fraction of circulating radioactivity according to the result of thin-layer chromatography (Wakogel B5FM cyclohexane: acetone 1:1). Content of unchanged drug I (1.02 μg/ml at 30 min) accounted for about 12% of circulating radioactivity (8.61 μg/ml), indicating that I underwent extensive metabolism. We found 1-^{14}C-ecarazine hydrochloride given orally was well absorbed by rats, and 85.5% of the administered radioactivity was recovered in urine within 48 hr.[1] Only a small amount of unchanged drug was recovered in urine, indicating I was further transformed in rat. The applicability of the present method to the determination of urine and tissue levels of I is currently investigated.

[Chem. Pharm. Bull. 26(7)2246—2249(1978)]

UDC 547.497.04 : 546.271.04

Synthesis of Formamidines from Carbodiimides with Sodium Borohydride in Isopropanol

Kenji Kaji, Hiromitsu Matsubara, Hiromu Nagashima,[1a] Yasuo Kikugawa,[1b] and Shun-ichi Yamada[1b]

Gifu College of Pharmacy[1a] *and Faculty of Pharmaceutical Sciences, Josai University*[1b]

(Received December 26, 1977)

Reduction of the N,N′-disubstituted carbodiimides with sodium borohydride in isopropanol performs a convenient synthetic method of the corresponding formamidines.

tert-Butanol, pyridine, and tetrahydrofuran proved also available as solvents for the procedure, while methanol or ethanol was unsuitable for the lower yield of the formamidine, probably due to the further reduction to proceed.

Keywords——sodium borohydride; formamidines; carbodiimides; reduction; isopropanol

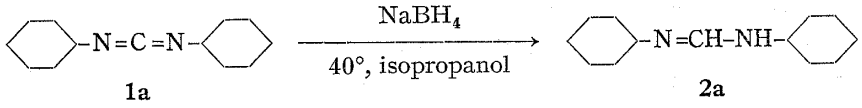
In connection with the new synthesis of formamidines from the 1,3-disubstituted ureas with sodium borohydride in pyridine,[2] we have investigated the reduction of carbodiimides to give the corresponding formamidines. Readily available sodium borohydride was employed for the reduction of carbodiimides to obtain formamidines under simple operating conditions, although the catalytic hydrogenation of carbodiimides had already been reported as a useful synthetic method.[3]

The reduction of N,N′-dicyclohexylcarbodiimides (**1a**) with sodium borohydride carried out at 50° for 4 hr in methanol and ethanol which are quite commonly available solvents in borohydride reduction, and N,N′-dicyclohexylformamidine (**2a**) was obtained in low yields (19% and 50% respectively). Unexpectedly shortening the reaction time (30 min, 30°, EtOH) raised the yield of **2a** to 88%. The explanation of the results is that the formamidine formed in the reaction mixture is unstable under this condition and decompose gradually during the reduction,[4] however the exact reason explaining the results is still obscure.

On the other hand, in isopropanol N,N′-dicyclohexylformamidine (**2a**) was obtained in a good yield as shown in Table I and no extensive decomposition of **2a** or the formation of significant side products was not observed even with 8 hr stirring.

1) Location: *Mitahora, East 5-6-1, Gifu 502, Japan*; *a*) To whom inquiries should be adressed; *b*) *Keyakidai, 1-1, Sakado, Saitama, 350-02, Japan.*
2) Y. Kikugawa, S. Yamada, H. Nagashima, and K. Kaji, *Tetrahedron Lett.*, **1969**, 699.
3) J.C. Jochims, *Chem. Ber.*, **98**, 2128 (1965).
4) Several spots other than that of **2a** were detected by the thin-layer chromatography of the reaction mixture.

Table I. Study of Reduction Conditions of **1a** with $NaBH_4$



1a **2a**

Reaction time (hr)	Molar ratio $NaBH_4$/DCCD	Product[a] (%)
3	1/4	48
	1/2	76
	1	90
	2	88
4	1/4	49
	1/2	82
	1	90
	2	92
8	1/4	53
	1/2	78
	2	87

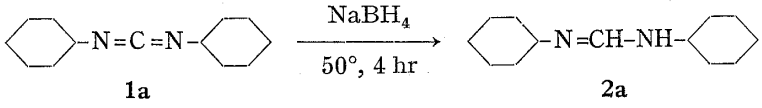
a) Yields were calculated by converting the formamidine into its picrate.

To clarify the reason why the yield of the formamidine (**2a**) is poor in methanol and is high in isopropanol, the stability of the formamidine (**2a**) in alcohols–sodium borohydride solutions was investigated. The authentic formamidine (**2a**) was dissolved in an alcohol–sodium borohydride solution and after 2 hr stirring at 50°, **2a** was recovered in a poor yield from methanol– or ethanol–sodium borohydride and in a high yield from isopropanol–sodium borohydride solution.

