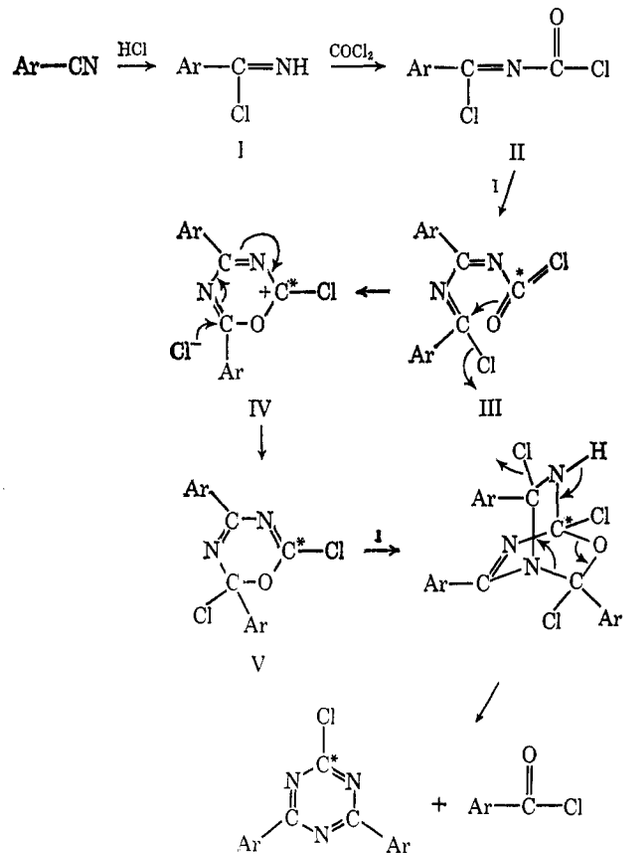
SCHEME II



(*) designates labeled atom

B. In Nitrobenzene.—To a mixture of nitrile (0.02–0.03 mol), nitrobenzene (3.3 g), and hydrogen chloride (0.01–0.02 mol) in a 50-ml glass tube was added a solution of phosgene (0.9–1.0 g, 0.009–0.01 mol) in nitrobenzene (3.0 g). The tube was sealed carefully and heated to 95–100° in an oil bath for 200 hr. The reaction mixture was treated as above (see Tables I and II).

Isolation of N-(1-Chlorobenzylidene)carbamoyl Chloride (II, Ar = Phenyl).—In accordance with procedure A, the reaction was carried out at a molar ratio of 4:2:1 (C_6H_5CN:$COCl_2$:HCl). After removal of the triazine by filtration, the filtrate was distilled under reduced pressure giving 10 g (15% based on phosgene used) of the carbamoyl chloride (II, Ar = phenyl): bp 85–90° (1 mm); ir(neat) 1740, 1640, 1040, 767, 740, and 677 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 201 (8) (M^+), 168 (34), 166 (98), 65 (33), 63 (100), 77 (34), 76 (49), 51 (33), 50 (34).

Anal. Calcd for $C_8H_5Cl_2NO$: C, 47.56; H, 2.50. Found: C, 47.55; H, 2.80.

Reaction of II (Ar = Phenyl) with Benzonitrile in the Presence of Hydrogen Chloride.—In a 20-ml glass tube were placed a solution of hydrogen chloride (0.95 g, 0.026 mol) in benzonitrile (4 g) and 2 g of II (Ar = phenyl). The glass tube was sealed and heated to 100–105° for 90 hr. The formation of 2-chloro-4,6-diphenyl-*s*-triazine (3.69 g, 70% yield) and benzoyl chloride was confirmed by ir spectrum and glpc.

Reaction of II (Ar = Phenyl) with *p*-Tolunitrile in the Presence of Hydrogen Chloride.—The mixture of II (Ar = phenyl) (2.77 g), *p*-tolunitrile (3.00 g), and hydrogen chloride (1.05 g) was heated to 100–105° for 130 hr. The precipitate (1.31 g) obtained was purified by sublimation and recrystallization from acetone giving a crystalline product which melted at 145–148°; mass spectrum (70 eV) *m/e* (rel intensity) 297 (15), 295 (42), 283 (20), 281 (52), 267 (0.3), 143 (23), 129 (15), 117 (100), 103 (41). The peaks at 297 and 295, 283 and 281, and 267 were in accord with the parent ions of 2-chloro-4,6-bis(*p*-tolyl)-*s*-triazine, 2-chloro-4-phenyl-6-*p*-tolyl-*s*-triazine, and 2-chloro-4,6-diphenyl-*s*-triazine, respectively.

