

ISOLATION OF THE INTERMEDIATES AND IMPROVED SYNTHESIS OF
PYRIDO[1',2':1,2]IMIDAZO[4,5-*b*]PYRAZINES AND -QUINOXALINES

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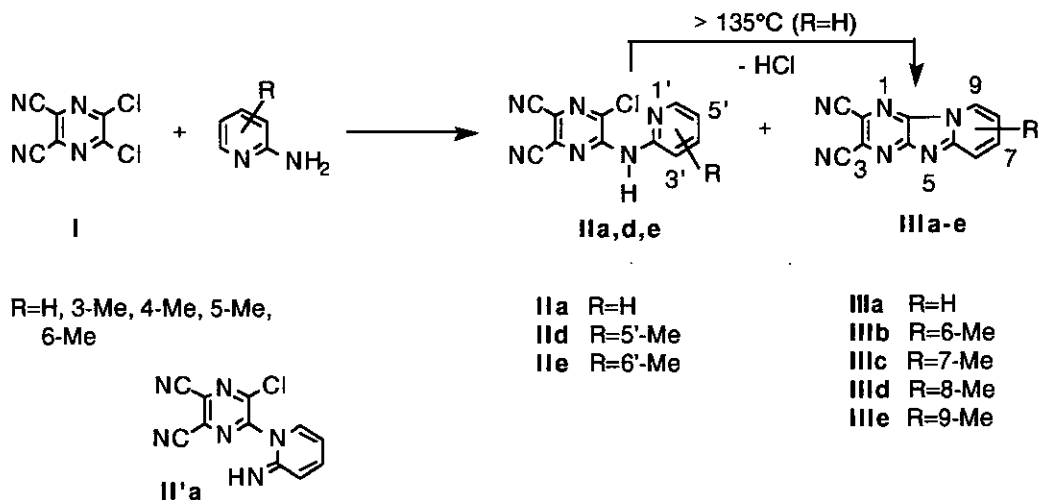
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Abstract --- 2-(Pyrid-2'-yl)amino-3-chloro-5,6-dicyanopyrazines (**Ila**, **Ild**, and **Ile**) and 2-(pyrid-2'-yl)amino-3-chloro-6-nitroquinoxalines (**Va-c**) were isolated for the first time in the course of the reaction of 2,3-dichloro-5,6-dicyanopyrazine (**I**) and 2,3-dichloro-6-nitroquinoxaline (**IVa**), respectively, with 2-aminopyridines. Furthermore, the yield of pyrido[1',2':1,2]imidazo[4,5-*b*]quinoxalines was remarkably improved due to the modification of the reaction conditions.

Nitrogen-containing fused polycyclic compounds have been paid much attention owing to the characteristic structure with a bridgehead nitrogen and pharmaceutical interest.^{1,2} In 1986, we have published the novel synthesis of pyrido[1',2':1,2]imidazo[4,5-*b*]pyrazines by reaction of 2,3-dichloro-5,6-dicyanopyrazine with 2-aminopyridines or 2-amino-3-chloro-5,6-dicyanopyrazines with substituted pyridines.^{3,4} In 1990, Tomoda has reported on the synthesis and the fluorescent property of pyridoimidazoquinoxalines.⁵ Recently Tanaka has reported the extended synthesis of them bearing substituents on the pyridine and/or quinoxaline ring.⁶ However, these methods gave the products in only low to moderate yields. Since these heterocyclic compounds particularly are of interest in chemiluminescence⁷ as well as the fluorescent property, the improvement of the yield in the previous methods was undertaken. In this paper, we describe the improved synthesis of pyrido[1',2':1,2]imidazo[4,5-*b*]pyrazines and -quinoxalines as well as the isolation of their intermediates.