It was reported[5] that sodium borohydride was converted to its alkoxyborohydride and finally to tetraalkoxyborohydride in methanol or ethanol and not in isopropanol or *tert*-butanol.[6] The study of the reaction of **2a** with sodium tetramethoxyborohydride showed that tetramethoxyborohydride did not affect the decomposition of **2a** in methanol.

On the other hand, sodium alkoxyborohydride which has available hydrogens shows a stronger reducing ability[5a] than sodium borohydride and it is presumable that alkoxyborohydride affects the formamidine (**2a**) to its extensive reduction or decomposition. In the case of the aprotic solvents such as pyridine or tetrahydrofuran, in which sodium borohydride

Table II. Reduction of **1a** with $NaBH_4$ in Various Solvents



1a **2a**

Solvent	Product[a] (%)
Methanol	19
Ethanol	50
Isopropanol	83
tert-Butanol	81
Pyridine	89
Tetrahydrofuran	74

a) Yields were calculated by converting the formamidine into its picrate.

5) a) H.C. Brown and E.J. Mead, *J. Am. Chem. Soc.*, **75**, 6263 (1953); b) W. Gerrard, "The Organic Chemistry of Boron," Academic Press, New York, 1961, p. 141; c) Y. Kikugawa, *Chem. Pharm. Bull.* (Tokyo), **24**, 1059 (1976).

6) H.C. Brown, E.J. Mead, and B.C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).

has mild reducing ability at ambient temperature, the formamidine (**2a**) was obtained in reasonable yields as expected. Table II shows the results.

As isopropanol is the easiest to handle in sodium borohydride reduction, various carbodiimides were reduced in isopropanol to give the corresponding formamidines in moderate yields as presented in Table III.

Table III. Formamidines (**2**) R–N=CH=N–R′ (H)

2	R	R′	mp (°C) (lit. mp)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
a	Cyclohexyl	Cyclohexyl	220—222[a] (220[b])	83	$C_{19}H_{27}N_5O_7$	52.16 (52.39)	6.22 (6.52)	16.01 (16.15)
b	Cyclohexyl	Iso-C_3H_7	172—173[a] (173[b])	68	$C_{16}H_{23}N_5O_7$	48.36 (48.51)	5.83 (5.93)	17.63 (17.72)
c	Iso-C_3H_7	Iso-C_3H_7	188—190[a] (189—191[c])	52	$C_{13}H_{19}N_5O_7$	43.69 (43.71)	5.36 (5.38)	19.60 (19.81)
d	Cyclohexyl	*sec*-C_4H_9	164—166[a] (168[b])	61	$C_{17}H_{25}N_5O_7$	49.63 (49.87)	6.13 (6.33)	17.02 (16.89)
e	*sec*-C_4H_9	*sec*-C_4H_9	180—182[a]	65	$C_{15}H_{23}N_5O_7$	46.75 (46.84)	6.02 (6.10)	18.17 (17.99)
f	C_6H_5	C_6H_5	136—138 (135—136[d])	45	$C_{13}H_{12}N_2$	79.56 (79.31)	6.16 (6.33)	14.28 (14.34)
g	*o*-$CH_3C_6H_4$	*o*-$CH_3C_6H_4$	153—154 (153[e])	66	$C_{15}H_{16}N_2$	80.32 (80.18)	7.19 (7.28)	12.63 (12.49)
h	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	138—139 (141.8—142.8[f])	57	$C_{15}H_{16}N_2$	80.32 (80.19)	7.19 (7.12)	12.63 (12.54)
i	*o*-$CH_3OC_6H_4$	*o*-$CH_3OC_6H_4$	105—106 (105[g])	65	$C_{15}H_{16}N_2O_2$	70.29 (70.08)	6.29 (6.13)	10.93 (11.02)
j	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	111—113 (114—115[c])	62	$C_{15}H_{16}N_2O_2$	70.29 (70.49)	6.29 (6.08)	10.93 (10.87)

a) Picrate of **2**. *b*) Y. Kikugawa, S. Yamada, H. Nagashima, and K. Kaji, *Tetrahedron Lett.*, **1969**, 700. *c*) J.C. Jochims, *Chem. Ber.*, **98**, 2132 (1965). *d*) W. Weith, *Ber.*, **9**, 455 (1876). *e*) A. Ladenburg, *Ber.*, **10**, 1260 (1877). *f*) L.M. Roberts, *J. Am. Chem. Soc.*, **71**, 3848 (1949). *g*) F.B. Dains and E.W. Brown, *J. Am. Chem. Soc.*, **31**, 1149 (1909).

This simple procedure will offer the alternative synthetic method of formamidines in the case that the catalytic hydrogenation of carbodiimides is inconvenient.

Experimental[7]

Materials——$NaBH_4$ and **1a** were purchased from Wako Chemical Industries, Ltd. Other starting carbodiimides (**1b—j**) were prepared by the usual method.[8] Alcohols used as solvent were dehydrated by metallic sodium and distilled, and pyridine was distilled over KOH.

