N-Halogen Compounds of Cyanamide Derivatives. I[1] Rearrangement of *N*-Alkylhaloamidines

Toshio FUCHIGAMI, Eiichi ICHIKAWA, and Keijiro ODO

Faculty of Engineering, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152

(Received October 13, 1972)

The reactions of *N*-chloroamidines with various dehydrochlorinating reagents were studied. *N*-Alkyl-*N'*-chloroamidines were treated with sodium alkoxide, sodium hydroxide, and silver oxide to form *O*-alkylisoureas, ureas, and carbodiimides, respectively. However, *N*-chloro-*N',N'*-dialkylamidines did not afford corresponding products. The mechanisms for the rearrangements are discussed.

N-Haloamidines are unique in reactivity and useful as transient intermediates. A few reports on *N*-haloamidines have appeared, among which the synthesis of thiadiazoles by Goerdeler[2] and that of benzimidazoles by Grenda[3] are notable. However, no systematic examination of *N*-haloamidines has been made.

The present investigation was undertaken to prepare *N*-alkyl-*N'*-chlorobenzamidines and study their reactivity. We have attempted to prepare various *N*-chloroamidines and to reveal their chemical behavior with various kinds of dehydrochlorinating reagents and the relationship between their structure and reactivity.

Results and Discussion

Preparation of Amidines. *N*-Methyl-*N'*-phenylbenzamidine[4] was prepared from *N*-phenylbenzimidoylchloride and methylamine. The other amidine hydrochlorides were prepared from the corresponding iminoethers and amines by Pinner's method.[5]

Chlorination of Amidines. *N*-Chloroamidines were prepared from amidine hydrochlorides and sodium hypochlorite in water at −5—5 °C. Most of the *N*-chloroamidines were solids with low melting points, their active chlorine contents determined iodometrically being in good agreement with the corresponding calculated values. No effects of substituents were observed on the yield in chlorination except for *N,N*-pentamethylenebenzamidine.

Structure of N-*Alkyl*-N'-*chloroamidines.* The most possible structure of *N*-chloroamidine is (**K**) in consideration of the kinetic study of *N*-chlorination,[6] NMR spectra of *N*-haloamidines[7] and substitution reactions with thiocyanate or cyanide ion.[2,8]

$$\mathrm{R{-}\overset{\overset{\mathrm{NCl}}{\|}}{C}{-}NHR'} \qquad (\mathbf{K})$$

Reaction of N-*Chloroamidines with Alkaline Reagents. Reaction of* N-*Chloroamidines with Sodium Alkoxides*: Methoxide was mainly employed but other alkoxides such as ethoxide, isopropoxide, and *t*-butoxide were also tested in certain cases.

When *N*-alkylhaloamidine (**2**∼**5**) was treated with sodium alkoxide in alcohol at 60 °C (under reflux in case of sodium methoxide in methanol), an oily material was obtained. A larger part of the material was identified as a mixture of *N*-alkyl-*N'*-phenyl-*O*-alkylisourea (**Al**∼**7**) (main product) and benzoate (**B**). Products (**A6,7**) were isolated as their picrates but the others (**Al**∼**5**) were identified by means of preparative gas chromatography since they coud not be separated by distillation *in vacuo*. The yields of **A** and **B** were determined using glc. **5** gave a small amount of a by-product, cyaphenine (**C**).

An active chlorine did not disappear even when **7** was treated with such a strong base as sodium *t*-butoxide. The Neber rearrangement[9] was expected in the treatment of **10** which has an α-methylene group with sodium *t*-butoxide, but no product due to such a rearrangement was formed.

Structures of new compound (**Al**∼**7**) were established by the following examinations.

a) Acid hydrolysis: **Al**∼**7** were converted into the corresponding ureas.

b) Elemental analysis of their free bases or picrates.

c) Comparison of the IR spectra and glc retention times with those of authentic samples prepared by the reactions of carbodiimides and alcohols.

The boiling points of authentic samples (**Al**∼**5**) are shown in Table 4.

