH_4:NiCl_2:\mathbf{1}=2:1:1$ (mol).
——, $NaBH_4:NiCl_2:\mathbf{1}=3:1:1$ (mol).
——, $NaBH_4:NiCl_2:\mathbf{1}=4:1:1$ (mol).

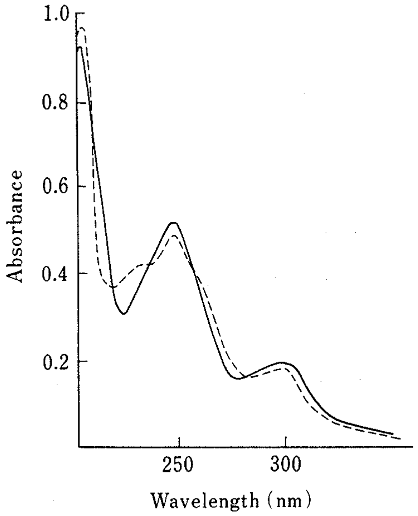


Fig. 4. UV Spectra of Quinaldine (**1**) in the $NaBH_4$–$NiCl_2$ System

——, $NaBH_4:NiCl_2:\mathbf{1}=4:0.17:1$ (mol); $NaBH_4:NiCl_2:\mathbf{1}=4:1:1$ (mol).
------, $NaBH_4:NiCl_2:\mathbf{1}=4:0.12:1$ (mol).

Furthermore, in order to compare the reducing activities of $NaBH_4$–transition metal salt systems ($CoCl_2$ and $NiCl_2$), similar reactions with 0.5 mol eq of these transition metal salts were examined. The reduction using $NiCl_2$ proceeded completely to give **2**, in contrast to the reaction using $CoCl_2$ as shown in Fig. 2. Accordingly, it can be assumed that $NiCl_2$ possesses the strongest activity among the transition metal salts tested for reduction in $NaBH_4$–transition metal salt systems.

As shown in Figs. 3 and 4, some starting material remained when less than 3 mol eq of $NaBH_4$ was used with respect to both $NiCl_2$ and the substrate, while the reaction using 4 mol eq of $NaBH_4$ proceeded completely. When 4 mol eq of $NaBH_4$ with respect to **1** was used, the

Table I. Reduction of Quinoline Derivatives with the $NaBH_4$–$NiCl_2$ System

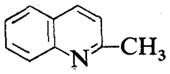
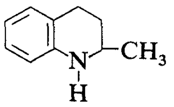
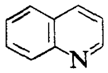
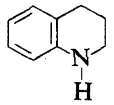
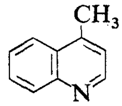
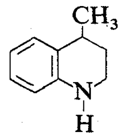
Compound	(No.)	mmol	$NaBH_4$ (mmol)	$NiCl_2$ (mmol)	Solvent	Temperature	Product	(No.)	Yield (%)
	(**1**)	8	32	1.4	MeOH	Room temp.		(**2**)	93.5
	(**3**)	8	32	4	MeOH	Room temp.		(**5**)	82.8
	(**4**)	8	80	8	MeOH	Room temp.		(**6**)	83.0

Table II. Reduction of Isoquinoline Derivatives with the $NaBH_4$–$NiCl_2$ System

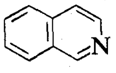
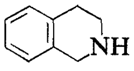
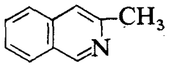
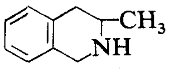
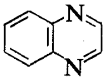
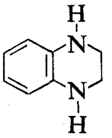
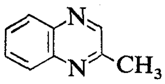
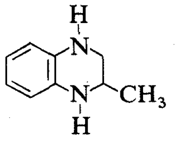
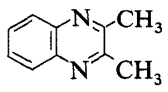
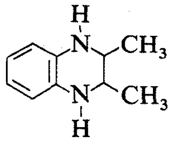
Compound	(No.)	mmol	$NaBH_4$ (mmol)	$NiCl_2$ (mmol)	Solvent	Temperature	Product	(No.)	Yield (%)
	(**7**)	8	96	8	MeOH	Room temp.		(**9**)	86.7
	(**8**)	8	96	8	MeOH	Room temp.		(**10**)	96.1

Table III. Reduction of Quinoxaline Derivatives with the $NaBH_4$–$NiCl_2$ System

Compound	(No.)	mmol	$NaBH_4$ (mmol)	$NiCl_2$ (mmol)	Solvent	Temperature	Product	(No.)	Yield (%)
	(**11**)	8	160	16	MeOH	Room temp.		(**14**)	54.2
	(**12**)	8	160	16	MeOH	Room temp.		(**15**)	52.4
	(**13**)	8	64	8	MeOH	Room temp.		(**16**)	99.2

reduction proceeded completely in the presence of more than 0.17 mol eq of $NiCl_2$.

