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Reduction of 2,2,2-Trichloroethylamines with Lithium Aluminum Hydride

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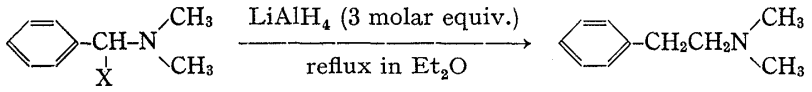
It has been found that the lithium aluminum hydride reduction of 2,2,2-trichloroethylamines occurs to give amines with rearranged carbon skeletons or aziridines, depending on the precise substrate structure.

Keywords——2,2,2-trichloroethylamines; lithium aluminum hydride; rearrangement; aziridines; ring expansion

As a part of our continuing interest in the chemistry of 2,2,2-trichloroethylamines,[1] we report in the present paper details of the lithium aluminum hydride reduction of these compounds. The reaction is of interest in that it occurs with rearrangement of the carbon skeleton to give amines with rearranged structures or aziridines.

The lithium aluminum hydride reduction was initiated with representative 2-chlorinated amines *i.e.*, 2,2,2-trichloro- (**1a**), 2,2-dichloro- (**2a**) and 2-chloro-N,N-dimethyl-1-phenylethylamine (**3**). Each of the three substrates gave the same product (**4a**) with rearrangement of the carbon skeleton, as shown in Table I.

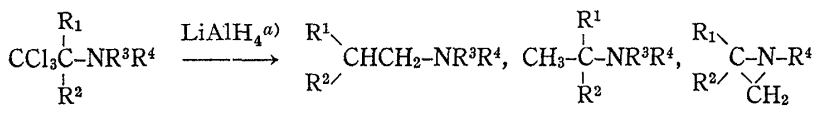
TABLE I.



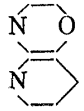
1a, 2a, 3 **4a**

	Reaction time (hr)	Yield (%)
1a X=CCl_3	30	50
2a X=$CHCl_2$	24	59
3 X=CH_2Cl	3	83

TABLE II.



1b—q **4b—m** **5a—b** **6a—d**

Subst.	R^1	R^2	NR^3R^4	Reaction time (hr)	Product (Yield[b)] %)
1b	$-(CH_2)_4-$			2	**4b**(75)
1c	$-(CH_2)_4-$			3	**4c**(51)
1d	$(CH_3)_2CH$	H		20	**4d**(26), **5a**(60)
1e	$(CH_3)_2CH$	H		48	**4e**(45), **5b**(29)
1f	C_6H_5	H		300[c)]	**4f**(54)
1g	C_6H_5	H		46	**4g**(63)

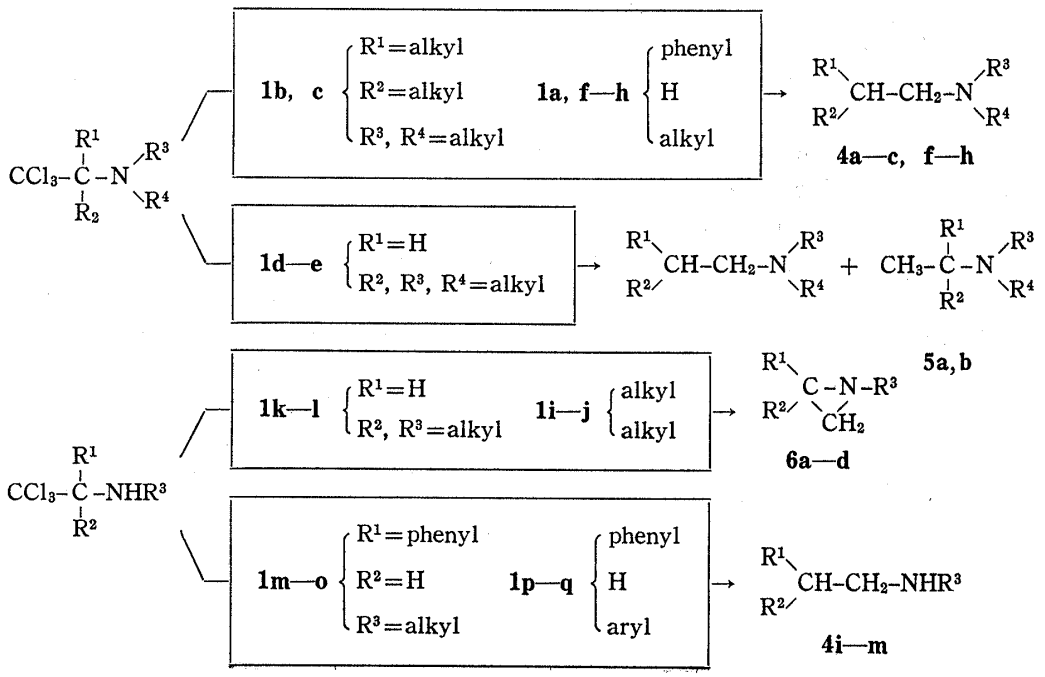
Subst.	R^1	R^2	NR^3R^4	Reaction time (hr)	Product (Yield[b] %)
1h	C_6H_5	H	$N<^{CH_3}_{CH_2C_6H_5}$	150	**4h** (36)
1i	$-(CH_2)_5-$		$NHCH(CH_3)_2$	10	**6a** (65)
1j	$-(CH_2)_5-$		NH-⟨⟩	8	**6b** (67)
1k	$(CH_3)_2CH$	H	$NHCH(CH_3)_2$	20	**6c** (71)
1l	$(CH_3)_2CH$	H	NH-⟨⟩	20	**6d** (70)
1m	C_6H_5	H	$NHCH(CH_3)_2$	20	**4i** (67)
1n	C_6H_5	H	NH-⟨⟩	30	**4j** (74)
1o	C_6H_5	H	$NHCH_3$	10	**4k** (71)
1p	C_6H_5	H	NH-⟨⟩-OCH_3	20	**4l** (71)
1q	C_6H_5	H	NH-⟨⟩-CH_3	20	**4m** (55)