Reaction of N-*Chloroamidines with Sodium Hydroxide in a* 50% *Aqueous Methanolic Solution*: An aqueous solution of amidine hydrochloride was treated with sodium hypochlorite to form *N*-chloroamidine, which was refluxed with sodium hydroxide in aqueous methanol, yielding colorless crystalline solid and an oily material. The former was identified as *N*-alkyl-*N'*-arylurea (**D**) by comparison of its melting point and IR spectrum with those of the authentic sample. A larger part of the latter was identified as *N*-alkyl-*N'*-phenyl-*O*-alkylisourea (**A**) on the basis of IR spectrum and glc retention time.

In an aqueous methanolic solution, most *N*-chloroamidines gave **A**, while in the absence of methanol, they afforded **D** instead.

1 gave no **D** but sodium phenyl cyanamide (**F**), which was converted further into phenylurea by acid hydrolysis.

In the case of *N,N*-disubstituted amidines (**7**—**10**), no rearrangement took place and the products of hydrolysis (**E**) were obtained.

1) Part LXXXIV of "Studies of Cyanamide Derivatives"
2) J. Goerdeler, *Chem. Ber.*, **87**, 57 (1954).
3) V. J. Grenda, R. E. Jones, G. Gale, and M. Sletzinger, *J. Org. Chem.*, **30**, 259 (1965).
4) C. Gerhart, *Ann.*, **108**, 219 (1858).
5) A. Pinner, "Organic Syntheses," Coll. I, p. 5 (1956).
6) E. W. C. M. Thomm and M. Wayman, *Can. J. Chem.*, **47**, 3289 (1969).
7) A. Heesing and G. Maleck, *Tetrahedron Lett.*, 1967, 3851.
8) J. Goerdeler and D. Loevenich, *Chem. Ber.*, **86**, 890 (1953).
9) C. O'Bren, *Chem. Rev.*, **64**, 81 (1964).

Table 1. Preparation of amidines

Amidine	Yield %	Mp °C	Anal (Calcd) (%) C	H	N
Ph–C(=NH·HCl)–NH_2	89	78— 82 (74— 82)[5]			
Ph–C(=NH·HCl)–NHMe	100	225 (223)[13]			
Ph–C(=NH·HCl)–NHEt	81	162—164 (161)[10]			
Ph–C(=NH·HCl)–NH*iso*Pr	92	232—233	60.34 (60.28)	7.72 (7.59)	14.09 (14.06)
Ph–C(=NH·HCl)–NHBzl	89	230—232 (222—225)[11]			
Ph–C(=NH·HCl)–NMe_2	100	258—260 (255—256)[12]			
Ph–C(=NH·HCl)–N⟨ ⟩	95	215 (204—207)[9]			
p-$CH_3C_6H_4$–C(=NH·HCl)–NHMe	88	209—211	58.61 (58.54)	7.11 (7.10)	15.13 (15.17)
$PhCH_2$–C(=NH·HCl)–NMe_2	100	213—215	60.23 (60.45)	7.86 (7.61)	14.12 (14.10)
Ph–C(=N–Ph)–NHMe	93	132—133 (134)[4]			

Table 2. Preparation of *N*-Chloroamidines

No	*N*-Chloroamidine	Yield %	Mp °C	Appearance	Cl Anal[a] (Calcd%)
1	Ph–C(=NCl)–NH_2	92	74	colorless needles	22.84 (22.93)
2	Ph–C(=NCl)–NHMe	91	69.5—70	colorless needles	21.01 (21.02)
3	Ph–C(=NCl)–NHEt	96	—	light yellowish liquid	19.63 (19.41)
4	Ph–C(=NCl)–NH*iso*Pr	87	49—49.5	colorless needles	17.94 (18.03)
5	Ph–C(=NCl)–NHBzl	70	54.5—55	colorless needles	14.24 (14.49)
6	*p*-$CH_3C_6H_4$–C(=NCl)–NHMe	85	98—99	colorless needles	19.30 (19.41)
7	Ph–C(=NCl)–NMe_2	87	—	light yellowlish liquid	18.86 (19.41)
8	Ph–C(=NCl)–N⟨ ⟩	32	83	colorless needles	15.92 (15.92)
9	Ph–C(=N–Ph)–NClMe	90	61—61.5	yellowish plates	14.05 (14.49)
10	$PhCH_2$–C(=NCl)–NMe_2	87	61	colorless granular form	17.97 (18.03)

The solids were recrystallized from ether–petroleum ether.
a) The active chlorine contents were iodometrically determined.