Typical Procedure for Reduction of Carbodiimides——A mixture of $NaBH_4$ (136 mg, 3.6 mmol) and DCCD (**1a**) (619 mg, 3.0 mmol) in isopropanol (25 ml) was maintained at 50° for 4 hr under stirring. After the reaction isopropanol was distilled off *in vacuo*, H_2O (10 ml) was added to the residue and it was extracted with benzene (20 ml × 3) which was dried over anhyd. Na_2SO_4. Benzene was distilled off *in vacuo* and the residue (**2a**) was dissolved in a small volume of ethanol, to which was added ethanol solution saturated with picric acid (824 mg, 3.6 mmol). After 12 hr standing the precipitate (picrate of **2a**) was collected by filtration and dried in a desiccator under reduced pressure (mp 220—222°, 518 mg, yield 83%). In the case of **2f—g**, purification was carried out by recrystallization (petroleum ether).

7) All melting points are uncorrected.
8) *a*) E. Schmidt and W. Striewsky, *Ber.*, **74**, 1285 (1941); *b*) C.L. Stevens, G.H. Singhal, and A.B. Ash, *J. Org. Chem.*, **32**, 2895 (1967).

Reaction of Sodium Tetramethoxyborohydride[9] and N,N'-Dicyclohexylformamidine (2a) in Methanol——113 mg (3 mmol) of $NaBH_4$ was dissolved in methanol (25 ml) and the solution was stirred for 2 hr at room temperature. To this solution[10] was added 625 mg (3 mmol) of **2a** and the reaction mixture was heated to 50 °C for 4 hr. Methanol was distilled off *in vacuo* and to the residue was added H_2O (10 ml). The aqueous layer was extracted with ether (15 ml × 3) which was dried over anhyd. Na_2SO_4. After evaporation of ether, the residue was dissolved in ethanol (2 ml), to which the ethanol solution saturated with 687 mg (3 mmol) of picric acid was added and the solution was allowed to stand overnight. The precipitate appeared was collected and dried to give N,N'-dicyclohexylformamidine picrate (mp 220—222° 110.9 mg, Y. 84.5%).

Solvent Effect for Stability of N,N'-Dicyclohexylformamidine (2a)——378 mg (1 mmol) of $NaBH_4$ was added to an alcohol solution (10 ml) (methanol, ethanol, and isopropanol) dissolving 208 mg (1 mmol) of N,N'-dicyclohexylformamidine (**2a**) and the reaction mixture was stirred for 2 hr at 50°. After evaporation of the solvent, the reaction mixture was processed as above and N,N'-dicyclohexylformamidine picrate was obtained in the yields of 32%, 39%, and 78% corresponding to methanol, ethanol, and isopropanol solvents, respectively.

9) H.I. Schlesinger, H.C. Brown, H.R. Hoekstra, and L.A. Rapp, *J. Am. Chem. Soc.*, **75**, 204 (1953).
10) Evolution of hydrogen from the solution was not observed even when the reaction temperature rose to 50 °.

[Chem. Pharm. Bull. 26(7)2249—2253(1978)]

UDC 547.235.5.04 : 541.14.04

Thermal and Photochemical Behaviors of N-[(N-Nitrosobenzylamino)-methyl]benzamide in Acidic Media

Hirotugu Yamashita, Keiichi Ito, and Minoru Sekiya

Shizuoka College of Pharmacy[1]

(Received January 10, 1978)

Thermal and photochemical behaviors of N-[(N-nitrosobenzylamino)methyl]benzamide in acidic media at room temperature have been demonstrated in characteristic fashions of its acid-catalyzed decompositions, *i.e.*, *in situ* formation of phenyldiazomethane, thermal denitrosation, photolytic denitrosation, and photorearrangement of nitroso group. These reactions are controlled by the acid and the solvent used.

Keywords——N-[(N-nitrosobenzylamino)methyl]benzamide; acid-catalyzed decomposition; phenyldiazomethane formation; denitrosation; photoelimination; photorearrangement

Synthetic value of N-[(N-nitrosoalkylamino)methyl]benzamides as excellent diazoalkane-generating agents has been already reported from this laboratory.[2] The base-catalyzed generation of diazoalkane is represented by the following general equation.

$$2C_6H_5CONHCH_2\underset{\underset{NO}{|}}{N}CH_2R \xrightarrow{\text{alkali}} 2RCHN_2 + (C_6H_5CONH)_2CH_2 + CH_2O + H_2O$$

In contrast to this decomposition in alkaline media how the N-nitroso compounds behave in non-basic or acidic media drew our attention. Lately, there has been reported from this laboratory[3] an interesting information on this subject, in which N-[(N-nitrosobenzylamino)-methyl]benzamide benzylated trifluoroacetic acid and, in the presence of ferric chloride,

1) Location: *2-2-1 Oshika, Shizuoka, 422, Japan.*
2) M. Sekiya, Y. Ohashi, Y. Terao, and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **24**, 369 (1976).
3) Y. Ohashi, Y. Terao, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **26**, 653 (1978).