a) Conditions: reflux in ether. Molar ratio: $LiAlH_4$/Subst.=3.
b) Based on the product actually isolated.
c) In this run 6 molar equivalents of $LiAlH_4$ was used.

Compound **1a** was prepared by the reaction between N,N,N′,N′-tetramethylbenzylidenediamine and trichloroacetic acid, and **2a** was prepared by the reaction of **1a** with lithium aluminum hydride reduction, as described later. A preparation of **3** has been reported,[2] but it is rather laborious.

The lithium aluminum hydride reduction of 2,2,2-trichloroethylamines is of great potential interest, because many types of compounds are readily obtainable by the reactions of enamines, N,N′-alkylidenediamines and Schiff bases with trichloroacetic acid.

The lithium aluminum hydride reduction of 2,2,2-trichloroethylamines, **1b**—**q**, of various structures was examined under reflux in ether, with the results shown in Table II. Three classes of reactions occurred to give amines of rearranged (**4a**—**m**) and non-rearranged (**5a, b**) structures and aziridines (**6a**—**c**). The following general sequences can be written. The method is certainly useful for syntheses of these amines, the nature of the product being controlled by the nature of R^1, R^2, R^3 and R^4 of the amine substrates.



The rearranged and non-rearranged amines, **4a**—**m** and **5a**, **b**, were identified by ^{1}H-nuclear magnetic resonance (NMR) spectroscopy (see Table IV). The aziridines, **6a**—**d**, were identified by ^{13}C-NMR spectroscopy (see Table V); the chemical shifts of C^2 and C^3 at high magnetic field provided strong evidence for the aziridine structures.

In the experiments in Table II, the NMR spectra of the materials produced at earlier reaction times were checked by NMR measurement. 2,2-Dichloroethylamines were detected as intermediates in the runs with the substrates **1a** and **1d**—**o** (the methine proton of the dichloromethyl moiety appeared as a doublet in the cases of R^1=H or as a singlet in the cases of R^1, R^2=alkyl at 5.8—6.2 ppm in the NMR spectra). Actually, the reactions of **1a**, **1d**, **1f**, **11** and **1m** for shorter times, with less lithium aluminum hydride, gave the corresponding 2,2-dichloroethylamines in considerable yields (see Table III). Data for the assignment of these products are listed in Table VI.