10) W. Lossen and M. Kobbert, *Ann.*, **265**, 158 (1891).
11) A. W. Hofmann and S. Gabriel, *Ber.*, **25**, 1585 (1892).
12) F. L. Pyman, *J. Chem. Soc.*, **123**, 3370 (1923).

Table 3. Reaction of *N*-chloroamidines with sodium alkoxide

$$R^1\text{-}\underset{\underset{NCl}{\|}}{C}\text{-}NR^2R^3 \xrightarrow[\text{in } R^4OH]{R^4ONa} R^1N{=}\underset{\underset{OR^4}{|}}{C}\text{-}NR^2R^3 \;(\mathbf{A}) + R^1COOR^4 \;(\mathbf{B})$$

No	*N*-Chloroamidine R^1	R^2	R^3	Alkoxide R^4	R. Time (hr)	Products (%)[a] (A)	(B)	(C)[b]
2	Ph	H	Me	Me	3.0	46	15	—
				Et	0.7	45	22	—
				iso-Pr	0.2	44	5	—
3	Ph	H	Et	Me	1.0	41	22	—
4	Ph	H	*iso*-Pr	Me	1.5	18	29	—
5	Ph	H	Bzl	Me	2.5	33	3	1
				Et	1.5	47	4	1
7	Ph	Me	Me	Me	30.0[c]	—	—	—
				Et	11.0[c]	—	—	—
10	$PhCH_2$	Me	Me	*t*-Bu	2.0[d]	—	—	—

a) gas chromatography column: Silicone H. V., column temp.: 140°C, carrier gas: H_2 20 ml/min.
b) 2,4,6-triphenyl-*s*-triazine. c) Active chlorine did not disappear. d) The product could not be isolated.

Table 4. Analytical data of *O*-alkylisourea (**A**)

$$R^1N{=}\underset{\underset{OR^4}{|}}{C}\text{-}NR^2R^3 \quad (R^1{=}Ph) \quad (\mathbf{A}) \quad (R^2{=}H)$$

	O-Alkylisourea R^3	R^4	Free base Bp[a] (°C/mmHg)	Anal (Calcd) (%) C	H	N	Picrate Mp (°C)	Anal (Calcd) (%) C	H	N
A1	Me	Me	135—196/31	65.89 (65.83)	7.52 (7.37)	17.01 (17.06)	—	—	—	—
A2	Me	Et	110/32	67.31 (67.39)	7.81 (7.92)	15.60 (15.72)	124—125	47.27 (47.18)	4.30 (4.21)	17.26 (17.19)
A3	Me	*iso*-Pr	110—120/19	68.48 (68.72)	8.39 (8.39)	14.60 (14.52)	142—143 (decmp)	48.54 (48.46)	4.37 (4.55)	16.61 (16.62)
A4	Et	Me	87—88/23	66.66 (67.39)	8.10 (7.92)	15.84 (15.72)	—	—	—	—
A5	*iso*-Pr	Me	57—60/ 2	68.89 (68.72)	8.47 (8.39)	14.12 (14.52)	—	—	—	—
A6	Bzl	Me	—	—	—	—	148—149	53.76 (53.73)	4.12 (4.18)	14.90 (14.92)
A7	Bzl	Et	—	—	—	—	88— 92	52.70 (52.73)	4.55 (4.63)	13.93 (13.97)[b]

a) Boiling point of authentic sample. b) Monohydrate.

