Acknowledgments. The authors wish to thank Mr. Richard Oterson for some of the preliminary experimental work and Dr. J. Martin Grisar for providing us with an authentic sample of **11a**. The authors are also grateful to the Research Corporation and the National Institute for Neurological Diseases and Stroke (Research Grant NS 12007) for financial support of this research.

Registry No.—**2,** 4396-01-4; **3,** 63459-11-0; **3** picrate, 68423-27-8; **4,** 57934-06-2; **4** picrate, 57934-07-3; **9,** 63459-12-1; **10,** 68423-28-9; **11a,** 55047-44-4; **12,** 68423-29-0; **15,** 68423-30-3; **17,** 68423-31-4; **18,** 68423-32-5; **19,** 68423-33-6; **20,** 68423-34-7; **21,** 68423-14-3; **22,** 68423-15-4; piperidine, 110-89-4; *N*-chloropiperidine, 2156-71-0; 2,3,4,5-tetrahydropyridine, 505-18-0; sodium acetoacetate, 623-58-5; benzaldehyde, 100-52-7; *tert*-butyl azidoformate, 1070-19-5; *N*-benzoylpelletierine, 68423-16-5; ethylene glycol, 107-21-1.

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(38) A sample of **11a** obtained from Dr. Grisar exhibited the same NMR spectra. It also behaved in the same manner as our sample upon neutralization.

Aminohaloborane in Organic Synthesis. 2.[1] Simple Synthesis of Indoles and 1-Acyl-3-indolinones Using Specific Ortho α-Chloroacetylation of Anilines[2]

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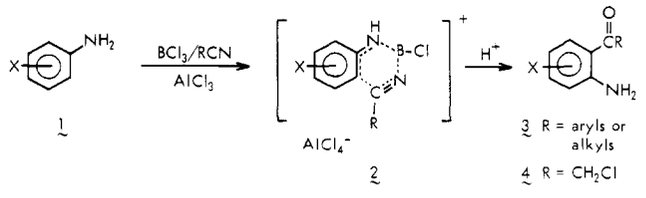
A general simple synthesis of 2,3-unsubstituted indoles (**5**) and 1-acyl-3-indolinones (**9** and **10**) was performed from anilines in two steps. The general procedure involved (a) specific ortho chloroacetylation of anilines to give 2-amino-α-chloroacetophenones (**4**), and (b) reductive cyclization of **4** to produce **5** and dehydrochlorination of 2-(acylamino)-α-chloroacetophenones (**7** and **8**) to yield **9** and **10**.

The search for an efficient synthesis of indoles has been a problem for nearly a century in organic synthesis. Beginning with the classical Fischer[3] and Reissert[4] methods, many reports[5] have appeared from practical and/or academic points of view. Among these, only the Leimgruber method[6] is a general one for synthesizing indoles which are substituted in the benzene ring but not in the heterocyclic nucleus.

We present here a new, efficient method for synthesizing such substituted indoles in two steps from anilines. In the preceding paper,[1] we reported the regiospecific synthesis of 2-amino phenyl ketone (**3**) from anilines (**1**) and nitriles using boron trichloride in the presence of aluminum trichloride, presumably via a cyclic transition state involving a boronium cationic species stabilized by tetrachloroaluminate (**2**).



1 **2** **3** R = aryls or alkyls **4** R = CH_2Cl

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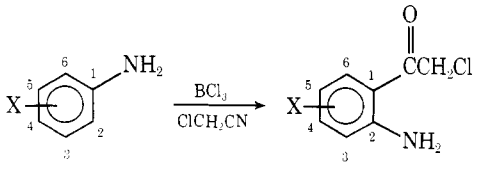
Table I. Synthesis of 2-Aminochloroacetophenones (4) from Anilines (1) and Chloroacetonitrile