Isolation of the Intermediates. 2,3-Dichloro-5,6-dicyanopyrazine (**I**) was allowed to react with 2-aminopyridine at room temperature to give 2-(pyrid-2'-yl)amino-3-chloro-5,6-dicyanopyrazine (**Ila**)

together with the reported product,³ 2,3-dicyanopyrido[1',2':1,2]imidazo[4,5-b]pyrazine (**IIIa**). (Scheme 1)



Scheme 1

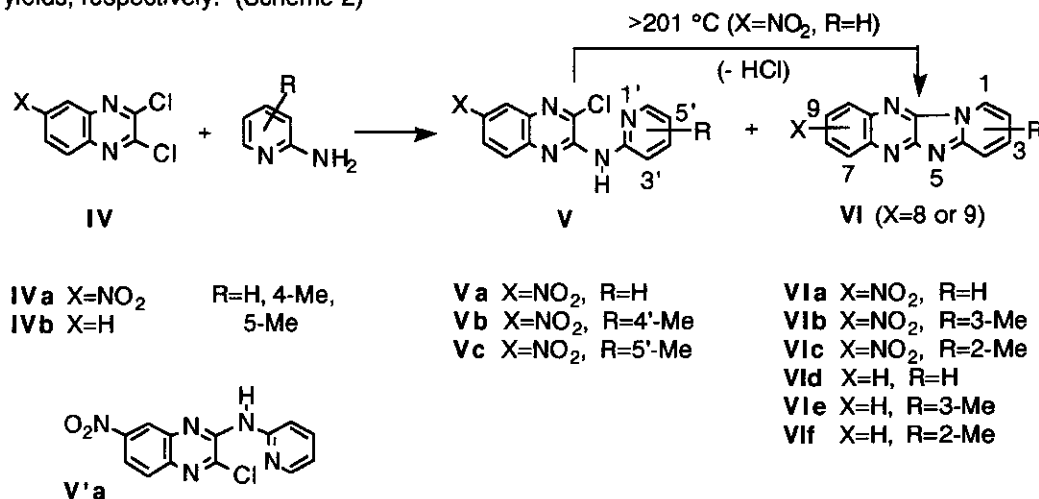
Ir spectrum of the product (**IIa**) shows absorption bands at 3360 and 2230 cm^{-1} , attributed to N-H and C=N stretching vibrations, respectively. ^1H Nmr spectrum shows the proton signals between 7.2 and 8.4 ppm similarly to those of 2-aminopyridine and a broad singlet at 8.5 ppm due to N-H proton. The possibility of the isomer (**II'a**) was ruled out by the fact that the proton signals of 1-substituted pyridine-2(1*H*)-imines usually appear at higher field than 7 ppm. Further, **IIa** was converted into pyridoimidazopyrazine (**IIIa**) in quantitative yield on heating over 135 °C, indicating that **IIa** obtained for the first time is the intermediate of pyridoimidazopyrazine (**IIIa**). The reaction of pyrazine (**I**) with other substituted 2-aminopyridines was carried out, and the results are summarized in Table 1. In two cases (R=3-Me and R=4-Me), the intermediate could not be isolated under the present conditions.

Table 1 Reaction of 2,3-Dichloro-5,6-dicyanopyrazine with Substituted 2-Aminopyridines

R ^{a)}	Reaction time (h)	Product	Yield (%)	Mp (°C)	Product ^{b)}	Yield (%)
H	4	IIa	23	135	IIIa	50
3-Me	5	—	—	—	IIIb	70
4-Me	4	—	—	—	IIIc	90
5-Me	4	IIId	13	150	IIId	38
6-Me	21	IIe	14	160	IIIe	60

a) The substituents in 2-aminopyridines. b) The structure of compounds (**IIIa-e**) was identified by comparison with authentic samples.³

When 2,3-dichloro-6-nitroquinoxaline (**IVa**) was treated with 2-aminopyridine in dioxane under reflux for 6 h, a new compound, 2-(pyrid-2'-yl)amino-3-chloro-6-nitroquinoxaline (**Va**) and a mixture of 8-nitro- and 9-nitropyrido[1',2':1,2]imidazo[4,5-*b*]quinoxaline (**VIa**, in the ratio of 4:6) were obtained in 18 and 33% yields, respectively. (Scheme 2)



Scheme 2

The newly obtained product (**Va**) was found to be a single component from the fact that **Va** was converted into only the 9-nitro derivative in quantitative yield on heating over 201 °C. The structure of 9-nitro derivative was identified by comparison with an authentic sample prepared from 2-amino-3-chloro-6-nitroquinoxaline and pyridine.⁶ Another intermediate (**V'a**), which would afford the 8-nitro derivative, could not be isolated in this reaction. The reaction of quinoxaline (**IVa**) with other substituted 2-aminopyridines was carried out, and the results are presented in Table 2.