Table 5. Reaction of *N*-chloroamidines with sodium hydroxide (part 1)

$$R^1\text{-}\underset{\underset{NCl}{\|}}{C}\text{-}NHR^2 \xrightarrow[\text{in 50\% aq. MeOH}]{NaOH} R^1N{=}\underset{\underset{OMe}{|}}{C}\text{-}NHR^2 \;(\mathbf{A}) + R^1COOMe \;(\mathbf{B}) + R^1NHC(=O)NHR^2 \;(\mathbf{D})$$

No	*N*-Chloroamidine (R^1)	(R^2)	Solvent	R. Time (hr)	Products (Yield %) (A)	(B)	(D)	(E)[a]	(F)[b]
1	Ph	H	50% aq. MeOH	10.0	—	—	—	65	9[c]
2	Ph	Me	50% aq. MeOH	2.5	3	—	23	—	—
			50% aq. Dioxane	10.0	—	—	24	—	—
3	Ph	Et	50% aq. MeOH	2.5	35	7	—	—	—
			H_2O	4.0	—	—	31	—	—
4	Ph	*iso*-Pr	50% aq. MeOH	3.0	18	6	—	—	—
5	Ph	Bzl	50% aq. MeOH	6.0	3	3	10	4	—
6	*p*-$CH_3C_6H_4$	Me	H_2O	12.0	—	—	17	—	—

a) R^1CONH_2. b) $R^1\underset{|}{\overset{Na}{N}}\text{-}C{\equiv}N$. c) Yield of phenylurea.

Table 6. Reaction of *N*-chloroamidines with sodium hydroxide (Part 2)

N-Chloroamidine $\xrightarrow[\text{in 50 \%aq. MeOH}]{\text{NaOH}}$ R^1CONH_2 (**E**)

N-Chloroamidine No	(R^1)	R. Time (hr.)	Product (**E**) (yield %)
7	Ph	3.0	31
8	Ph	6.0	42
9	Ph	3.0	—[a]
10	Bzl	2.0	19

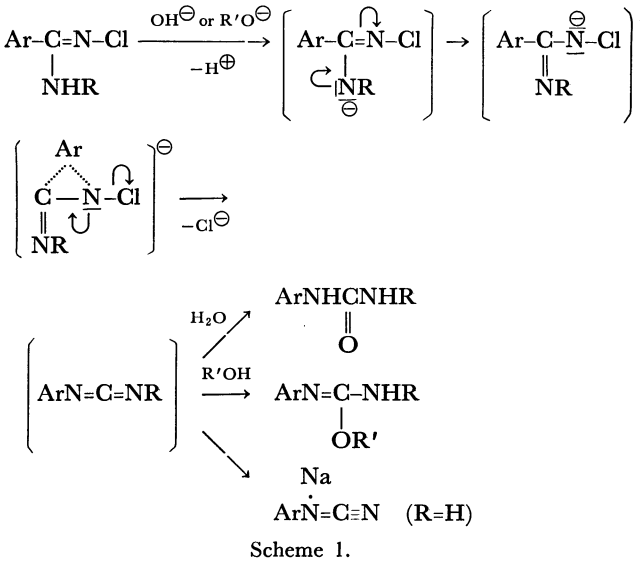
a) The structure has not been established yet. The same product can be obtained from alkaline hydrolysis of *N*-methyl-*N'*-phenylbenzamidine.

Mechanisms of Rearrangement. The basicity of alkoxide ions was found to have large effects on the rates of dehydrochlorination. The reactivity of alkoxide ions was found to be in the order *iso*-$PrO^{\ominus}$> $EtO^{\ominus}$> $MeO^{\ominus}$.