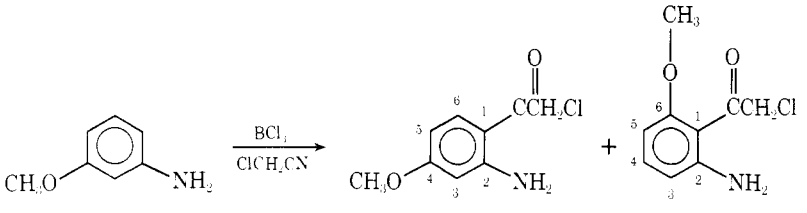


1 4

run no.	compd	registry no.	X	solvent	additional Lewis acid	refluxing time, h	compd	registry no.	X	yield,[a] %	recovered 1, %
1	**1a**	62-53-3	H	$(CH_2Cl)_2$	none	6	**4a**	64605-23-8	H	23	
2	**1a**		H	$(CH_2Cl)_2$	$AlCl_3$	3	**4a**		H	52	
3	**1b**	104-94-9	4-OCH_3	C_6H_6	$TiCl_4$	3	**4b**	64605-34-1	5-OCH_3	40	40
4	**1c**	95-51-2	2-Cl	C_6H_6	$AlCl_3$	6	**4c**	64605-35-2	3-Cl	63	6
5	**1d**	106-47-8	4-Cl	C_6H_6	$AlCl_3$	6	**4d**	64605-36-3	5-Cl	66	16
6	**1e**	108-42-9	3-Cl	C_6H_6	$AlCl_3$	6	**4e**	64605-39-6	6-Cl	14[b]	12
										11	
							4f	64605-37-4	4-Cl	52[b]	
										45	
7	**1f**	372-19-0	3-F	C_6H_6	$AlCl_3$	8	**4g**	68438-31-3	6-F	7	
							4h	68438-32-4	4-F	47	
8	**1g**	6315-89-5	3,4-$(OCH_3)_2$	$(CHCl_2)_2$	none	1.5	**4i**	68438-33-5	4,5-$(OCH_3)_2$	35	
9	**1g**		3,4-$(OCH_3)_2$	CH_2Cl_2	$AlCl_3$	16	**4i**		4,5-$(OCH_3)_2$	24	
10	**1i**	136-90-3	3-CH_3-4-OCH_3	C_6H_6	$TiCl_4$	2	**4l**	68438-34-6	4-CH_3-5-OCH_3	45	

[a] Isolated yield of a pure product based on the aniline used. [b] Determined by NMR analysis by comparing the intensity of the corresponding methylene protons.

Table II. Synthesis of 4-Methoxy-2-amino-α-chloroacetophenone (4j) and 6-Methoxy-2-amino-α-chloroacetophenone (4k) from 3-Methoxyaniline (1h)



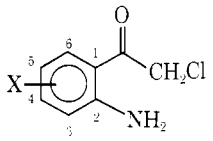
1h 4j 4k

run no.	solvent	additional Lewis acid	reaction[a] time, h	yield,[b] % 4j[f]	4k[g]	recovered 1h[h]
1	C_6H_6	cat. $AlCl_3$	15	5	1	
2	C_6H_6	$AlCl_3$	15	50	3	23
3	C_6H_6	none	3	44	18	30
				39[c]	15[c]	
4	C_6H_6	$AlCl_3$	3	48	8	10
5	C_6H_6	$TiCl_4$	3	53	18	29
6	CH_2Cl_2	$TiCl_4$	3	45	29	11
				33[d]	9[d]	
				38[e]	27[e]	
7	CH_2Cl_2	$SnCl_4$	3	42	28	24
8	CH_2Cl_2	$ZnCl_2$	3	39	28	28

[a] 15 h at room temperature or 3 h at refluxing temperature in the indicated solvent. [b] Yield was determined by GLC analysis. [c] Isolated yield. [d] Calculated from corresponding *N*-acetyl derivatives **7h** and **7j**. [e] Estimated by NMR analysis. [f] Registry no. 64605-24-9. [g] Registry no. 64605-25-0. [h] Registry no. 530-90-3.

In continuation of our method, we studied the reaction with chloroacetonitrile in detail. As shown in Table I, this reaction was applicable to chloroacetonitrile to obtain 2-amino-α-chloroacetophenones (**4**). Hitherto such a substituted acetophenone has been accessible only by an elaborate route.[7] Namely, Ruggli et al. reported the synthesis of 2-amino-α-chloroacetophenone (**4a**) from 2-nitrobenzoyl chloride by successive treatment with diazomethane and hydrochloric acid followed by reduction of the resulting 2-nitro-α-chloroacetophenone. As can be noted from the comparison of runs 1 and 2, the presence of aluminum trichloride raised the yield of **4a** significantly. In run 3, titanium tetrachloride was used instead of aluminum trichloride to minimize the possible cleavage of the ether function of anisidine. In runs 6 and 7, two products were isolated and their structures were deduced from the H^1-NMR spectral pattern of the corresponding aromatic protons (see Table III). The presence of aluminum trichloride in the case of 3,4-dimethoxyaniline (**1g**, runs 8 and 9) gave the

Table III. Physical Data for Substituted 2-Amino-α-chloroacetophenone (4)



