Ring Opening Reaction of *N*-Substituted Dihydropyrimidines with Metal Hydride Complexes

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N-Substituted dihydropyrimidines, **1**, **3**, and **4**, easily afforded *N,N'*-disubstituted 2,4-diaminopentanes **2** in good yield by the ring opening reaction with sodium borohydride. The reaction with lithium aluminum hydride was also examined.

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In the previous paper [1], we reported the independent synthesis of *N*-substituted 1,2-, 1,4-, and 1,6-dihydropyrimidines by desulfurization of pyrimidine-2(1*H*)-thiones and corresponding dihydro derivatives. Dihydropyrimidines are expected to have reaction sites for various reagents. However, in the reaction of *N*-substituted dihydropyrimidines, it has only been reported [2] that 1,6-dihydro-1-methyl-4,6-diphenylpyrimidine was treated with methyllithium to give 1,2,5,6-tetrahydro-1,2-dimethyl-4,6-diphenylpyrimidine *via* enamine-imine isomerization of 1,2,3,6-tetrahydro derivatives.

It was reported that dihydropyridines reacted with sodium borohydride to afford tetrahydro- and/or hexahydropyridines [3]. Meanwhile, vinylogous amidines and their salts reacted with sodium borohydride to give 1,3-diaminopropanes [4]. Since *N*-substituted dihydropyrimidines could be regarded as either aza analogs of dihydropyridines or vinylogous cyclic amidines, the reaction with sodium borohydride was investigated.

When 1,4-dihydro-4,6-dimethyl-1-phenylpyrimidine (**1a**) was treated with a large excess of sodium borohydride in ethanol at room temperature for 24 hours, an oily colorless product (bp 114°/5 mm Hg) was obtained. In the ir spectrum, the absorption band of N-H stretching at 3300 cm^{-1} was observed, and the absorption band at 1680 cm^{-1} due to C=C-N-C=N moiety in the starting material **1a** disappeared. The nmr spectrum showed signals at δ 1.02 (d, 3H, J = 6.0 Hz, CH_3), 1.13 (d, 3H, J = 6.0 Hz, CH_3), and 2.33 ppm (s, 3H, CH_3), and peaks characteristic to aniline protons at δ 6.5-6.8 (m, 3H) and 7.2-7.4 ppm (m, 2H). From these data, the product was determined to be 4-anilino-2-methyl-2-methylaminopentane (**2a**). The structure was also confirmed by comparison with authentic spectral data which were obtained by the treatment of hexahydro-4,6-dimethyl-2-oxo-1-phenylpyrimidine with lithium aluminum hydride [5]. The reductive ring opening reactions of similar *N*-substituted dihydropyrimidines with sodium borohydride were examined, and the results are listed in Table

Table 1

Compound No.	Product No.	Yield %	Bp °C/10^{-4} mm Hg	Formula	Analysis, % Calcd. (Found) C	H	N
1a	**2a**	61	[a]				
1b	**2b**	75	[b]				
1c	**2c**	51	63	$C_{14}H_{24}N_2$	76.30 (76.03)	10.97 (11.05)	12.71 (12.59)
1d	**2d**	30	76	$C_{14}H_{24}N_2O$	71.14 (70.91)	10.23 (10.20)	11.85 (11.65)
1e	**5e**	70	39	$C_{14}H_{22}N_2 \cdot 0.1H_2O$	76.36 (76.58)	10.10 (10.18)	12.73 (12.72)
6a	**7a**	52	34	$C_{14}H_{24}N_2$	76.30 (76.06)	10.97 (11.06)	12.71 (12.67)
	8a	31	34	$C_{14}H_{22}N_2$	77.01 (76.73)	10.15 (10.21)	12.83 (12.79)
6b	**7b**	66	37	$C_{15}H_{26}N_2$	76.89 (77.00)	11.18 (11.29)	11.95 (11.99)
6c	**7c**	41	43	$C_{15}H_{26}N_2O$	71.95 (71.85)	10.46 (10.47)	11.18 (11.27)
	8c	47	53	$C_{15}H_{24}N_2O$	72.53 (72.47)	9.74 (9.81)	11.27 (11.18)

[a] 114°/5 mm Hg (lit 58°/10^{-4} mm Hg [5]). [b] 120°/5 mm Hg (lit 63°/10^{-4} mm Hg [5]).