Table III.

$$\underset{\text{(1a,d,f,l,m)}}{CCl_3CH(R^1)\text{-}NR^2R^3} \xrightarrow{LiAlH_4{}^{a)}} \underset{\text{(2a—e)}}{CHCl_2CH(R^1)\text{-}NR^2R^3}$$

Subst.	R^1	NR^2R^3	Molar ratio ($LiAlH_4$/Subst.)	Reaction time (hr)	Product(Yield[b]%)
1d	$(CH_3)_2CH$		1.5	6	**2b**(46)
1a	C_6H_5	$N(CH_3)_2$	3	4	**2a**(58)
1f	C_6H_5		3	3.5	**2c**(54)
1l	$(CH_3)_2CH$		1.5	1.5	**2d**(41)
1m	C_6H_5	$NHCH(CH_3)_2$	3	1	**2e**(56)

a) Conditions: reflux in ether.
b) Based on the product actually isolated.

The mechanism of the lithium aluminum hydride reduction may be as shown in Chart 1 and 2. The rearrangements of the substrates, **1m**—**q**, possessing secondary amine moieties may involve aziridine intermediates (Chart 1), and those of **1a**—**h**, possessing tertiary amine moieties, may involve aziridinium salt intermediates (Chart 2). This view is strengthened by the actual formation of aziridines from **1i**—**l**. The aziridines or aziridinium may undergo attack of hydride with ring opening to give the amine products. The attack of hydride is selective toward C^2 or C^3 of the aziridine rings, whichever is more electron-deficient. When C^2 is attacked by hydride, nonrearranged products are formed (see Chart 2), as illustrated by some of the products from **1d** and **1e**. A 1-phenyl-substituent renders C^3 electron-deficient. A 2-chloro-substituent makes C^2 electron-deficient, but the effect of the degree of hydrogen substitution of the original 2-chloro-substituents on the attack of hydride is obscure, and may depend upon the substrate structure.

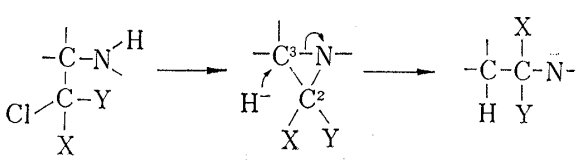
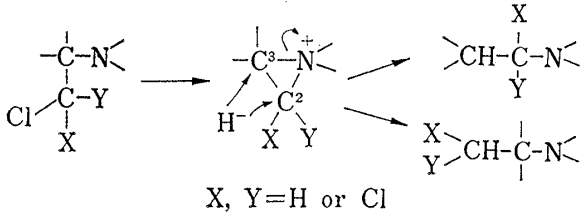


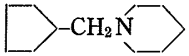
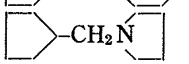
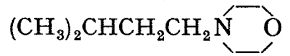
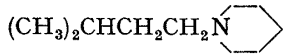
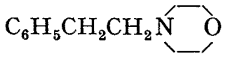
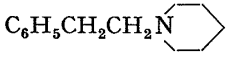
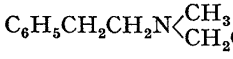
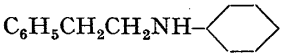
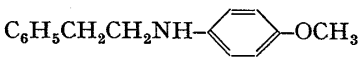
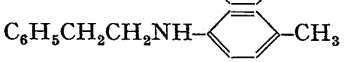
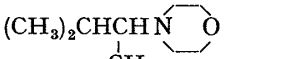
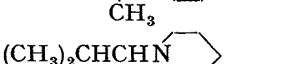
Chart 1



X, Y=H or Cl

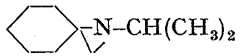
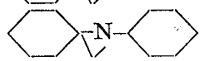
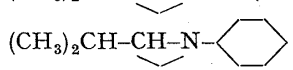
Chart 2