4

compd	X	mp, °C (from)	IR ($CHCl_3$), cm^{-1} (ν_{NH_2}, $\nu_{C=O}$)	^{1}H-NMR ($CDCl_3$), δ	empirical[a] formula
4a	H	112–113 (CH_2Cl_2–*n*-hexane) lit.[7] 112–113	3505 3364 1664 1644	4.65 (2 H, s, CH_2), 6.2–6.5 (2 H, br s, NH_2), 6.5–7.8 (4 H, m, arom. H)	
4b	5-OCH_3	103–104 (CH_2Cl_2–2-propanol)	3510 3371 1649	3.77 (3 H, s, OCH_3), 4.62 (2 H, s, CH_2), 6.0 (2 H, br s, NH_2), 6.5–7.1 (3 H, m, arom. H)	$C_9H_{10}NO_2Cl$
4c	3-Cl	61–62 (C_2H_5OH–*n*-hexane)	3498 3352 1666 1649	4.64 (2 H, s, CH_2), 6.18 (2 H, br s, NH_2), 6.4–7.7 (3 H, m, arom. H)	$C_8H_7NOCl_2$
4d	5-Cl	140–141 (C_2H_5OH–*n*-hexane)	3503 3363 1669 1649	4.60 (2 H, s, CH_2), 6.3 (2 H, br s, NH_2), 6.62 (1 H, d, J = 8 Hz, C_3–H), 7.25 (1 H, d of d, J = 8 Hz, J = 2 Hz, C_4–H), 7.60 (1 H, d, J = 2 Hz, C_6–H)	$C_8H_7NOCl_2$
4e	6-Cl	60–61 (C_2H_5OH–*n*-hexane)	3405 3395 1673	4.70 (2 H, s, CH_2), 4.91 (2 H, br s, NH_2), 6.60 and 6.71 (2 H, two d of d, J = 8 Hz, J = 1 Hz, C_3–H and C_5–H), 7.12 (1 H, t, J = 8 Hz, C_4–H)	$C_8H_7NOCl_2$
4f	4-Cl	134–135 (C_2H_5OH–*n*-hexane)	3505 3358 1666 1648	4.60 (2 H, s, CH_2), 6.4 (2 H, br s, NH_2), 6.56–7.65 (3 H, m, arom. H)	$C_8H_7NOCl_2$
4g	6-F	128–129 (CH_2Cl_2–*n*-hexane)	3516 3370 1661 1626	4.69 (2 H, d, $^5J_{FX}$ = 4 Hz, CH_2), 6.14–7.38 (3 H, m, arom. H)	C_8H_7NOClF
4h	4-F	90–91 (CH_2Cl_2–*n*-hexane)	3512 3360 1666 1647 1627	4.57 (2 H, s, CH_2), 6.52–6.22 (4 H, m, NH_2, C_3–H and C_5–H), 7.63 (1 H, d of d, J_{BX} = 9.6 Hz, J_{FX} = 6.0 Hz, C_6–H)	C_8H_7NOClF
4i	4,5-$(OCH_3)_2$	123–124 (CH_2Cl_2–petroleum ether)	3490 3340 1635	3.82 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 4.70 (2 H, s, CH_2), 6.12 (1 H, s, C_3–H), 7.03 (1 H, s, C_6–H)	$C_{10}H_{12}NO_3Cl$
4j	4-OCH_3	107–108 (CH_2Cl_2–2-propanol)	3510 3371 1649	3.87 (3 H, s, OCH_3), 4.57 (2 H, s, CH_2), 6.08 (1 H, d, J = 3 Hz, C_3–H), 6.23 (1 H, d of d, J = 9 Hz, J = 3 Hz, C_5–H), 6.43 (2 H, bs, NH_2), 7.53 (1 H, d, J = 9 Hz, C_6–H)	$C_9H_{10}NO_2Cl$
4k	6-OCH_3	133–134 (CH_2Cl_2–2-propanol)	3510 3362 1650	3.85 (3 H, s, OCH_3), 4.74 (2 H, s, CH_2), 6.35–6.08 (4 H, m, NH_2, C_3–H and C_5–H), 7.16 (1 H, t, J = 8 Hz, C_4–H)	$C_9H_{10}NO_2Cl$
4l	4-CH_3-5-OCH_3	126–128 dec (ether–petroleum ether)	3437[b] 3320 1648	2.2 (3 H, s, CH_3), 3.78 (3 H, s, OCH_3), 4.6 (2 H, s, CH_2), 5.2–6.2 (2 H, bs, NH_2), 6.5 (1 H, s, C_3–H), 6.9 (1 H, s, C_6–H)	$C_{10}H_{12}NO_2Cl$

[a] All products gave satisfactory elemental analyses (C ±0.4, H ±0.2, N ±0.2, Cl ±0.3, F ±0.2). [b] In Nujol.

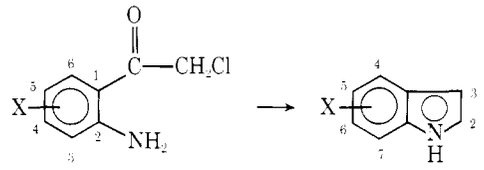
poorer yield, presumably due to the cleavage of the methoxy groups of **1g**.

Next, we explored the reaction of 3-methoxyaniline (**1h**). In this case, the reaction proceeded at room temperature giving 4-methoxy- and 6-methoxy-2-amino-α-chloroacetophenone (**4j** and **4k**). This facile reaction is probably due to activation of the electrophilic attack at the para position of the methoxy group. To obtain a better regiospecificity for **4j** over **4k**, other Lewis acids were tested as shown in Table II. The combined yield could be improved to some extent, but better regioselectivity could not be attained.