Furthermore, similar reactions of quinoline (**3**) and lepidine (**4**) gave 1,2,3,4-tetrahydroquinoline (**5**) and 1,2,3,4-tetrahydrolepidine (**6**), respectively, in good yields. However, the reduction of **3** proceeded with larger amounts of $NiCl_2$ in comparison with that of **1**, and the yield of **6** increased with increase of both $NaBH_4$ and $NiCl_2$.

Similar reactions of isoquinoline (**7**) and 3-methylisoquinoline (**8**) yielded 1,2,3,4-tetrahydroisoquinoline (**9**) and 3-methyl-1,2,3,4-tetrahydroisoquinoline (**10**) in quantitative yield. In these reactions, the yield of tetrahydro derivatives increased with increasing amount of $NaBH_4$.

Quinoxaline derivatives, such as quinoxaline (**11**), 2-methylquinoxaline (**12**) and 2,3-dimethylquinoxaline (**13**), gave 1,2,3,4-tetrahydroquinoxaline (**14**), 2-methyl-1,2,3,4-tetrahydroquinoxaline (**15**) and 2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (**16**), respectively, under similar conditions (Table III). The heterocyclic ring of quinoxaline is more easily reducible with $LiAlH_4$ or diborane to give tetrahydro derivatives. In spite of a detailed investigation, the yield could not be improved in the reduction of **11** and **12**, though some improvement was obtained with **13**. It is assumed that these reactions were accompanied with some side reactions since resinification tended to occur and the starting materials were not recovered.

In the reduction with $NaBH_4$–$NiCl_2$, it is assumed that heterocyclic compounds first formed complexes with $NiCl_2$ and these complexes were reduced by $NaBH_4$. In order to confirm this, further studies were carried out. The reduction of quinaldine **1** proceeded under all of the following conditions to give **2**: a) addition of $NiCl_2$ to a methanol solution of **1** and $NaBH_4$, b) addition of $NaBH_4$ to a methanol solution of **1** and $NiCl_2$, c) addition of $NaBH_4$ and $NiCl_2$ alternately to a methanol solution of **1**. In contrast to these results, reduction did not occur when **1** was added after $NaBH_4$ to a methanol solution of $NiCl_2$, and the starting material was recovered. $NaBH_4$ reacted vigorously with $NiCl_2$ with the evolution of hydrogen gas to give a black precipitate of Ni_2B, but the reaction of **1** with 0.5 mol eq of Ni_2B and 4 mol eq of $NaBH_4$ yielded the starting material, and the catalytic reduction with Ni_2B–H_2 did not proceed. Similar reaction with 0.5 mol eq of Ni_2B and 20 mol eq of $NaBH_4$ gave the tetrahydro derivative **2** in poor yield (31.6%). These results suggest that the reduction of heterocyclic compounds with the $NaBH_4$–$NiCl_2$ system proceeds *via* the complexes of the heterocyclic compounds and $NiCl_2$, and these complexes were reduced by $NaBH_4$.

Experimental

Commercially available $NiCl_26H_2O$, $CoCl_26H_2O$, $CrCl_36H_2O$, $CuCl_22H_2O$ and $NaBH_4$ were used throughout this work. Melting points were determined on a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. Infrared (IR) spectra were measured in Nujol mulls or as liquid films with a Nihon Bunko IRA-1 infrared spectrometer, and UV spectra were recorded on a JASCO Uvidec-505 UV spectrometer. Chromatography columns of alumina were prepared with "aluminiumoxid 90" (70—230 mesh ASTM; Merck).

The procedure for the reduction of **1** with the $NaBH_4$–$NiCl_2$ system will be described in detail as a typical example. The other heterocyclic compounds **3**, **4**, **7** and **8** were reduced similarly, and the reaction conditions are listed in Tables I and II. All spectral data of products were identical with those of the corresponding authentic samples.