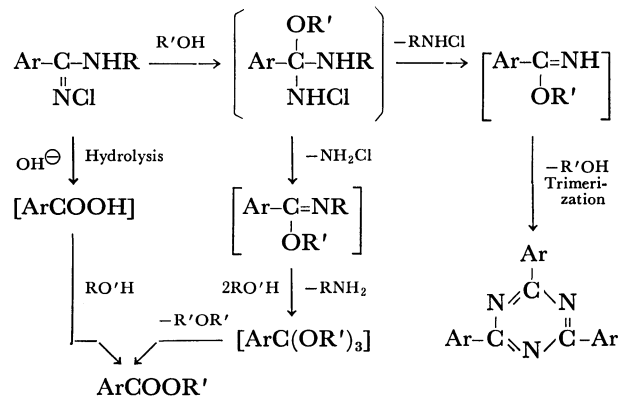
In the reactions of *N*-chloroamidines having no hydrogen on the nitrogen atom with sodium alkoxide in alcohol or sodium hydroxide in an aqueous alcohol, the active chlorine did not disappear and no rearrangement took place. (Tables 3 and 6).

This rearrangement may be initiated by removal of a proton from the NH group with an alkoxide ion or hydroxide ion. The loss of a chloride ion from the resulting anion and the migration of the aryl group to a nitrogen atom probably take place simultaneously to form a carbodiimide as an intermediate. The carbodiimide thus produced may react with water or alcohol to give urea or *O*-alkylisourea (Scheme 1), and by-products esters of benzoic acid and cyaphenine may be formed (Scheme 2).

Reaction of N-*Chloroamidines with Silver Oxide.* *N*-Alkyl-*N'*-chloroamidines were mixed with silver oxide in ligroin and then refluxed. This gave rise to rearrangement, giving carbodiimides (**G**). Their infrared spectra showed a characteristic carbodiimide absorption at 2150 cm^{-1} and agreed completely with those of authentic samples. When these carbodiimides were refluxed in dilute hydrochloric acid, the corresponding ureas were obtained.



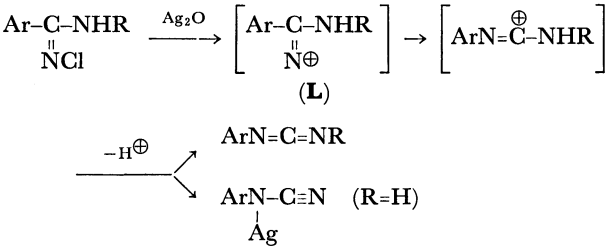
Scheme 1.



Scheme 2.

N-Methyl-*N'*-chloroamidine (**2**) gave no carbodiimide at all, but *N*-chlorobenzamidine (**1**) gave silver phenylcyanamide, which was converted into phenylurea by acid hydrolysis.

The rearrangement may proceed via a nitrenium cation (**L**) to form carbodiimide or cyanamide. The same mechanism was suggested by Haruki *et al.*[13]



Scheme 3.

Experimental

Amidines. *N*-Methyl-*N'*-phenylbenzamidine was prepared from *N*-phenylbenzimidoyl chloride in ethereal solution and aqueous methylamine.[4] The other amidine hydrochlorides were prepared from the corresponding iminoethers and amines in water or ethanol by Pinner's method.[5]

N-*Chloroamidines.* As a typical experiment the preparation of *N*-chloro-*N'*-methylbenzamidine (**2**) is given. To a stirred solution of *N*-methylbenzamidine hydrochloride[14] (3.14 g, 0.02 mol) in water–ether (20 ml–40 ml) was gradually added 0.024 mol of sodium hypochlorite, the temperature being kept below 5 °C. After about 5 min of continued stirring, the ether layer was separated and residual *N*-chloroamidine was extracted twice with 10 ml portions of ether. The combined ether extracts were dried (Na_2SO_4) for 2 hr, filtered, and evaporated under reduced pressure at room temperature. The yield of **2** was 3.06 g (91%), mp 69 °C. Recrystallization from ether–petroleum ether gave a pure product, mp 69.5—70 °C.

The other *N*-chloroamidines were prepared as above.

Reaction of N-*Chloroamidines with Sodium Alkoxide.* *Reaction of* ***5*** *with Sodium Methoxide in Methanol*: To a stirred so-

13) E. Haruki, T. Inaike, and E. Imoto, This Bulletin, **41**, 1361 (1968).