The compound **4** obtained was converted directly into indoles (**5**) by reduction with sodium borohydride in refluxing dioxane. When the reduction was performed at room temperature, the intermediate α-chloromethylbenzyl alcohol (**6**) was isolated, which was rapidly led to indoles (**5**) by treatment under basic condition at room temperature.

Next, we tried to synthesize 1-acyl-3-indolinones (**9** and **10**) from the compounds (**4**). Indolinones have been regarded as useful intermediates for the synthesis of 3-substituted indoles.

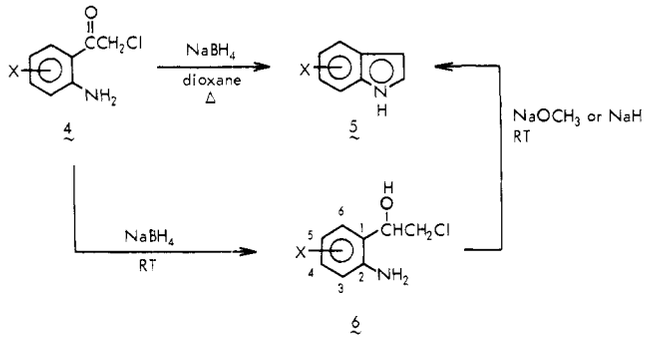
Table IV. Synthesis of Indoles (5) from 2-Amino-α-chloroacetophenones (4)



4 5

run no.	compd	X	refluxing time, h	compd	registry no.	X	yield, %	mp, °C (from)
1	**4a**	H	2.0	**5a**	120-72-9	H	83	50–51 (lit.[6] 52–53) (petroleum ether)
2	**4b**	3-Cl	6.0	**5b**	53924-05-3	7-Cl	64 (74)[a]	57–58 (lit.[10] 57–58) (petroleum ether)
3	**4c**	4-Cl	5.5	**5c**	17422-33-2	6-Cl	79	85–86 (lit.[6] 89–89.5) (petroleum ether)
4	**4d**	5-Cl	5.5	**5d**	17422-32-1	5-Cl	69	67–68 (lit.[6] 71–72) (petroleum ether)
5	**4e**	6-Cl	2.5	**5e**	25235-85-2	4-Cl	90	170–173[c] (lit.[11] 171–173) (EtOH)
6	**4f**	4-F	5.0	**5f**	399-51-9	6-F	72	75–76 (lit.[6] 74–75) (ether–petroleum ether)
7	**4g**	6-F	5.0	**5g**[d]	387-43-9	4-F	86	28–29 (ether–petroleum ether)
8	**4h**	4-OCH_3	4.0	**5h**	3189-13-7	6-OCH_3	34 (47)[a] (40)[b]	87–88 (lit.[6] 88–90) (petroleum ether)
9	**4i**	5-OCH_3	4.0	**5i**	1006-94-6	5-OCH_3	90	54–55 (lit.[6] 56–57) (petroleum ether)
10	**4j**	6-OCH_3	1.0	**5j**	4837-90-5	4-OCH_3	92	67–68 (lit.[6] 69.5) (CH_2Cl_2–petroleum ether)
11	**4k**	4,5-$(OCH_3)_2$	1.0	**5k**	14430-23-0	5,6-$(OCH_3)_2$	54	158–159 (lit.[6] 154–155) (CH_2Cl_2–petroleum ether)
12	**4l**	4-CH_3-5-OCH_3	1.0	**5l**	3139-10-4	5-OCH_3-6-CH_3	84	117–118 (lit.[13] 119–120 °C) (ether–petroleum ether)

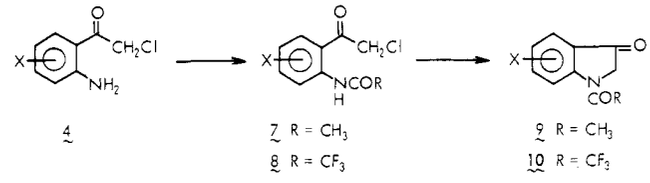
[a] Overall yield from **4** via **6**. [b] Yield obtained by lithium aluminum hydride. [c] Melting point of its picrate. [d] Anal. Calcd for C_8H_6NF: C, 71.10; H, 4.48; N, 10.37; F, 14.06. Found: C, 71.11; H, 4.63; N, 10.24; F, 13.84. IR ($CHCl_3$) ν_{max} 3489 and 1634 cm^{-1}.



4 5 6

Although the Knovenagel or Reformatsky reaction[8] and very recently the Wittig–Horner[9] reaction of the compounds (**9**) have been reported, these routes have been little exploited, because of the relative inaccessibility of the required indolinones.[8] Namely, 2-carboxyphenylglycines prepared from anthranilic acids and bromoacetic acid or from 2-chlorobenzoic acid and glycine are dehydrocyclized in acetic anhydride to 1-acetyl-3-acetoxyindoles. They are selectively hydrolyzed to the desired products (**9**). In contrast, our process is very simple. It involves N-acylation of the amines (**4**) followed by treatment with base at ice to room temperature for a short time. When 1-trifluoroacetyl derivatives (**8**) were used, the cyclization was effected by potassium carbonate in acetonitrile.