Table IV. Amines Obtained by the Lithium Aluminum Hydride Reduction

Compd. No.		bp(°C) (mmHg)	NMR($CDCl_3$) δ(ppm)[a]	Formula	Analysis(%) Found (Calcd) C	H	N
4a	$C_6H_5CH_2CH_2N(CH_3)_2$	87—88 (15)	2.98—2.39(4H, m, $C_6H_5C\underline{H}_2C\underline{H}_2$–)	$C_{10}H_{15}N$	80.31 (80.48	10.10 10.13	9.03 9.39)
4b		108—109 (20)	2.45—2.15 (6H, m, >CHC$\underline{H}_2$–N< and $N(CH_2)_2$)	$C_{11}H_{21}N$	78.47 (78.97	12.61 12.65	8.35) 8.37)
4c		119—121 (65)	2.63—2.23 (6H, m, >CHC$\underline{H}_2$–N< and $N(CH_2)_2$)	$C_{10}H_{19}N$	78.52 (78.37	12.52 12.50	9.15 9.14)
4d		78 (15)	2.35 (2H, t, J=7.0 Hz, $-CH_2N<$) 1.39 (2H, t, J=7.0 Hz, $(CH_3)_2CHC\underline{H}_2$–)	$C_9H_{19}NO$	68.55 (68.74	12.09 12.18	8.85 8.91)
4e		61 (20)	2.50—2.12 (6H, m, >CHC$\underline{H}_2$C$\underline{H}_2$– and $N(CH_2)_2$) 1.80—1.10 (9H, m, $-(CH_2)_3$– and $(CH_3)_2C\underline{H}C\underline{H}_2CH_2$–)	$C_{10}H_{21}N$	76.77 (77.35	13.38 13.63	8.53 9.02)
4f		108—110 (3)	3.02—2.35 (4H, m, $C_6H_5C\underline{H}_2C\underline{H}_2$–)	$C_{12}H_{17}NO$	75.40 (75.35	8.95 8.96	7.10 7.32)
4g		135—137 (15)	3.01—2.35 (4H, m, $C_6H_5C\underline{H}_2C\underline{H}_2$–)	$C_{13}H_{19}N$	81.94 (82.48	10.04 10.12	7.40 7.40)
4h		116—118 (0.07)	3.03—2.36 (4H, m, $C_6H_5C\underline{H}_2C\underline{H}_2$–)	$C_{16}H_{19}N$	85.31 (85.28	8.37 8.50	5.72 6.22)
4i	$C_6H_5CH_2CH_2NHCH(CH_3)_2$	97—99 (6)	2.81 (4H, s, $C_6H_5C\underline{H}_2C\underline{H}_2$–)	$C_{11}H_{17}N$	80.92 (81.24	10.50 10.57	8.58 8.34)
4j		120—122 (3)	2.98—2.80 (4H, m, $C_6H_5C\underline{H}_2C\underline{H}_2$–)	$C_{14}H_{21}N$	82.55 (82.70	10.35 10.41	6.87 6.89)
4k	$C_6H_5CH_2CH_2NHCH_3$	75—76 (10)	2.79 (4H, s, $C_6H_5C\underline{H}_2C\underline{H}_2$–)	$C_9H_{13}N$	79.76 (79.95	9.66 9.69	10.18 10.36)
4l		138—140 (0.1)	3.28 (2H, t, J=6.0 Hz, $-CH_2N<$) 2.81 (2H, t, J=6.0 Hz, $C_6H_5C\underline{H}_2$–)	$C_{15}H_{17}NO$	79.46 (79.26	7.67 7.54	5.96 6.16)
4m		118—120 (0.1)	3.32 (2H, t, J=6.0 Hz, $-CH_2N<$) 2.82 (2H, t, J=6.0 Hz, $C_6H_5C\underline{H}_2$–)	$C_{15}H_{17}N$	85.30 (85.26	8.14 8.11	6.46 6.63)
5a		82 (14)	2.31—1.81 (1H, m, >CHN<) 1.07—0.78 (9H, m, $(C\underline{H}_3)_2CH$– and $>NCHC\underline{H}_3$)	$C_9H_{19}NO$	68.55 (68.74	12.04 12.18	8.83 8.91)
5b		84—85 (37)	2.22—1.79 (1H, m, >CHN–) 1.06—0.75 (9H, m, $(CH_3)_2CH$– and $>NCHCH_3$)	$C_{10}H_{21}N$	77.38 (77.35	13.78 13.63	9.08 9.02)

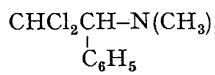
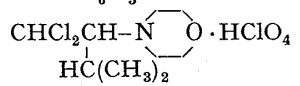
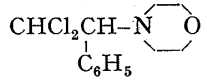
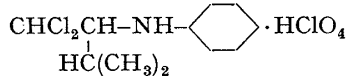
a) NMR spectra were taken with a Hitachi R-24 spectrometer (at 60 MHz), with tetramethylsilane as an internal standard.