Reduction of 1——Compound **1** (1.145 g, 8 mmol) and $NiCl_26H_2O$ (0.333 g, 1.4 mmol) were dissolved in 99% methanol (30 ml) and $NaBH_4$ (1.21 g, 32 mmol) was added in portions with stirring under cooling for 30 min, then the stirring was continued for 30 min at room temperature (20 °C). After the removal of methanol by distillation, the black precipitate was dissolved in 10% hydrochloric acid, the acidic solution was basified by the addition of conc. ammonium hydroxide and extracted with ether. The extract was dried over magnesium sulfate. The ether was evaporated off, and the residue was distilled under reduced pressure to give 1.101 g (93.5%) of 1,2,3,4-tetrahydroquinaldine **2**, bp 105—106 °C (9 mmHg) (lit.[7] bp 115—116 °C (12 mmHg)), picrate (from ethanol) mp 149.5—150 °C (lit.[7] mp 150 °C). This product was identical with an authentic sample on the basis of mixed mp determination and comparison of IR and UV spectra.

The following products were similarly obtained. 1,2,3,4-Tetrahydroquinoline **5** (0.881 g, 82.8%), bp 108—109 °C (7 mmHg) (lit.[8] bp 251 °C). Picrate mp 141—141.5 °C (lit.[8] mp 141.5 °C). 1,2,3,4-Tetrahydrolepidine **6** (0.976 g, 83.0%), bp 115—116 °C (7 mmHg) (lit.[7] bp 130 °C (12 mmHg)), 1-benzoyl-1,2,3,4-tetrahydrolepidine (from ethanol) mp 128—129 °C (lit.[7] mp 129 °C). 1,2,3,4-Tetrahydroisoquinoline **9** (0.922 g, 86.7%), bp 232—233 °C (lit.[9] bp 234—236 °C). Picrate (from ethanol) mp 196—197 °C (lit.[10] mp 197—198 °C). 3-Methyl-1,2,3,4-tetrahydroisoquinoline **10** (1.13 g, 96.1%), bp 105—107 °C (7 mmHg) (lit.[11] bp 236—237 °C (751 mmHg)). MS *m/e*: 147 (M^+), 146, 132, 130, 105, 104 (base peak), 103, 78, 77.

Reduction of 11——Compound **11** (1.041 g, 8 mmol) and $NiCl_26H_2O$ (3.803 g, 16 mmol) were dissolved in 99%

methanol (40 ml) and $NaBH_4$ (6.06 g, 160 mmol) was added in portions with stirring under cooling for 30 min, then the stirring was continued for 30 min at room temperature. After treatment as described above, the residue was chromatographed over alumina (column) using benzene. The eluate was recrystallized from ether to give 1,2,3,4-tetrahydroquinoxaline **14** (0.582 g, 58.2%) as colorless leaflets, mp 97 °C (lit.[12] mp 98.5—99 °C). This product was identical with an authentic sample on the basis of mixed mp determination and the comparison of IR and UV spectra.

Reduction of 12——The method used here was virtually identical with that described for **11**, but the latter was replaced with 1.153 g (8 mmol) of **12**. The residue was chromatographed over alumina using benzene. The eluate was recrystallized from ether to give 2-methyl-1,2,3,4-tetrahydroquinoxaline **15** (0.621 g, 52.4%) as colorless leaflets, mp 72 °C (lit.[13] mp 72 °C). This product was identical with an authentic sample on the basis of mixed mp determination and the comparison of IR and UV spectra.

Reduction of 13——Compound **13** (1.265 g, 8 mmol), $NiCl_2 6H_2O$ (1.902 g, 8 mmol) and $NaBH_4$ (2.42 g, 64 mmol) were reacted as described above. After work-up as described above, the product was recrystallized from ether to give *cis*-2,3-dimethyl-1,2,3,4-tetrahydroquinoxaline **16** (1.287 g, 99.2%) as colorless leaflets, mp 111—114 °C (lit.[14] mp 113—114 °C). This was identical with an authentic sample on the basis of mixed mp determination and the comparison of IR and UV ($\lambda_{\max}^{\text{methanol}}$ nm: 256, 312) spectra.

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References and Notes

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