In summary, our process provides the simplest and most practical new synthesis of 2,3-unsubstituted indoles (**5**) and 1-acyl-3-indolinones (**9** and **10**). The method has an advantage similar to that of Gassman's method,[5d] because it is in principle a specific ortho substitution reaction of anilines (**1**). Therefore, the starting materials generally are readily available, and moreover, in our case, all reagents used are very common and inexpensive. The serious limitation of our method is that indoles and indolinones bearing nitro or carboalkoxy group cannot be obtained, because the specific ortho



4 7 R = CH_3 8 R = CF_3 9 R = CH_3 10 R = CF_3

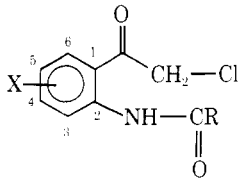
α-chloroacetylation of nitroaniline or carboalkoxyaniline does not afford the desired products.

Experimental Sections

Melting points were determined on a Yanagimoto micromelting apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ solution by a Koken DS-207B or JASCO IRS spectrophotometer. Wavenumbers are expressed in reciprocal centimeters. NMR spectra were taken in $CDCl_3$ solution on a Varian A-60 or T-60 spectrophotometer. Chemical shifts are expressed as δ values (parts per million) from tetramethylsilane. Column chromatography was conducted using silica gel (E. Merck, 70-230 mesh ASTM) and aluminum oxide (E. Merck, Standarisiert). Silica gel GF (E. Merck) was used for both analytical and preparative thin-layer chromatography (TLC). In cases where products were isolated by solvent extraction, the procedure generally followed was to extract the aqueous layer with two to three portions of the indicated solvent, then wash the organic layer with saturated NaCl–H_2O or H_2O and dry it over Na_2SO_4 or $MgSO_4$.

5-Chloro-2-amino-α-chloroacetophenone (4d) (General Procedure). To a stirred solution of boron trichloride (645 mg, 5.5 mmol) in dry benzene (6 mL), a solution of 4-chloroaniline (**1d**) (638

Table V. Physical Data of 2-(Acylamino)-α-chloroacetophenone (7 and 8)