14) H. L. Wheeler, *J. Amer. Chem. Soc.*, **20**, 489 (1898).

TABLE 7. FORMATION OF CARBODIIMIDES FROM *N*-CHLOROAMIDINES

$$Ph\text{–}\underset{\underset{NCl}{\|}}{C}\text{–}NHR \xrightarrow[\text{in Ligroin}]{Ag_2O} PhN{=}C{=}NR \quad (\mathbf{G})$$

R	R. Time (hr)	Product	Bp (°C/mmHg) (Ref.)	Yield %	Anal (Calcd) (%) C	H	N
H	2.0	(**H**)[a]	—	10[b]	—	—	—
Me	0.3	dark tarry oil	—	—	—	—	—
Et	0.3	(**G**)	38—42/4	28	—	—	19.07 (19.16)
Isopr	0.3	(**G**)	75—80/2 (111—112/14)[15]	35	74.09 (74.94)	7.40 (7.55)	17.18 (17.48)
Bzl	0.3	(**G**)[c]	—	33[b]	—	—	—

a) $PhN(Ag)\text{–}C{\equiv}N$. b) Yield of the corresponding urea. c) This could not be distilled because of a by-product.

lution of sodium methoxide prepared from sodium (0.28 g, 0.012 mol) and 25 ml of absolute methanol was added 2.45 g of *N*-benzyl-*N'*-chlorobenzamidine (**5**).

The mixture was then refluxed for 2.5 hr when sodium chloride precipitated. The solvent was removed by distillation under reduced pressure and the residue was mixed with water (10 ml). The upper oily layer was extracted once with a 20 ml portion and twice with 10 ml portions of ether. After the combined ethereal extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure, colorless needle crystals of 2,4,6-triphenyl-*s*-triazine (**C**) and a yellowish oily material were obtained. **C** was separated by filtration and recrystallized from benzene, mp 230—235 °C. The yield was 0.04 g (1%). (Found: C, 81.53; H, 4.89; N, 13.58%. Calcd for $C_{21}H_{15}N_3$: C, 81.53; H, 4.85; N, 13.58%).

To an ethereal solution of the filtrate containing a yellowish oily material was added a saturated ethereal solution of picric acid. The picrate of *N*-benzyl-*N'*-phenyl-*O*-methylisourea (**A6**) precipitated was collected by filtration and recrystallized from methanol, mp 148—149 °C. The yield was 33%.

A small part of the above filtrate was subjected to glc analysis and methyl benzoate was detected.

Reaction of **2** *with Sodium Ethoxide in Ethanol*: A mixture of **2** (4.22 g, 0.025 mol) and sodium ethoxide prepared from sodium (0.69 g, 0.03 g atom) and 25 ml of absolute ethanol was stirred at 60 °C for 0.7 hr. After working up the mixture as described above, the oily material was distilled under reduced pressure to give a fraction, bp 80—88 °C/3—40 mmHg (2.86 g). The fraction was subjected to glc analysis. *N*-Methyl-*N'*-phenyl-*O*-ethylisourea (**A2**) and ethyl benzoate were isolated by preparative gas chromatography (Silicone H. V.).

The authentic sample of **A2** was prepared according to the method of Forman *et al.*[14]

Reactions with the other *N*-chloroamidines were carried out similarly. The products are given in Table 3.

Reaction of N-*Chloroamidines with Sodium Hydroxide. Reaction of* **2** *with Sodium Hydroxide in 50% Aqueous Methanol*: To a stirred solution of *N*-methylbenzamidine hydrochloride (1.71 g, 0.01 mol) in 12 ml of water was added sodium hypochlorite (0.012 mol) at −5—5 °C to yield a suspension of the intermediate *N*-chloro compound (**2**). After about 5 min of stirring, an aqueous methanolic solution (water-methanol, 5 ml—25 ml) of sodium hydroxide (0.48 g, 0.012 mol) was added and the mixture was refluxed for 2.5 hr. When the reaction mixture was evaporated under reduced pressure and methanol was almost removed, crystals precipitated and were washed with ether to yield *N*-methyl-*N'*-phenylurea, mp 149 °C (0.34 g, 23%). Recrystallization from aqueous methanol gave a pure product, which showed no depression of its melting point (149—150 °C) upon a mixed-melting-point determination with an authentic sample. The washings and ethereal extracts from the reaction mixture were combined, dried (Na_2SO_4) and filtered. **A1** was detected by glc.