Treatment of the filtrate with aqueous ammonia gave *p*-toluamide.

Registry No.—Phosgene, 75-44-5; 2-chloro-4,6-diphenyl-*s*-triazine, 3842-55-5; 2-chloro-4,6-bis(*p*-tolyl)-*s*-triazine, 21902-34-1; 2-chloro-4,6-bis-(*p*-methoxyphenyl)-*s*-triazine, 21902-35-2; II, Ar = phenyl, 4547-71-1.

The Reaction of Nitriles with Phosgene. IV.[1] A Facile One-Step Synthesis of the Isoquinoline Nucleus

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The treatment of arylacetonitrile or α-naphthylacetonitrile (I) with phosgene in the presence of hydrogen chloride leads to substituted 1,3-dichloroisoquinolines (II) with a trace of 6-chloro-2,5-disubstituted 4(3H)-pyrimidones (III) and 4,6-dichloro-2,5-disubstituted pyrimidines (IV). This method is general in nature and represents a new, facile, and one-step synthesis of 1,3-dichloroisoquinoline derivatives. The reaction of phenylacetamide with phosgene under the comparable conditions also gives 1,3-dichloroisoquinoline (IIa). The isocyanate derivatives (V) were confirmed as intermediates of the reaction. The mechanism of this reaction is discussed.

The frequent occurrence of the isoquinoline nucleus in alkaloids has led to interest in the synthesis of isoquinoline derivatives. Various methods have been developed, but most of them still require many steps.[2] In accompanying papers,[3,4] the reaction of aliphatic nitriles or amides with phosgene in the presence of hydrogen chloride was shown to give 6-chloro-2,5-dialkyl-4(3H)-pyrimidones in good yields, with a trace of 4,6-dichloro-2,5-dialkylpyrimidines. In an extension of the studies on this reaction, we have found a new, one-step synthesis of the isoquinoline nucleus.

In a sealed glass tube, phenylacetonitrile was allowed to react with phosgene in the presence of hydrogen chloride in chlorobenzene at 60–65° for 72 hr. 1,3-Dichloroisoquinoline (IIa) was obtained in 10.8% yield in addition to 6-chloro-2-benzyl-5-phenyl-4(3H)-pyrimidone (IIIa) and 4,6-dichloro-2-benzyl-5-phenylpyrimidine (IVa) (Table I). The isoquinoline IIa was identified by direct comparison of its physical properties with those of an authentic sample prepared from 1,3-

(1) Part III: S. Yanagida, H. Hayama, M. Yokoe, and S. Komori, *J. Org. Chem.*, **34**, 4125 (1969).

(2) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 72 (1951).

(3) S. Yanagida, M. Ohoka, M. Okahara, and S. Komori, *J. Org. Chem.*, **34**, 2972 (1969).

(4) S. Yanagida, H. Hayama, and S. Komori, *J. Org. Chem.*, **34**, 4180 (1969).

TABLE I

THE REACTION OF ARYLACETONITRILES WITH PHOSGENE IN THE PRESENCE OF HYDROGEN CHLORIDE AND THE PROPERTIES OF THE ISOQUINOLINES (II)