7, R = CH_3
8, R = CF_3

compd	registry no.	X	mp, °C (from)	yield, %	IR ($CHCl_3$), cm^{-1} (ν_{max})	^1H NMR ($CDCl_3$), δ (J, Hz)	molecular[a] formula
7a	68095-22-7	H	123–124 (CH_2Cl_2–EtOH) lit.[11] 123–125 °C	94			
7b	68438-35-7	3-Cl		*b*			
7c	68095-20-5	4-Cl	139–140 (CH_2Cl_2–EtOH)	98	3290 1703 1673 1658	2.20 (3 H, s, $COCH_3$), 4.69 (2 H, s, CH_2), 7.08 (1 H, d of d, J = 9 Hz; J = 2 Hz, C_5–H), 7.77 (1 H, d, J = 9 Hz, C_6–H), 8.85 (1 H, d, J = 2 Hz, C_3–H)	$C_{10}H_9NO_2Cl_2$
7d	68095-26-1	5-Cl	190–191 (CH_2Cl_2–EtOH)	97	3308 1702 1681 1662	2.24 (3 H, s, $COCH_3$), 4.73 (2 H, s, CH_2), 7.47 (1 H, d, J = 2 Hz, C_6–H), 7.70 (1 H, d of d, J = 9 Hz, J = 2 Hz, C_4–H), 8.75 (1 H, d, J = 9 Hz, C_3–H)	$C_{10}H_9NO_2Cl_2$
7e	68095-21-6	6-Cl	130–132 (EtOH–petroleum ether)	*c*	3420 1699	2.12 (3 H, s, $COCH_3$), 4.09 (2 H, s, CH_2), 7.18 (1 H, d of d, J = 8 Hz, J = 2 Hz, C_5–H), 7.38 (1 H, t, J = 8 Hz, C_4–H), 7.91 (1 H, d of d, J = 8 Hz, J = 2, C_3–H)	$C_{10}H_9NO_2Cl_2$
7f	68438-36-8	4-F	131–132 (CH_2Cl_2–EtOH)	*c*	3278 1704 1671 1655	2.23 (3 H, s, $COCH_3$), 4.68 (2 H, s, CH_2), 6.78 (1 H, m, J_{AB} = 9 Hz, J_{AX} = 3 Hz, J_{AF} = 6 Hz, C_5–H), 7.84 (1 H, d of d, J_{AB} = 9 Hz, J_{BF} = 6 Hz, C_6–H), 8.57 (1 H, d of d, J_{AX} = 3 Hz, J_{FX} = 11.8, C_3–H)	$C_{10}H_9NO_2ClF$
7g	68438-37-9	6-F	83–84 (ether–*n*-hexane)	*c*	3303 1704 1671	2.22 (3 H, s, $COCH_3$), 4.74 (2 H, d of d, $^5J_{FH}$ = 4 Hz, CH_2), 6.86 (1 H, m, J_{AB} = 8 Hz, J_{AX} = 1 Hz, J_{AF} = 12.0, C_5–H), 7.52 (1 H, m, J_{AB} = 8 Hz, J_{BX} = 8 Hz, J_{BF} = 7 Hz, C_4–H), 8.46 (1 H, d of d, J_{BX} = 8 Hz, J_{AX} = 1 Hz, C_3–H)	$C_{10}H_9NO_2ClF$
7h	68095-19-2	4-OCH_3	130–131 (CH_2Cl_2–EtOH)	93	3252 1700 1657	2.23 (3 H, s, $COCH_3$), 3.88 (3 H, s, OCH_3), 4.67 (2 H, s, CH_2), 6.63 (1 H, d of d, J = 9 Hz, J = 3 Hz, C_5–H), 7.74 (1 H, d, J = 9 Hz, C_6–H), 8.43 (1 H, d, J = 3 Hz, C_3–H)	$C_{11}H_{12}NO_3Cl$
7i	68095-24-9	5-OCH_3	134–135 (EtOH)	93	3505 1693 1677	2.20 (3 H, s, $COCH_3$), 3.83 (3 H, s, OCH_3), 4.73 (2 H, s, CH_2), 7.07–7.33 (2 H, m, C_4–H and C_6–H), 8.67 (1 H, d of d, J = 9 Hz, J = 1 Hz, C_3–H)	$C_{11}H_{12}NO_3Cl$
7j	68095-18-1	6-OCH_3	99–100 (ether)	*c*	3340 1698 1658	2.20 (3 H, s, $COCH_3$), 3.93 (3 H, s, OCH_3), 4.75 (2 H, s, 6.70 (1 H, d of d, J = 8 Hz, J = 1 Hz, C_5–H), 7.45 (1 H, t, J = 8 Hz, J = 1 Hz, C_3–H)	$C_{11}H_{12}NO_3Cl$
7k	68438-38-0	4,5-$(OCH_3)_2$	175–176 (95% EtOH)	82	3260 3400 1695 1655 1640	2.22 (3 H, s, $COCH_3$), 3.88 (3 H, s, OCH_3), 3.97 (3 H, s, OCH_3), 4.65 (2 H, s, CH_2), 7.20 (1 H, s, C_6–H), 8.52 (1 H, s, C_3–H)	$C_{12}H_{14}NO_4Cl$

Table V (*Continued*)

compd	registry no.	X	mp, °C (from)	yield, %	IR ($CHCl_3$), cm^{-1} (ν_{max})	^1H NMR ($CDCl_3$), δ (*J*, Hz)	molecular[a] formula
8a	68095-23-8	H	114–115 (CH_2Cl_2–*n*-hexane)	96	3235 3186 1734 1678 1661	4.75 (2 H, s, CH_2), 7.2–8.8 (m, 4 H, arom. H)	$C_{10}H_7NO_2ClF_3$
8b	68095-29-4	3-Cl	90–91 (CH_2Cl_2–*n*-hexane)	95	3404 1742 1700	4.64 (2 H, s, CH_2), 7.3–7.8 (m, 3 H, arom. H)	$C_{10}H_6NO_2Cl_2F_3$
8c	68095-28-3	4-Cl	114–115 (CH_2Cl_2–*n*-hexane)	94	3215 3117 1737 1678 1664	4.68 (2 H, s, CH_2), 7.27 (1 H, d of d, J = 9 Hz, J = 3 Hz, C_5–H), 7.88 (1 H, d, J = 9 Hz, C_6–H), 8.78 (1 H, d, J = 3 Hz, C_3–H)	$C_{10}H_6NO_2Cl_2F_3$
8d	68095-27-2	5-Cl	121–122 (EtOH–*n*-hexane)	97	3228 3163 3110 1744 1733 1685 1668	4.70 (2 H, s, CH_2), 7.63 (1 H, d of d, J = 9 Hz, J = 2 Hz, C_4–H), 7.90 (1 H, d, J = 2 Hz, C_6–H), 8.73 (1 H, d, J = 9 Hz, C_3–H)	$C_{10}H_6NO_2Cl_2F_3$
8e	68095-25-0	6-Cl	126–127 (CH_2Cl_2–*n*-hexane)	88	3200 1743 1700	4.70 (2 H, s, CH_2), 7.30 (1 H, d of d, J = 7 Hz, J = 2 Hz, C_5–H), 7.39 (1 H, t, J = 7 Hz, C_4–H), 8.12 (1 H, d of d, J = 7 Hz, J = 2 Hz, C_3–H)	$C_{10}H_6NO_2Cl_2F_3$

[a] All products gave satisfactory elemental analyses (C ±0.3, H ±0.2, N ±0.2, Cl ±0.5, F ±0.5). [b] No reaction. [c] For preparation of **7e, 7f, 7g,** and **7j,** see the corresponding experimental parts.