Table 2 Reaction of 2,3-Dichloro-6-nitroquinoxaline with Substituted 2-Aminopyridines

X	R ^{a)}	Product	Yield (%)	Mp (°C)	Product ^{b)}	Yield (%)
NO ₂	H	Va	18	201	VIa	33
	4-Me	Vb	23	179	VIb	35
	5-Me	Vc	9	182	VIc	18

a) The substituents in 2-aminopyridines. b) The structure of compounds (**VIa-c**) was identified by comparison with authentic samples.⁶

Improved Syntheses of Pyrido[1',2':1,2]imidazo[4,5-*b*]quinoxalines. A mixture of quinoxaline (**IVa**) and 2-aminopyridine was refluxed for 6 h in dioxane, and the solvent was evaporated

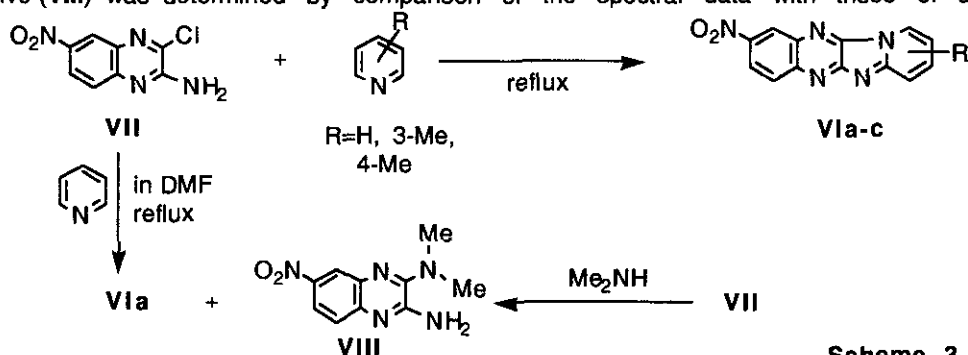
and then the residual solid was heated at 220 °C for 1 h without solvent to undergo the ring closure of the intermediate (Va) to give pyridoimidazoquinoxaline (VIa) in 85% yield. Heating at 220 °C results in the increase of the yield of VIa from 53% (33%+18%) up to 85%. Therefore an improved synthesis was achieved; quinoxaline (IVa) and 2-aminopyridine were homogenized well on a mortar, and then heated at 220 °C for 30 min without solvent to afford pyridoimidazoquinoxaline (VIa) in 80% yield. As a result, the yields of the desired products (VIa-f) remarkably increased compared with the previous method⁶ as seen in Table 3.

Table 3 Improved Synthesis of Pyrido[1',2':1,2]imidazo[4,5-b]quinoxalines

Compound	R ^{a)}	Product	Yield (%)	
			The present method	The previous method ^{b)}
IVa	H	VIa	80	24
IVa	4-Me	VIb	90	45
IVa	5-Me	VIc	63	—
IVb	H	VI d	15	3
IVb	4-Me	VI e	60	3
IVb	5-Me	VI f	47	5

a) The substituents in 2-aminopyridines. b) Ref. 6.

2,3-Dichloro-6-nitroquinoxaline (IVa) was treated with ammonium carbonate to give 2-amino-3-chloro-6-nitroquinoxaline (VII). The direction of the mono-amination was estimated by means of the MO calculation⁶ and Eu(fod)₃ induced shift method. A mixture of quinoxaline (VII) and 3 equivalents of pyridine in DMF was refluxed for 12 h to afford 2-amino-3-dimethylamino-6-nitroquinoxaline (VIII) in 20% yield as well as the reported single isomer (VIa, 9-nitro). The structure of 3-dimethylamino derivative (VIII) was determined by comparison of the spectral data with those of a sample



Scheme 3

obtained separately from quinoxaline (VII) and dimethylamine. (Scheme 3) For suppression of the formation of 3-dimethylamino derivative (VIII), then pyridine was used as a reagent and a solvent in stead of DMF. This improved method results in an apparent increase of the yields of pyridoimidazoquinoxalines (VIa-c) as shown in Table 4.