Table V. Aziridines

Compd. No.		bp(°C) (mmHg)	^{13}C-NMR($CDCl_3$)δ(ppm)[a] $>C^2—N—C^3<$ C^2	C^3	MS m/e[b]	Formula	Analysis(%) Found (Calcd) C	H	N
5a		96—97 (48)	42.85	38.62	153 (M^+)	$C_{10}H_{19}N$	78.12 (78.37	12.44 12.50	8.97 9.14)
5b		117—118 (8)	42.32	38.06	193 (M^+)	$C_{13}H_{23}N$	80.22 (80.76	11.96 11.99	7.15 7.24)
5c	$(CH_3)_2CH-CH-N-CH(CH_3)_2$	125—127	46.30	32.46	127 (M^+)	$C_8H_{17}N$	75.59 (75.46	13.57 13.47	10.73 11.01)
5d		104—105 (32)	45.69	32.54	167 (M^+)	$C_{11}H_{21}N$	78.54 (78.97	12.65 12.65	8.27 8.37)

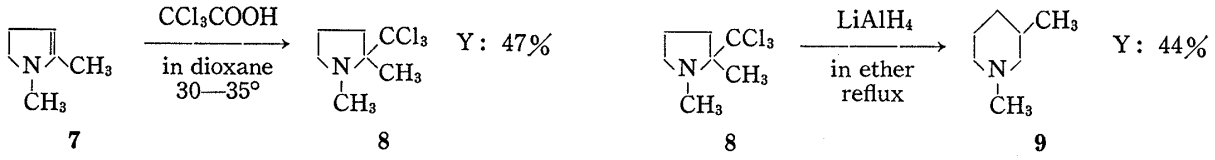
a) ^{13}C-NMR spectra were taken with a JEOL JNM-PFT 60 spectrometer (at 15.04 MHz), with tetramethylsilane as an internal standard.
b) Mass spectra were taken with a JEOL JMSD-100 spectrometer.

Table VI. 2,2-Dichloroethylamines

Compd. No.		bp(°C) (mmHg)	mp(°C)[a] (Recryst. Solv.)	NMR δ(ppm)[b] $-CHCl_2$	Formula	Analysis(%) Found (Calcd) C	H	N
2a			38 (petr.ether)	6.13 (1H, d, J=7.0 Hz) ($CDCl_3$)	$C_{10}H_{13}Cl_2N$	55.28 (55.06	6.02 6.01	6.41 6.42)
2b		(free base) 78 (0.04)	146—148 (MeOH)	6.82 (1H, d, J=2.0 Hz) (DMSO-d_6)	$C_9H_{18}Cl_3NO_5$	32.84 (33.10	5.58 5.56	4.19 4.29)
2c			50—52 (petr.ether)	6.09 (1H, d, J=6.0 Hz) ($CDCl_3$)	$C_{12}H_{15}Cl_2NO$	55.49 (55.40	5.81 5.81	5.51 5.38)
2d		(free base) 82 (0.07)	157—160 (MeOH)	6.73 (1H, d, J=3.0 Hz) (DMSO-d_6)	$C_{11}H_{22}Cl_3NO$	39.46 (39.01	6.56 6.55	4.21 4.14)
2e	$CHCl_2CH-NH-CH(CH_3)_2$ C_6H_5	106—108 (5)		5.74 (1H, d, J=5.0 Hz) ($CDCl_3$)	$C_{11}H_{15}Cl_2N$	57.10 (56.91	6.36 6.51	6.01 6.03)

a) Melting points of the crystallized products are uncorrected.
b) NMR spectra were taken with a Hitachi R-24 spectrometer (at 60 MHz), with tetramethylsilane as an internal standard.

In view of the synthetic significance of the reductive rearrangement, the ring expansion of a pyrroline derivative was examined as a potentially interesting application.



7 8 8 9

The reaction of 1,2-dimethyl-4,5-dihydropyrrole (**7**) with trichloroacetic acid gave 1,2-dimethyl-2-trichloromethylpyrrolidine (**8**), which underwent reductive rearrangement upon treatment with lithium aluminum hydride to give a six-membered 1,3-dimethyl-piperidine (**9**). Further examples of the ring expansion are under investigation.

Experimental

The reaction periods and yields in the lithium aluminum hydride reduction are recorded in Tables I, II and III. Physical, spectral and analytical data for the reaction products are recorded in Tables IV, V and VI.