Nitriles, I	Reaction conditions: Temp, °C	Time, hr	Mole ratio of nitriles: $COCl_2$: HCl	Product yield,[a] %: II	III	IV	Isoquinoline II	Mp, °C	Ir (Nujol), cm^{-1}	Nmr ($CDCl_3$), τ	Mol wt[b]	Elemental analysis: Calcd, %	Found, %
Ia	60–65	72	1:0.5:0.5	10.8	8.7	0.4	IIa	121.0–122.0[c]	1620, 1575[d] 1552	2.45 (c, 4H)[e] 1.82 (c, 1 H)	197	C, 54.58 H, 2.54 N, 7.07	C, 55.53 H, 2.51 N, 7.08
Ia	100–105	96	1:0.2:0.8	53.7	1.1	0.6							
Ib	60–65	109	1:0.5:0.4	3.3	2.7	0	IIb	120.5–122.0	1630, 1580[d] 1550	7.45 (s, 3 H)[e] 2.53 (c, 3 H) 2.10 (s, 1 H)	211	C, 56.63 H, 3.33 N, 6.64	C, 56.72 H, 3.07 N, 7.03
Ib	100–105	96	1:1.2:0.8	65.3	1.9	0							
Ic	100–105	96	1:1.2:0.8	66.3[f]	Trace	Trace	IIc + IIc′	82.0–85.0	1630 1550–1580	7.47 (s), 7.01 (s) *Ca.* 2.55 (c) 2.02 (s), 1.87 (s)	211	C, 56.63 H, 3.33 N, 6.64	C, 56.87 H, 3.19 N, 6.68
Id	100–105	96	1:1.2:0.8	60.3	Trace	Trace	IId	122.0–123.5	1612, 1585	7.40 (s, 3 H) *Ca.* 2.48 (c, 3 H) 1.97 (s, 1 H)	211	C, 56.63 H, 3.33 N, 6.64	C, 56.81 H, 3.34 N, 6.06
Ie	100–105	96	1:1.2:0.8	17.0	Trace	0	IIe	168.5–170.0	1613, 1572 1540.	*Ca.* 2.40 (c, 3H) 1.80 (s, 1 H)	231	C, 46.49 H, 1.73 N, 6.02	C, 46.28 H, 1.75 N, 6.08
If	100–105	216	1:1.7:0.5	4.4	0	0	IIf	141.5–143.0	1612, 1550[d]		231	C, 46.49 H, 1.73 N, 6.02	C, 46.74 H, 1.88 N, 6.06
Ig	100–105	96	1:1.2:0.8	19.4	0	0	IIg	92.0–96.0	1620, 1550	7.37 (s, 3 H) *Ca.* 2.30 (c, 3 H) *Ca.* 1.80 (c, 1 H)	211	C, 56.63 H, 3.33 N, 6.64	C, 57.10 H, 3.25 N, 6.65
Ih	100–105	96	1:1.2:0.7	61.3	0	0	IIh	172.5–174.0	1563		247	C, 62.93 H, 2.84 N, 5.65	C, 63.32 H, 2.82 N, 5.66

[a] Based on phosgene used. [b] By mass spectra. [c] Lit.[5] 122–123°. [d] KBr disk. [e] In CCl_4. [f] Total yield of IIc and IIc′.

dihydroxyisoquinoline and phosphorus oxychloride.[5] The structures of IIIa and IVa were confirmed on the basis of ir and nmr spectra and elemental analysis.

It has now been found that the yield of the isoquinoline IIa increases remarkably with the rise of the reaction temperature to 100°, while the yields of the pyrimidone IIIa and the pyrimidine IVa decrease (Table I). It is better to use a solvent such as chlorobenzene in this reaction, as otherwise the reaction mixture darkens considerably. Dehydrating agents such as phosphorus pentachloride, polyphosphoric acid, and phosphorus oxychloride had no catalytic effect on the reaction.