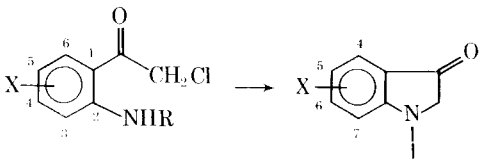
mg, 5 mmol) in dry benzene (6 mL) was added dropwise under ice-cooling. To the resulting mixture containing 4-chloroaniline boron trichloride complex, chloroacetonitrile (0.38 mL, 6 mmol) and aluminum trichloride (734 mg, 5.5 mmol) were added successively. The mixture was then refluxed for 6 h under nitrogen, becoming a solution of two layers. The evolved hydrogen chloride was absorbed through a drying tube containing silica gel or calcium chloride to a surface of aqueous sodium hydroxide. After cooling, ice 2 N hydrochloric acid was added and a yellow precipitate was formed. To hydrolyze the ketimine of **4d,** the mixture was warmed at 80 °C under stirring, until the precipitate had dissolved (ca. 30 min). The cooled mixture was extracted with dichloromethane (three times) and the organic layer was washed with water, dried ($MgSO_4$), and concentrated. The neutral fraction obtained (744 mg) was recrystallized to obtain pure **4d** (674 mg). The acidic layer was made alkaline with 2 N sodium hydroxide and extracted with dichloromethane. Washing, drying, and evaporation of the solvent gave the basic fraction (170 mg). Thin-layer chromatographic purification (silica gel, chloroform containing 10% methanol) gave recovered **1d** (103 mg).

5-Methoxy-2-amino-α-chloroacetophenone (4b). To a stirred solution of boron trichloride (586 mg, 5 mmol) in dry benzene (2 mL) was added a solution of 4-methoxyaniline (**1b**) (616 mg, 5 mmol) in benzene (6 mL) under ice-cooling. Chloroacetonitrile (453 mg, 6 mmol) and then titanium tetrachloride (0.61 mL, 5.5 mmol) were added and the resulting mixture was refluxed for 3 h, during which time the brown suspension present did not dissolve. After cooling, ice 2 N HCl was added and the mixture was warmed at 80 °C for 30 min. The cooled mixture was neutralized with 2 N sodium hydroxide at pH 3 to 4 and extracted with dichloromethane repeatedly. The organic layer was washed with water, dried, and concentrated. The resulting residue (409 mg) was purified analogously to the procedure used for **4d** to give **4b** (400 mg). The acidic layer was made alkaline with 2 N sodium hydroxide and the resulting precipitate was filtered off on a celite layer. The celite layer was washed with dichloromethane and the filtrate was extracted with dichloromethane. The combined solvent was evaporated giving crude **1b** (254 mg, ca. 40%).

6-Chloro-2-amino-α-chloroacetophenone (4e), 4-Chloro-2-amino-α-chloroacetophenone (4f), and Corresponding *N*-Acetyl Derivatives 7e and 7c. In a general procedure analogous to that used for **4d,** 3-chloroaniline (**1e**) (21.2 g) was treated with boron trichloride (21.4 g), chloroacetonitrile (12.0 g), and aluminum trichloride (24.3 g) in dry benzene (ca. 200 mL in total volume). The neutral fraction (22.2 g) containing **4e** and **4f** in a ratio of 14:52 (comparison of the methylene protons at δ 4.70 and 4.60) was recrystallized, giving **4f** (14.0 g, mp 133–134 °C). The concentrated mother liquor was chromatographed on silica gel (24 g). Elution with benzene (200 mL), evaporation of the solvent, and recrystallization gave additional **4f** (794 mg, mp 133–134 °C). The concentrated mother liquor (6.82 g) was warmed with acetic anhydride (20 mL) at 80 °C for 30 min. After evaporation of excess acetic anhydride, the residue obtained (6.82 g) was chromatographed on silica gel (45 g). Elution with benzene (800 mL) and recrystallization of the concentrated eluate gave **7c** (577 mg). Further elution with dichloromethane (800 mL) and recrystallization of the concentrated eluate gave **7e** (4.45 g). The total yield of **4f** amounted to 45%, calculated from isolated **4f** and **7c.** The yield of **4e** amounted to 11% calculated from **7e.** A solution of **7e** (2.0 g) in dry methanol (10 mL) was added to dry methanol containing hydrogen chloride (42 w/w%, 10 mL) and the solution was refluxed for 2 h. The solvent was evaporated, ice-concentrated ammonium hydroxide was added to the residue, and the mixture was extracted with dichloromethane. Washing, drying, evaporation, and recrystallization gave **4e** (1.48 g, 89%). Analogous treatment of **7c** gave **4f.**