1. In the same manner, 1,2- (**3**) and 1,6-dihydro-4,6-dimethyl-1-phenylpyrimidines (**4**) gave the same ring opened product, diamine **2a**, in 68 and 66% yield, respectively. However, in the case of the compound **1e**, 1-benzyl-hexahydro-4,4,6-trimethylpyrimidine (**5e**) was obtained in 70% yield instead of the ring opened product.

Compound **1a** (1 mmole) was treated with sodium borohydride (3 mmoles) in ethanol at room temperature for 24 hours to give a compound (mp 57-58°) which showed a formula of $C_{13}H_{20}N_2$ along with **2a** (yield 31%). The ir spectrum showed a band at 3260 cm^{-1} due to N-H stretching, but no absorption band in 1600-1700 cm^{-1} region. The ^{1}H-nmr spectrum showed a new peak at δ 3.86 ppm (s, 2H), due to methylene protons at C-2 position. However, the characteristic N-CH_3 signal of diamine **2a** at δ 2.27 ppm was not observed. From these data, the product was determined to be cyclic diamine, hexahydro-4,4,6-trimethyl-1-phenylpyrimidine (**5b**). Furthermore, **5b** gave ring opened diamine **2a** in 51% yield by the further reaction with a large excess of sodium borohydride. From this fact, **5b** was found to be the intermediate of reductive ring opening reaction.

The possible reaction mechanism for the reduction with sodium borohydride is speculated as follows. First, sodium borohydride reduced the two double bonds of dihydropyrimidines to give hexahydropyrimidines. It is known that hexahydropyrimidines frequently exist in an equilibrium [6] with an open-chain system with the position of the equilibirium being dependent on various factors such as the degree of substituent on the ring or solvent polarity [7]. Furthermore, the excess sodium borohydride should cause the reductive ring cleavage of hexahydropyrimidine. In the case of *N*-substituted hexahydropyrimidine **5b**, the anion which was generated from the cleavage between N-1 nitrogen and C-2 carbon is more stable than that of the cleavage between N-3 nitrogen and C-2 carbon. As the net reaction, 4-anilino-2-methyl-2-methylaminopentane (**2b**) was only product (Scheme 1).