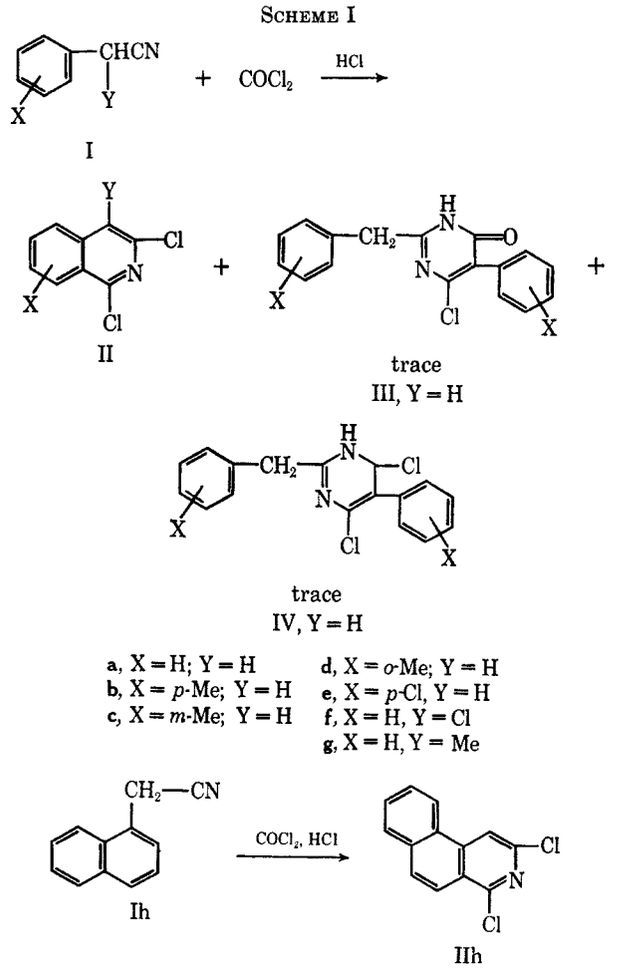
To determine the scope of this reaction, other substituted phenylacetonitriles or α-naphthylacetonitrile were treated with phosgene under the same conditions (Scheme I). The main products were the corresponding isoquinolines II (Table I). The formation of a trace of the pyrimidones III and pyrimidines IV was determined by ir spectra analyses.

Treatment of *m*-tolylacetonitrile with phosgene under the conditions shown in Table I has led to the formation of the mixture of 1,3-dichloro-6-methylisoquinoline (IIc) and 1,3-dichloro-8-methylisoquinoline (IIc′). The formation ratio of IIc and IIc′ was determined as 5 to 3 on the basis of the area of methyl proton signals at τ 7.47 and 7.01, respectively, in the nmr spectrum of the mixture.

Comparison of the yields of IIb, IIc, IIc′, and IId (Table I) indicates the absence of any strong orientation of the cyclization.

On close examination of the filtrates or the nitriles recovered by vacuum distillation in each experiment using glpc and ir spectra, the formation of a higher boiling product having the isocyanato group (2240 cm^{-1}) and a carbon–carbon double bond (1640–1650 cm^{-1}) was observed, although in a small amount. In order to determine the structure of these products, the distillate obtained from the filtrate of 1,3,7-trichloroiso-

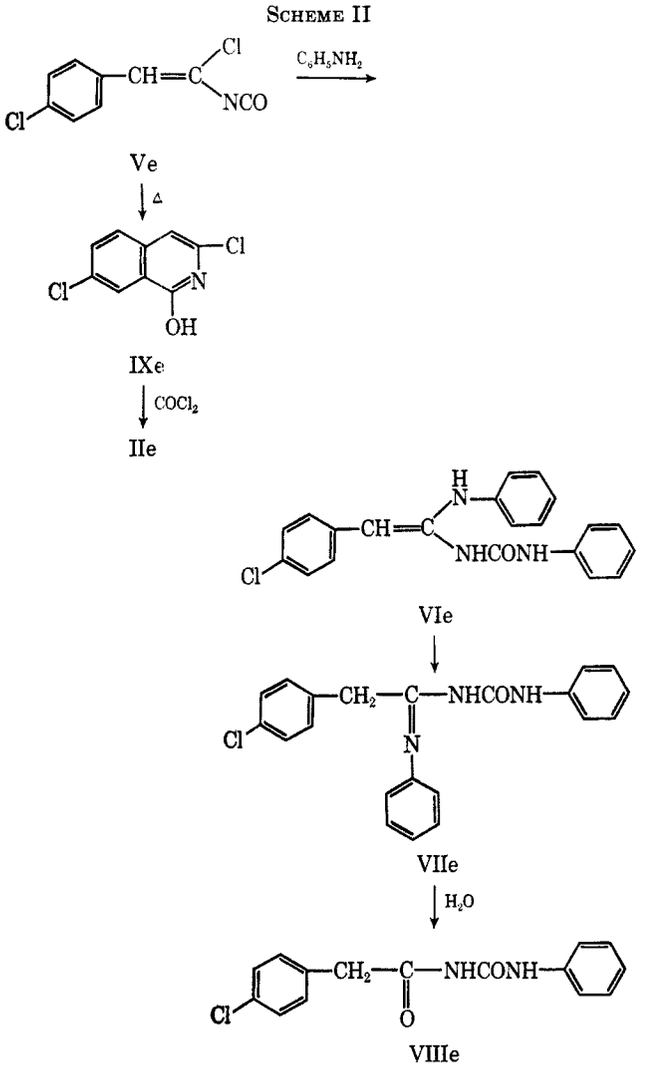
SCHEME I



(5) S. Gabriel, *Ber.*, **19**, 1655, 2355 (1886).