Reaction of **2** *with Sodium Hydroxide in 50% Aqueous Dioxane*: **2** obtained from *N*-methylbenzamidine hydrochloride (1.71 g, 0.01 mol) according to the same procedure as above was refluxed in 50% aqueous dioxane (50 ml) for 10 hr. When the reaction mixture was evaporated under reduced pressure and dioxane was almost removed, crystals precipitated. *N*-methyl-*N'*-phenylurea, mp 149 °C (0.36 g, 24%).

Reaction of **3** *with Sodium Hydroxide in* 50% *Aqueous Methanol*: Yellowish oily material was similarly obtained from *N*-chloro-*N'*-ethylbenzamidine (**3**) (0.01 mol). The yields of *N*-ethyl-*N'*-phenyl-*O*-methylisourea (**A4**, 35%) and methyl benzoate (7%) were determined using glc.

Reaction of **1** *with Sodium Hydroxide in 50% Aqueous Methanol*: **1** similarly obtained from benzamidine hydrochloride (3.85 g, 0.02 mol) was refluxed for 10 hr. When methanol was almost removed by evaporation under reduced pressure from reaction mixture, colorless leaflets (benzamide, 2.12 g, 65%) precipitated and were separated by filtration. The filtrate was evaporated and the residue extracted with hot ethanol (29 ml). The extract was concentrated to give the residual solid (sodium phenylcyanamide, **F**). Its infrared spectrum showed characteristic absorption of the cyano group at 2200 cm^{-1}. The residue was refluxed in 2 N hydrochloric acid (6 ml) for 40 min. After cooling and addition of aqueous sodium hydroxide solution to make the reaction mixture neutral, phenylurea was separated. (0.24 g, 9%, mp 146—148 °C).

The other *N*-chloroamidines were treated with sodium hydroxide by a similar method.

Reaction of N-*Chloroamidines with Silver Oxide. Reaction of* **4** *with Silver Oxide*: A suspension of **4** (11.80 g, 0.06 mol) and silver oxide (30 g, 0.13 mol) in anhydrous ligroin (60 ml) was heated under reflux for 0.3 hr. The insoluble matter was separated by filtration and the filtrate was distilled under reduced pressure to give a fraction with a bp of 75—80 °C/2 mmHg (3.37 g, 35%), which was identified

14) S. E. Forman, C. A. Erickson, and H. Adelman, *J. Org. Chem.*, **28**, 2653 (1963).
15) I. G. Hinton and R. F. Webb, *J. Chem. Soc.*, **1961**, 5051.

as *N*-isopropyl-*N'*-phenylcarbodiimide by comparison of its infrared spectrum with that of an authentic sample prepared by the treatment of *N*-isopropyl-*N'*-phenylthiourea with HgO. The distillate was refluxed in 1 N hydrochloric acid for 0.25 hr. After cooling and addition of aqueous sodium hydroxide solution to make the reaction mixture neutral, solid *N*-isopropyl-*N'*-phenylurea was obtained.

*Reaction of **1** with Silver Oxide*: A suspension of **1** (3.09 g, 0.02 mol) and silver oxide (10 g, 0.043 mol) in anhydrous ligroin (50 ml) was refluxed for 2 hr. The insoluble matter separated by filtration showed characteristic absorption of the cyano group at 2200 cm^{-1} in its infrared spectrum. The solid refluxed in 6 N hydrochloric acid and the insoluble matter was separated by filtration. After cooling, colorless plates were precipitated, which were identified as phenylurea, mp 147 °C, 0.26 g, 10%.