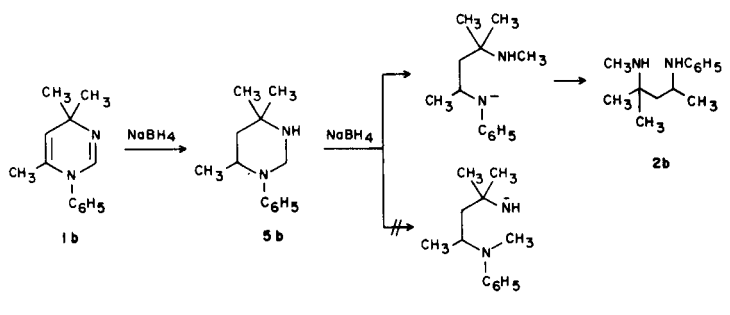
Table 2

IR and NMR Spectral Data of Diamines

Compound No.	IR Spectra [a] (cm^{-1})	NMR Chemical Shift [b] (ppm)
2c	3240, 1615	1.07 (s, 6H), 1.15 (d, 3H, J = 6.0 Hz), 1.4-1.7 (m, 2H), 2.23 (s, 3H), 2.30 (s, 3H), 3.2-3.7 (m, 1H), 6.5-7.1 (m, 4H)
2d	3240, 1615	1.07 (s, 6H), 1.14 (d, 3H, J = 6.0 Hz), 1.4-1.6 (m, 2H), 2.30 (s, 3H), 3.2-3.7 (m, 1H), 3.72 (s, 3H), 6.4-6.9 (m, 4H)
5e	3300	1.05 (s, 6H), 1.10 (d, 3H, J = 6.0 Hz), 1.3-1.5 (m, 2H), 2.4-2.8 (m, 1H), 3.08 (d, 1H, J = 14.0 Hz), 3.15 (d, 1H, J = 12.0 Hz), 3.51 (d, 1H, J = 12.0 Hz), 4.02 (d, 1H, J = 14.0 Hz), 6.9-7.5 (m, 5H)
7a	3240, 1600	0.93 (s, 3H), 1.03 (s, 3H), 1.11 (d, 3H, J = 6.0 Hz), 1.3-1.7 (m, 2H), 2.23 (s, 6H), 3.3-3.8 (m, 1H), 6.5-6.8 (m, 3H), 7.0-7.4 (m, 2H)
7b	3230, 1600	0.93 (s, 3H), 1.07 (s, 3H), 1.13 (t, 3H, J = 7.0 Hz), 1.18 (d, 3H, J = 6.0 Hz), 1.3-1.8 (m, 2H), 2.21 (s, 2H), 2.44 (q, 2H, J = 7.0 Hz), 3.2-3.7 (m, 1H), 6.5-6.8 (m, 3H), 7.0-7.3 (m, 2H)
7c	3230, 1620	0.93 (s, 3H), 1.05 (s, 3H), 1.17 (d, 3H, J = 6.0 Hz), 1.3-1.8 (m, 2H), 2.23 (s, 6H), 3.1-3.8 (m, 1H), 3.71 (s, 3H), 6.5-6.9 (m, 4H)
8a	1600	0.86 (d, 3H, J = 6.0 Hz), 1.07 (s, 3H), 1.17 (s, 3H), 1.5-1.7 (m, 2H), 2.28 (s, 3H), 3.1-3.5 (m, 1H), 3.67 (s, 2H), 7.1-7.4 (m, 5H)
8c	1600	0.89 (d, 3H, J = 6.0 Hz), 1.08 (s, 3H), 1.20 (s, 3H), 1.3-1.7 (m, 2H), 2.27 (s, 3H), 3.0-3.3 (m, 1H), 3.49 (d, 1H, J = 10.0 Hz), 3.63 (d, 1H, J = 10.0 Hz), 3.78 (s, 3H), 6.9-7.2 (m, 4H)

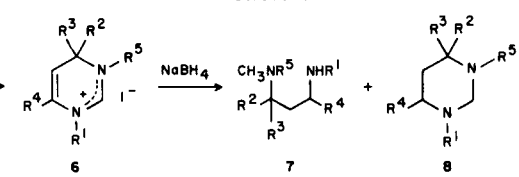
[a] Measured in liquid film. [b] Measured in deuteriochloroform.

Scheme 1



As the compounds related to the dihydropyrimidine, the reduction of dihydropyrimidinium salts with sodium borohydride was also attempted. When 1-alkyl-3,6-dihydropyrimidinium iodide (**6**) was treated with excess amount of sodium borohydride in ethanol at room temperature for 24 hours, *N,N,N'*-trisubstituted 1,3-diamine (**7**) and hexahydropyrimidine (**8**) were obtained.

Scheme 2



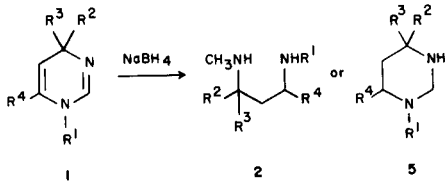
a, $R^1 = C_6H_5$, $R^2 = R^3 = R^4 = R^5 = CH_3$

b, $R^1 = C_6H_5$, $R^2 = R^3 = R^4 = CH_3$, $R^5 = C_2H_5$

c, $R^1 = p\text{-}CH_3OC_6H_4$, $R^2 = R^3 = R^4 = R^5 = CH_3$

When 1,4-dihydro-4,4,6-trimethyl-1-phenylpyrimidine (**1b**) (1 mmole) was treated with lithium aluminum hydride (3 mmoles) in ether at room temperature for 15 hours, an oily product was obtained showing absorption bands at

3330 and 1660 cm^{-1} attributable to N-H and C=N stretching, respectively. In the ^{1}H-nmr spectrum, the signals appeared at δ 1.18 (s, 6H, $2CH_3$), 1.80 (s, 3H, CH_3), 2.33 (s, 3H, NCH_3), and 2.47 ppm (s, 2H, CH_2). By treatment with an excess amount of sodium borohydride in methanol under reflux, the product was converted into 4-anilino-2-methyl-2-methylaminopentane (**2b**). From these data, the product was determined to be 4-methyl-4-methylamino-2-phenyliminopentane (**9**), with a double bond remaining in its molecule.