quinoline (IIe) was treated with excess aniline. The structure of the isolated crystalline product was confirmed as N-anilinocarbonyl-N′-phenyl-(*p*-chloro)-phenylacetamidine (VIIe) on the basis of composition and nmr, mass spectra, and hydrolysis. The mass spectrum gave the fragment ions at 125 and 127, these being assigned to chlorotropylium ions. Moreover the nmr spectrum, measured in deuteriochloroform, exhibited a singlet at τ 6.39, which was assigned to methylene protons. These facts excluded the enamine structure VIe (Scheme II). Furthermore, hydrolysis of

SCHEME II



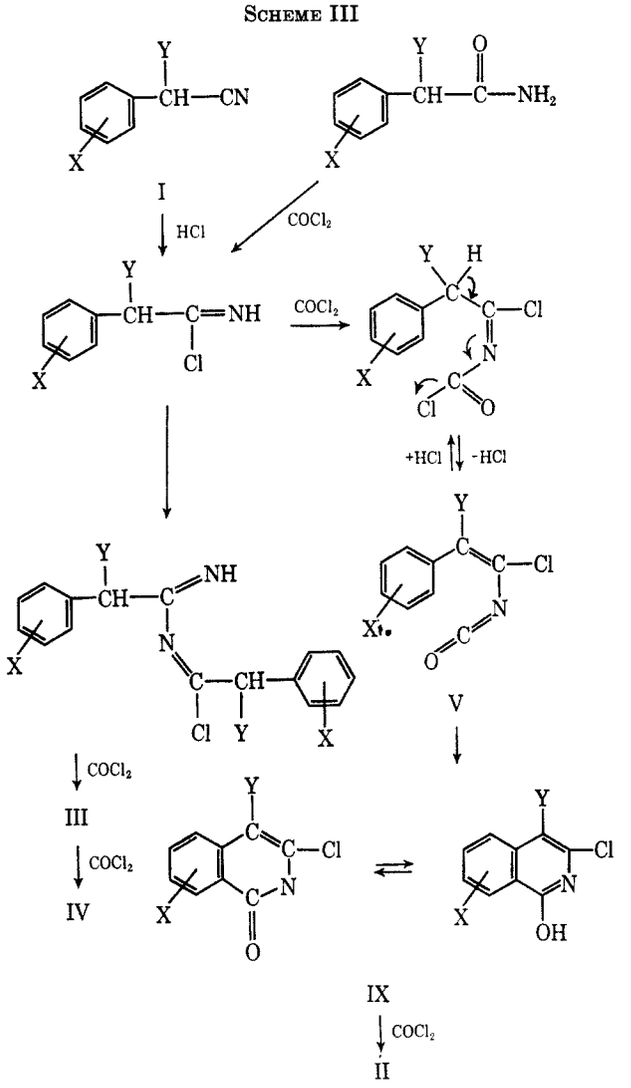
VIIe gave N-phenyl-N′-(*p*-chloro)benzoylurea (VIIIe). Thus we concluded that the first formed enamine VIe rearranged to the stable imino form VIIe. Accordingly, the structure of the original isocyanate could be assigned to β-chloro(*p*-chloro)styryl isocyanate (Ve).

The isolation of the corresponding isoquinolines from *p*-nitrophenylacetonitrile and diphenylacetonitrile were unsuccessful. In the case of *p*-nitrophenylacetonitrile, however, the formation of the corresponding isocyanate was detected by ir spectrum.

To clarify the reaction mechanism of the formation of the isoquinoline nucleus, the cyclization of Ve in chlorobenzene using a sealed glass tube was attempted. The resulting product was identified as 3,7-dichloro-1-hydroxyisoquinoline (IXe) on the basis of its spectral properties and elemental analysis. Further, treatment of IXe with phosgene in chlorobenzene did indeed give IIe almost quantitatively (Scheme II).