Table 4 Improved Synthesis of Pyridoimidazoquinoxalines (VIa-c) from
2-Amino-3-chloro-6-nitroquinoxaline (VII)

Ra)	Product	Yield (%)	
		The present method	The previous method ^{b)}
H	VIa	75	51
4-Me	VIb	67	27
3-Me	VIc	51	42

a) The substituents in pyridines. b) Ref. 6.

EXPERIMENTAL

Melting points were recorded on a Mel-Temp apparatus in open capillaries and are uncorrected. Ir spectra were recorded on a JASCO A-100 Infrared Spectrophotometer. ¹H Nmr spectra were recorded on a JEOL GX-270 NMR Spectrometer in CDCl₃ and DMSO-d₆ and are reported in ppm (δ) downfield from internal Me₄Si. Thin layer chromatographic (tlc) analyses were performed on silica gel 60F-254 with a 0.2 mm layer thickness. Column chromatography was carried out with Merck Kieselgel 60 (230-400 mesh). Combustion analyses were performed on a Yanaco MT-3 CHN CORDER.

2,3-Dichloro-5,6-dicyanopyrazines (I) and 2,3-dichloroquinoxalines (IVa,b) were prepared according to the literature methods.^{3,6}

General Procedure for Isolation of Intermediates (IIa, IIc, and IIe): a Typical Example, 2-(Pyrid-2'-yl)amino-3-chloro-5,6-dicyanopyrazine (IIa): A mixture of 2,3-dichloro-5,6-dicyanopyrazine (I, 1.03 g, 5 mmol) and 2-aminopyridine (1.41 g, 15 mmol) in dioxane (50 ml) was stirred for 4 h at room temperature. The resulting precipitate was filtered and then recrystallized from MeOH to give pyrido[1',2':1,2]imidazo[4,5-b]pyrazine (IIIa, 0.51 g, 50%) as pale yellow needles which was identical with an authentic sample.⁶ The filtrate was carefully evaporated and the residue was chromatographed on silica gel with CHCl₃:acetone:EtOH (200:5:1 v/v) to give the product (IIa) (0.3 g, 23%); ir (CHCl₃) ν_{\max} : 3360 and 2230 cm⁻¹; ¹H nmr (CDCl₃) δ: 7.23 (1H, t, J=4.8 Hz), 7.85 (1H, t,

$J=8.0$ Hz), 8.28 (1H, d, $J=8.0$ Hz), 8.40 (1H, d, $J=4.8$ Hz), and 8.53 ppm (1H, br s). Anal. Calcd for $C_{11}H_5N_5Cl$: C, 51.34; H, 2.22; N, 32.61. Found: C, 51.46; H, 1.95; N, 32.75.

2-(5'-Methylpyrid-2'-yl)amino-3-chloro-4,6-dicyanopyrazine (IIId): Similar reaction of compound (I) with 2-amino-5-methylpyridine gave the product (IIId) in 38% yield and the product (IIId)⁸ in 13% yield; ir (CHCl₃) ν_{max} : 3360 and 2230 cm^{-1} ; ¹H nmr (CDCl₃) δ : 2.40(3H, s), 7.68 (1H, d, $J=2.2$ and 8.5 Hz), 8.18 (1H, d, $J=8.5$ Hz), and 8.23 ppm (1H, d, $J=2.2$ Hz).

2-(6'-Methylpyrid-2'-yl)amino-3-chloro-5,6-dicyanopyrazine (IIe): Similar reaction of compound (I) with 2-amino-6-methylpyridine gave the product (IIe) in 60% yield and the product (IIe)⁸ in 14% yield; ir (CHCl₃) ν_{max} : 3370 and 2240 cm^{-1} ; ¹H nmr (CDCl₃) δ : 2.53 (3H, s), 7.06 (1H, d, $J=8.4$ Hz), 7.75 (1H, t, $J=8.4$ Hz), and 8.09 ppm (1H, d, $J=8.4$ Hz).