1 2 5

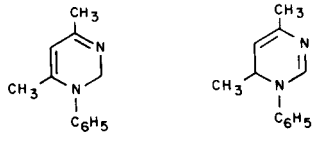
a, $R^1 = C_6H_5$, $R^2 = H$, $R^3 = R^4 = CH_3$

b, $R^1 = C_6H_5$, $R^2 = R^3 = R^4 = CH_3$

c, $R^1 = p\text{-}CH_3C_6H_4$, $R^2 = R^3 = R^4 = CH_3$

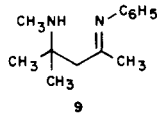
d, $R^1 = p\text{-}CH_3OC_6H_4$, $R^2 = R^3 = R^4 = CH_3$

e, $R^1 = C_6H_5CH_2$, $R^2 = R^3 = R^4 = CH_3$



3 4

In conclusion, sodium borohydride reduced all double bonds in the pyrimidine ring, then caused ring cleavage. On the contrary, lithium aluminum hydride reduced only the amidine moiety. Although diamines are useful compounds as synthetic intermediates and ligands of metal chelates [8], few synthetic papers of 2,4-diaminopentanes which have substituents on nitrogen atom have been reported [5]. Therefore, the reductive cleavage of dihydropyrimidines is a good method for *N*-substituted 2,4-diaminopentanes under the mild reaction condition in good yield.



9

EXPERIMENTAL

Melting and boiling points were uncorrected. The ir spectra were recorded on a Jasco IRA-1 infrared spectrophotometer. The ^{1}H-nmr spectra were given by Hitachi R-24 type nuclear magnetic resonance spectrometer using TMS as an internal standard.

Materials.

Alkylation of Dihydropyrimidines.

General Procedure.

The mixture of dihydropyrimidine (2 mmoles) and alkyl halide (20 mmoles) was heated at 80° for 0.5 hour in a sealed tube. The crude product was recrystallized from appropriate solvent.

3,6-Dihydro-1,4,6,6-tetramethyl-3-phenylpyrimidinium Iodide (**6a**).

This product was obtained in a yield of 84% and recrystallized from isopropanol-ethyl acetate, mp 187°; ir (potassium bromide): 1700, 1660, 1635 cm^{-1}; nmr (deuteriochloroform): δ 1.62 (s, 9H), 3.48 (s, 3H), 5.22 (s, 1H), 7.4-7.8 (m, 5H), 8.62 (s, 1H).

Anal. Calcd. for $C_{14}H_{19}IN_2$: C, 49.13; H, 5.59; N, 8.18. Found: C, 48.75; H, 5.65; N, 8.13.

1-Ethyl-3,6-dihydro-4,6,6-trimethyl-3-phenylpyrimidinium Iodide (**6b**).

This product was obtained in a yield of 99% and recrystallized from ethanol-ethyl acetate, mp 143-144°; ir (potassium bromide): 1710, 1660, 1630 cm^{-1}; nmr (deuteriochloroform): δ 1.47 (t, 3H, J = 7.0 Hz), 1.63 (s, 9H), 3.93 (q, 2H, J = 7.0 Hz), 5.10 (s, 1H), 7.4-7.8 (m, 5H), 8.47 (s, 1H).

Anal. Calcd. for $C_{15}H_{21}IN_2$: C, 50.57; H, 5.94; N, 7.86. Found: C, 50.26; H, 6.06; N, 7.80.

3,6-Dihydro-3-(*p*-methoxyphenyl)-1,4,6,6-tetramethylpyrimidinium Iodide (**6c**).