2,2,2-Trichloroethylamines (1a—q)——The materials used for the lithium aluminum hydride reduction were prepared by the reactions of Schiff bases, N,N′-alkylidenediamines and enamines with trichloroacetic acid according to the reported procedures.[1,3-7] Only **1i** has not been described previously, and its physical and analytical data are described below. N-Isopropyl-1-trichloromethylcyclohexylamine Hydrochloride (**1i**): mp 109—111°. *Anal.* Calcd for $C_{10}H_{19}Cl_4N$: C, 40.70; H, 6.49; N, 4.75. Found: C, 40.67; H, 6.38; N, 4.86.

Reactions of 1a—q Leading to 4a—m, 5a—b and 6a—d (see Table II)——General Procedure: A cooled solution of 0.033 mol of a 2,2,2-trichloroethylamine (**1a—q**) in 70 ml of dry ether was treated with 0.1 mol (3.8 g) of $LiAlH_4$ in small portions with stirring. After the addition, the reaction mixture was refluxed with stirring. Aqueous NaCl was then added to the mixture to decompose excess reagent. The separated ethereal solution was dried over $MgSO_4$ and the solvent was removed by evaporation. In the runs with **1a—c** and **1f—q**, the products, **4a—c** and **4f—m**, were obtained by distillation of the resulting oily residue. In the runs with **1d** and **1e**, the resulting residue was chromatographed through Al_2O_3 with benzene as an eluent to give the products, **4d—e** and **5a—b**.

Reactions of 2a and 3 Leading to 4a (see Table I)——The reaction mixture were worked up by the procedures described for the above experiments with **1a—q**.

Reactions of 1a, 1d, 1f and 1l—m Leading to 2a—e (see Table III)——General Procedure: A cooled solution of 0.033 mol of a 2,2,2-trichloroethylamine (**1a, 1d, 1f** and **1l—m**) in 70 ml of dry ether was treated with $LiAlH_4$ (the amount of which is listed in Table III) in small portions with stirring. The reaction mixture was then refluxed with stirring. The reaction mixture was worked up by the procedure described for the experiments with **1a—q**. In the runs with **1a** and **1f**, the products, **2a** and **2c**, were obtained by recrystallization of the resulting solid residues. In the runs with **1d, 1l** and **1m**, the products, **2b, 2d** and **2e**, were obtained by distillation of the resulting residues under reduced pressure. Compounds **2b** and **2c** were also identified as their $HClO_4$ salts.

1,2-Dimethyl-2-trichloromethylpyrrolidine (8)——A solution of 11.7 g (0.072 mol) of CCl_3COOH in 20 ml of dry dioxane was added dropwise to a solution of 5.8 g (0.06 mol) of 1,2-dimethyl-4,5-dihydropyrrole (**7**) in 40 ml of dry dioxane with stirring at 30—35°. After the addition, the reaction mixture was heated at 30—35° with stirring for 3.5 hr until evolution of CO_2 ceased. The solvent was removed by evaporation under reduced pressure and the residue was dissolved in benzene. The benzene solution was washed with aqueous $KHCO_3$ and dried over $MgSO_4$. Removal of the benzene gave an oily residue which was distilled under reduced pressure to give the product (**8**); yield 6.1 g (47%), bp 80—82°/10 mmHg, mp 55—57°. NMR ppm ($CDCl_3$): 3.50 (2H, m, $>NCH_2-$), 2.56 (3H, s, NCH_3), 2.38—1.98 (2H, m, $-CH_2CH_2N<$), 1.96—1.59 (2H, m, $-CH_2-CCH_3$), 1.50 (3H, s, $>CCH_3$). *Anal.* Calcd for $C_7H_{12}Cl_3N$: C, 38.83; H, 5.59; N, 6.47. Found: C, 38.84; H, 5.54; N, 6.40.

1,3-Dimethylpiperidine (9)——A cooled solution of 5.7 g (0.026 mol) of **8** in 60 ml of dry ether was treated with 3.0 g (0.08 mol) of $LiAlH_4$ in small portions with stirring. After the addition, the reaction mixture was refluxed with stirring for a further 5 hr. Aqueous NaCl was then added to the mixture to decompose excess reagent. The separated ethereal solution was dried over $MgSO_4$ and the solvent was removed by evaporation. The resulting residue was distilled to give **9**; yield 1.3 g (44%). This product was identified as 1,3-dimethylpiperidine, bp 123—125°, by comparison of its infrared (IR) and NMR spectra with those of an authentic specimen prepared by another route.

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