General Procedure for Isolation of Intermediates (Va-c): a Typical Example, 2-(Pyrid-2'-yl)amino-3-chloro-6-nitroquinoxaline (Va):

A mixture of 2,3-dichloro-6-nitroquinoxaline (IVa, 2.42 g, 10 mmol) and 2-aminopyridine (2.82 g, 30 mmol) in dioxane (90 ml) was refluxed for 6 h. The resulting precipitate was filtered off, washed with hot water (1 l), and dried over anhydrous P₂O₅ for 3 h at 80 °C. The residual solid was chromatographed on silica gel with CHCl₃:acetone:EtOH (100:5:1 v/v) to give nitropyridoimidazoquinoxaline (VIa, $R_f=0.2$, 0.88 g, 33%) which was identical with an authentic sample⁶ and the product (Va) (0.54 g, 18%); ir (KBr) ν_{max} : 3380, 1520, and 1345 cm^{-1} ; ¹H nmr (DMSO-*d*₆) δ : 7.23 (1H, dd, $J=2.4$ and 7.3 Hz), 7.95 (1H, dd, $J=2.4$ and 7.3 Hz), 8.01 (1H, d, $J=9.2$ Hz), 8.45-8.50 (2H, m), 8.46 (1H, dd, $J=2.7$ and 9.2 Hz), and 8.68 ppm (1H, d, $J=2.7$ Hz). Anal. Calcd for $C_{13}H_{18}N_5O_2Cl$: C, 51.76; H, 2.67; N, 23.22. Found: C, 51.46; H, 2.76; N, 23.06.

2-(4'-Methylpyrid-2'-yl)amino-3-chloro-6-nitroquinoxaline (Vb): Similar reaction of compound (IVa) with 2-amino-4-methylpyridine afforded the product (Vb) in 35 % yield and the product (Vb) in 23 % yield; ir (KBr) ν_{max} : 3370, 1515, and 1345 cm^{-1} ; ¹H nmr (DMSO-*d*₆/CDCl₃) δ : 2.50 (3H, s), 6.98 (1H, d, $J=5.1$ Hz), 7.98 (1H, d, $J=9.1$ Hz), 8.25 (1H, d, $J=5.1$ Hz), 8.48 (1H, dd, $J=2.4$ and 9.1 Hz), 8.58 (1H, s), and 8.79 ppm (1H, d, $J=2.4$ Hz). Anal. Calcd for $C_{14}H_{10}N_5O_2Cl$: C, 53.25; H, 3.17; N, 22.19. Found: C, 53.52; H, 3.22; N, 22.09.

2-(5'-Methylpyrid-2'-yl)amino-3-chloro-6-nitroquinoxaline (Vc): Similar reaction of compound (IVa) with 2-amino-5-methylpyridine afforded the product (Vc) in 18 % yield and the product (Vc) in 9 % yield; ir(KBr) ν_{max} : 3390, 1520, and 1345 cm^{-1} ; ¹H nmr (DMSO-*d*₆/CDCl₃) δ : 2.37 (3H, s), 7.66 (1H, d, $J=5.8$ Hz), 7.94 (1H, d, $J=7.4$ Hz), 8.22 (1H, s), 8.46 (1H, d, $J=7.4$ Hz), 8.63 (1H, d, $J=5.8$ Hz), and 8.76 ppm (1H, s). Anal. Calcd for $C_{14}H_{10}N_5O_2Cl$: C, 53.25; H, 3.17; N, 22.19. Found: C, 53.41; H,

3.26; N, 22.35.

2-Amino-3-chloro-6-nitroquinoxalines (VII): Ammonium carbonate was used as the amination reagent instead of ammonia. To a solution of 2,3-dichloro-6-nitroquinoxaline (IVa, 1.22 g, 5 mmol) in DMF (50 ml) was added ammonium carbonate (30% as ammonia, 0.85 g, 15 mmol). The reaction mixture was stirred for 4 h at room temperature. After removal of DMF under reduced pressure, the crude product was recrystallized from acetone to give the product (VII) (0.52 g) in 46% yield; mp 285-287 °C (lit.,⁶ mp 279-280 °C).