This product was obtained in a yield of 94% and recrystallized from ethanol, mp 238° dec; ir (potassium bromide): 1705, 1660, 1630 cm^{-1}; nmr (deuteriochloroform): δ 1.63 (s, 9H), 3.42 (s, 3H), 3.88 (s, 3H), 5.10 (s, 1H), 6.9-7.6 (m, 4H), 8.32 (s, 1H).

Anal. Calcd. for $C_{15}H_{21}IN_2O$: C, 48.39; H, 5.68; N, 7.52. Found: C, 48.40; H, 5.65; N, 7.57.

Reaction of Dihydropyrimidine with Sodium Borohydride.

General Procedure.

To a stirred solution of dihydropyrimidine (1 mmole) in 20 ml of dry ethanol, sodium borohydride (10 mmoles) was added. The reaction mixture was stirred for 24 hours at room temperature. It was diluted with water, extracted with dichloromethane, and dried over anhydrous magnesium sulfate. After removal of the solvent, the crude product was chromatographed on silica gel with hexane-acetone-diethylamine (13:6:1) mixture, then purified by vacuum distillation.

Hexahydro-4,4,6-trimethyl-1-phenylpyrimidine (**5b**).

Compound **1b** (1 mmole) was treated with sodium borohydride (3 mmoles) according to the same manner described above. The crude product was purified by column chromatography on silcia gel with hexane-acetone-diethylamine (13:6:1) mixture, followed by recrystallization from hexane giving **5b** in 56% yield, mp 57-58°; ir (liquid film): 3260, 1600 cm^{-1}; nmr (deuteriochloroform): δ 0.93 (d, 3H, J = 6.0 Hz), 1.17 (s, 6H), 1.4-1.7 (m, 2H), 3.0-3.5 (m, 1H), 3.86 (s, 2H), 6.9-7.5 (m, 5H).

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.86; N, 13.71. Found: C, 76.25; H, 9.81; N, 13.68.

Reaction of **5b** with Sodium Borohydride.

Compound **5b** (1 mmole) was treated with sodium borohydride (10 mmoles) according to the same manner described above. The crude product was purified by column chromatography on silica gel with hexane-acetone-diethylamine (13:6:1) mixture, followed by vacuum distillation. Compound **2b** was obtained in 51% yield.

Reaction of Dihydropyrimidinium Iodide (**6a-c**) with Sodium Borohydride.

General Procedure.

Dihydropyrimidinium iodide (1 mmole) was treated with sodium borohydride (10 mmoles) according to the same manner described above. The crude product was purified by column chromatography on silica gel with

hexane-acetone-diethylamine (50:5:1) mixture, followed by vacuum distillation.

4-Methyl-4-methylamino-2-phenyliminopentane (**9**).

To a stirred solution of **1b** (1 mmole) in dry ether (10 ml), lithium aluminum hydride (3 mmoles) was added, and the mixture was stirred for 15 hours at room temperature under argon atmosphere. Lithium aluminum hydride was decomposed with acetone and water. The reaction mixture was extracted with dichloromethane, and dried over anhydrous magnesium sulfate. After removal of the solvent, the crude product was chromatographed on silica gel with hexane-acetone-diethylamine (13:6:1) mixture, then purified by vacuum distillation giving **9** in a yield of 57%; bp 34°/10^{-4} mm Hg; ir (liquid film): 3330, 1660 cm^{-1}; nmr (deuteriochloroform): δ 1.18 (s, 6H), 1.80 (s, 3H), 2.33 (s, 3H), 2.47 (s, 2H), 6.6-6.8 (m, 2H), 7.0-7.5 (m, 3H).

Anal. Calcd. for $C_{13}H_{20}N_2 \cdot 0.5H_2O$: C, 73.18; H, 9.94; N, 13.13. Found: C, 72.79; H, 9.81; N, 12.92.

Reaction of **9** with Sodium Borohydride.

To a stirred solution of **9** (1 mmole) in 10 ml of methanol, 3.5 mmoles of sodium borohydride were added, and the reaction mixture was refluxed for 1 hour. The reaction mixture was diluted with water, extracted with dichloromethane, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the crude product was chromatographed on silica gel with hexane-acetone-diethylamine (13:6:1) mixture, then purified by distillation. Compound **2b** was obtained in 60% yield.

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