As expected from our previous paper,[4] the reaction of phenylacetamide with phosgene in the presence of hydrogen chloride has also led to the isolation of 1,3-dichloroisoquinoline (IIa). The overall reaction sequence given in Scheme III is proposed.

SCHEME III



The electrophilic intramolecular attack of the isocyanato group at the *ortho* position would become difficult if a strongly electron-attracting group such as chloro or nitro were present in the benzene ring. Isoquinoline formation apparently is relatively slow at lower temperatures, and the pyrimidone-forming reaction then competes seriously.

Experimental Section[6]

General Procedure.—The nitrile I (0.03–0.04 mol) and 5 ml of chlorobenzene were placed in a 100-ml glass tube, and dry

(6) Melting points were determined on a Yanagimoto micro melting point apparatus and were corrected. The nmr spectra were obtained using a Model J. N. M-G-60 spectrometer (Japan Electronic Optics Laboratory Co.) with tetramethylsilane as an internal reference. The ir spectra were recorded with a Japan Electroscopic IR-E spectrophotometer. The mass spectra were recorded with a Hitachi mass spectrometer Model RMU-6E. Glpc was performed with a column of Silicone DC 200, 10% on Diasolid L (60–80 mesh, 2-m column, 150° with hydrogen as the carrier gas.)

hydrogen chloride (0.02–0.03 mol) was absorbed in it. A 10-ml portion of a chlorobenzene–phosgene solution (0.035–0.040 mol of phosgene) was then added and the glass tube was stoppered, cooled in Dry Ice–acetone, and sealed carefully. The sealed glass tube was placed with 50 ml of dichloromethane in a 250-ml stainless steel autoclave. The autoclave was sealed and heated to 100–105° in an oil bath. At the end of the reaction, the autoclave was chilled in Dry Ice–acetone and opened. The sealed glass tube taken out was also chilled in Dry Ice–acetone and opened carefully. The precipitate formed was filtered and washed with a small portion of carbon tetrachloride. Further material precipitated on concentration of the filtrate. This was treated in the same way. The residue was chromatographed on alumina. The isoquinolines (II) were eluted with petroleum ether. The pyrimidones (III) were eluted with benzene–petroleum and the pyrimidines (IV) with chloroform–ethanol. The isoquinolines (II) were purified by sublimation. The pyrimidones (III) were purified by recrystallization. The results are summarized in Table I.

Warning.—In the course of the reaction, the inner pressure of the reaction tube increases due to the formation of carbon dioxide. In addition, phosgene reacts with water to evolve carbon dioxide. Thus all of the material should be dried thoroughly and all of the experiments should be handled with care.

6-Chloro-2-benzyl-5-phenyl-4(3H)-pyrimidone (IIIa) was recrystallized from acetonitrile: mp 235–236.5°; ir(Nujol) 1658 cm^{-1} (C=O); nmr (CF_3COOH) τ 5.51 (s, 2 H) methyl protons, 2.60 (m, 10 H) ring protons.

Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.80; H, 4.42; N, 9.44. Found: C, 68.85; H, 4.39; N, 9.70.

4,6-Dichloro-2-benzyl-5-phenylpyrimidine(IVa) had mp 136.0–138.0°; ir (Nujol) 1553 cm^{-1} (ring); nmr ($CDCl_3$) τ 5.77 (s, 2 H) methylene protons, 2.65 (m, 10 H) ring protons.

6-Chloro-2-(*p*-methyl)benzyl-5-*p*-tolyl-4(3H)-pyrimidone (IIIb) was recrystallized from acetonitrile: mp 204.0–207.0°; ir (Nujol) 1658 cm^{-1} (C=O); nmr (CF_3COOH) τ 7.61 (s, 3 H), 7.59 (s, 3 H), 5.23 (s, 2 H), 2.72 (m, 8 H).

Anal. Calcd for $C_{19}H_{17}ClN_2O$: C, 70.26; H, 5.28; N, 8.60. Found: C, 70.54; H, 5.14; N, 8.79.