2-Amino-3-dimethylamino-6-nitroquinoxaline (VIII): A mixture of compound (VII) (0.5 g, 2.2 mmol) and pyridine (0.52 g, 6.6 mmol) in DMF (20 ml) was refluxed for 12 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in CHCl₃ (200 ml). The organic phase was washed with H₂O (100 ml x 5), and dried over anhydrous Na₂SO₄. After evaporation of the solvent, the residue was chromatographed on silica gel with CHCl₃:acetone:EtOH (200:5:1 v/v) to give compound (VIa) (R_f=0.13) in 22% yield and compound (VIII) (R_f=0.25, 0.15 g, 20%) as pale brown needles after recrystallization from MeOH; mp 228-232 °C; ir (KBr) ν_{max} : 3450, 1540, and 1330 cm⁻¹; ¹H nmr (CDCl₃) δ : 3.00 (6H, s), 7.40 (2H, br s), 7.55 (1H, d, J=8.0 Hz), 8.00 (1H, d, J=8.0 Hz), and 8.30 ppm (1H, s). Anal. Calcd for C₁₀H₁₁N₅O₂: C, 51.50; H, 4.72; N, 30.04. Found: C, 51.66; H, 4.79; N, 29.81. This product (VIII) was identical with a sample obtained from 2-amino-3-chloro-6-nitroquinoxaline (VII) and dimethylamine in DMF.

Measurement of Eu(fod)₃ Induced Shift: To a solution of 2-amino-3-chloro-6-nitroquinoxaline (VII) (2 mg) in CDCl₃ (0.6 ml) was added Eu(fod)₃ (2 mg), and ¹H nmr was measured. The magnitude of the induced shift was in the order of 8-H>5-H=7-H.

Improved Syntheses of Pyrido[1',2':1.2]imidazo[4,5-b]quinoxalines: From the Reaction of 2,3-Dichloroquinoxalines and 2-Aminopyridines, A General Procedure: 2,3-Dichloroquinoxalines (IV, 1 mmol) and 2-aminopyridines (3 mmol) were homogenated on a mortar, and then heated at 220 °C for 30 min without solvent, while the vigorous evolution of HCl gas was observed. The residual solid was washed with hot water (300 ml) and then dried over anhydrous P₂O₅. The crude products were purified by column chromatography on silica gel with CHCl₃:acetone:EtOH (100:5:1 v/v). The yields of pyridoimidazoquinoxalines (VI) are presented in Table 3. In this reaction new compounds

(VIc), a mixture of 2-methyl-8-nitro- and -9-nitropyrido[1',2':1,2]imidazo[4,5-b]quinoxaline (4:6), were obtained in 63% yield; mp 319-322 °C (decomp.); $\nu_{\max}(\text{KBr})$ 1538 and 1344 cm^{-1} ; ^1H nmr (DMSO- d_6) δ : 2.45 (s, 1.8H), 2.55 (s, 1.2H), 7.75 (d, 0.4H, $J=8.7$ Hz), 7.83 (d, 0.6H, $J=6.8$ Hz), 7.87 (d, 0.4H, $J=8.7$ Hz), 7.96 (d, 0.6H, $J=8.9$ Hz), 8.42 (d, 0.6H, $J=9.9$ Hz), 8.44 (d, 0.4H, 9.2 Hz), 8.48 (dd, 0.4H, $J=2.2$ and 9.2 Hz), 8.57 (dd, 0.6H, $J=2.8$ and 9.9 Hz), 8.90-8.93 (m, 0.4H), 9.0-9.03 (m, 0.6H), 9.01 (d, 0.6H, $J=2.2$ Hz), and 9.06 ppm (d, 0.4H, $J=2.8$ Hz). Anal. Calcd for $\text{C}_{14}\text{H}_9\text{N}_5\text{O}_2 \cdot 0.2\text{H}_2\text{O}$: C, 59.57; H, 3.32; N, 24.77. Found: C, 59.77; H, 3.35; N, 24.63.

From the Reaction of 2-Amino-3-chloro-6-nitroquinoxaline and Pyridines; A general Procedure: A solution of compound (VII) (0.23 g, 1 mmol) in pyridines (10 ml) was refluxed for 12 h. After evaporation of the solvent, the residual solid was washed well with hot water (300 ml) and dried over anhydrous P_2O_5 . The residue was chromatographed on silica gel with CHCl_3 :acetone:EtOH (100:5:1 v/v) to give the pure products (VI). The yields of pyridoimidazoquinoxalines (VI) are presented in Table 4.

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8. Attempts to purify the intermediates (IId) and (IIe) by column chromatography or recrystallization were unsuccessful due to the partial ring closure to pyridoimidazopyrazines even at room temperature.

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