Identification of β-Chloro(*p*-chloro)styryl Isocyanate (Ve).—The concentration of the filtrate of 1,3,7-trichloroisoquinoline (IIe) under reduced pressure gave a distillate consisting of *p*-chlorophenylacetonitrile and a higher boiling material determined by glpc. Ir analysis of the mixture showed strong absorption bands at 2240 (–NCO) and 1640 (>C=C<) cm^{-1}. The mixture was treated with excess aniline giving a white precipitate. This was filtered, washed with water, dried, crystallized from methanol–acetonitrile, and identified as N-anilinocarbonyl-N′-phenyl(*p*-chloro)phenylacetamidine (VIIe): mp 190.0–193.0°; ir(Nujol) 3240, 1705, 1650, 1595, and 1560 cm^{-1}; nmr($CDCl_3$) τ 6.39 (s); mass spectrum (70 eV) *m/e*(rel intensity) 363 (M^+), 246 (5), 244 (14), 127 (2), 125 (7), 119 (100), 93 (10), 91 (30), 77 (27).

Anal. Calcd for $C_{21}H_{18}ClN_3O$: C, 69.32; H, 4.99; N, 11.55. Found: C, 69.30; H, 4.86; N, 11.41.

Hydrolysis of VIIe.—The amidine VIIe (1.0 g) was dissolved in a water–methanol (1:3 v/v, 30 ml) and refluxed for 1 hr. Concentration of the reaction mixture gave a white precipitate. This was recrystallized from methanol and identified as N-(*p*-chlorobenzoyl)-N′-phenylurea (VIIIe): mp 210.0–212.0; ir (KBr disk) 3240, 1710, 1605, and 1560 cm^{-1}; nmr (*d*-DMSO) τ 6.28 (s, 2 H), *ca.* 2.73 (m, 9 H); mass spectrum (70 eV) *m/e* (rel intensity) 290 (13), 288 (40) (M^+), 171 (8), 169 (22), 154 (12), 152 (37), 136 (22), 127 (24), 125 (72), 119 (100), 93 (51), 91 (81), 77 (18), 54 (25).

Anal. Calcd for $C_{15}H_{13}ClN_2O_2$: C, 62.40; H, 4.54; N, 9.70. Found: C, 62.16; H, 4.58; N, 9.52.

Cyclization of Ve in a Sealed Glass Tube.—The above-mentioned distillate (1 g) was heated in a 10-ml sealed glass tube at 100–105° for 44 hr. The glpc analysis showed the disappearance of Ve and the resulting white precipitate was purified by sublimation and identified as 3,7-dichloro-1-hydroxyisoquinoline (IXe): mp 253.0–257.0°; ir (KBr disk) 1660, 1625, and 1600 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 215 (63), 213 (100) (M^+), 177 (85), 151 (37), 149 (39), 125 (21), 123 (61).

Anal. Calcd for $C_9H_5Cl_2NO$: C, 50.50; H, 2.35; N, 6.54. Found: C, 50.42; H, 2.26; N, 6.54.

Reaction of IXe with Phosgene.—The hydroxyisoquinoline IXe (0.04 g) and 2 ml of chlorobenzene–phosgene solution (0.8 g of phosgene) were placed in a 20-ml sealed glass tube and heated to 100–105° for 37 hr giving 0.04 g of 1,3,7-trichloroisoquinoline (IIe), which was confirmed by direct comparison with an authentic sample.

Reaction of Phenylacetamide with Phosgene in the Presence of Hydrogen Chloride.—According to the general procedure, the mixture of phenylacetamide (0.46 g), hydrogen chloride (0.1 g), phosgene (1.0 g), and nitrobenzene (10 ml) was heated in a 50-ml sealed glass tube at 100–105° for 140 hr giving 0.133 g of 1,3-dichloroisoquinoline (IIa). The yield was 21% based on phenylacetamide.

Registry No.—IIa, 7742-73-6; IIb, 21902-37-4; IIc, 21902-38-5; IIc′, 21902-39-6; IId, 21902-40-9; IIe, 21902-41-0; IIf, 21902-42-1; IIg, 15787-23-2; IIh, 21902-44-3; IIIa, 21893-39-0; IIIb, 21893-40-3; IVa, 21585-52-4; VIIe, 21893-42-5; VIIIe, 21893-43-6; IXe, 21893-44-7; phosgene, 75-44-5.