6-Fluoro-2-amino-α-chloroacetophenone (4g), 4-Fluoro-2-amino-α-chloroacetophenone (4h), and Corresponding *N*-Acetyl Derivatives 7g and 7f. In a general procedure analogous to that used for **4d,** 3-fluoroaniline (**1f**) (15.7 g) was treated with boron trichloride (18.1 g), chloroacetonitrile (12.8 g), and aluminum trichloride (20.7 g) in dry benzene (ca. 170 mL). The neutral fraction was dissolved in benzene and passed through a silica gel layer (10 g) to remove a polar fraction. The concentrated residue to benzene eluate (16.65 g) was acetylated with acetic anhydride (51 mL) as for a mixture of **4e** and **4f.** The evaporated residue was recrystallized to give **7f** (11.4 g). The concentrated mother liquor (5.59 g) was dissolved in dichloromethane and passed through a silica gel layer (10 g). The eluate with dichloromethane was concentrated and recrystallized giving additional **7f** (1.55 g). The combined mother liquor was concentrated (2.17 g) and chromatographed (silica gel 60, pre-packed column size C, Merck, benzene–ethyl acetate (5:2, 5 mL/min)). From the less polar fraction, additional **7f** (2.22 g) was obtained. Total yield of **7f,** 46.9%. From the more polar fraction, **7g** (2.41 g) was obtained. Hydrolysis of **7g** and **7f** by the method analogous to that used for **7e** gave **4g** and **4h,** respectively (84 and 95%).

Table VI. Synthesis of 1-Acyl-3-indolinones (9 and 10) from 2-(Acylamino)-α-chloroacetophenone (7 and 8)



7, R = $COCH_3$
8, R = $COCF_3$

9, R = $COCH_3$
10, R = $COCF_3$

compd	X	reaction condition: temp	reaction condition: time	compd	registry no.	X	mp, °C (from)	yield, %	IR $CHCl_3$), cm^{-1} (ν_{max})	^1H NMR ($CDCl_3$), δ (J, Hz)	molecular[c] formula
7a	H	I[a]	3 h	**9a**	16800-68-3	H	135–140 (CH_2Cl_2–*n*-hexane) lit.[12] 138	65			
7c	4-Cl	I	10 min	**9c**	68095-16-9	6-Cl	176–178 (EtOH) lit.[12] 171	55	1726 1690	2.32 (3 H, s, $COCH_3$), 4.30 (2 H, s, CH_2), 8.83 (1 H, d of d, J = 8 Hz, J = 2 Hz, C_5–H), 7.65 (1 H, d, J = 8 Hz, C_4–H), 8.52 (1 H, br s, C_7–H)	
7d	5-Cl	I	15 min	**9d**	62486-02-6	5-Cl	154–155 (CH_2Cl_2–EtOH) lit.[12] 163	30	1725 1680	2.31 (3 H, s, ($COCH_3$), 4.28 (2 H, s, CH_2), 7.4–7.6 (2 H, m, C_4–H and C_6–H), 8.48 (1 H, d, J = 8 Hz, C_7–H)	
7e	6-Cl	I	15 min	**9e**	68095-14-7	4-Cl	196–197 (EtOH) lit.[12] 190	83	1725 1690	2.32 (3 H, s, $COCH_3$), 4.30 (2 H, s, CH_2), 7.80 (1 H, d of d, J = 8 Hz, J = 1 Hz, C_5–H), 7.50 (1 H, t, J = 8 Hz, C_6–H), 8.40 (1 H, d of d, J = 8 Hz, J = 1 Hz, C_7–H)	
7f	4-F	I	30 min	**9f**	68438-39-1	6-F	123–126 (ether–petroleum ether)	65	1723 1690	2.32 (3 H, s, $COCH_3$), 4.31 (2 H, 3, CH_2), 6.89 (1 H, m, J_{AB} = 8 Hz, J_{AF} = 8 Hz, J_{AX} = 2 Hz, C_5–H), 7.73 (1 H, d of d, J_{AB} = 8 Hz, J_{BF} = 6 Hz, C_4–H), 8.21 (1 H, d of d, J_{FX} = 10 Hz, J_{AX} = 2 Hz, C_6–H)	C_8H_6NF
7g	6-F	I	30 min	**9g**	68438-40-4	4-F	152–154 (ether–petroleum ether)	54	1729 1691	2.31 (3 H, s, $COCH_3$), 4.30 (2 H, s, CH_2), 6.80 (1 H, m, J_{AB} = 8 Hz, J_{AF} = 8 Hz, J_{AX} = 1 Hz, C_5–H), 7.58 (1 H, m, J_{AB} = 8 Hz, J_{BX} = 8 Hz, J_{BF} = 6 Hz, C_6–H), 8.27 (1 H, d of d, J_{BX} = 8 Hz, J_{AX} = 1 Hz, C_6–H)	C_8H_6NF

7h	4-OCH_3	I	1.5 h	**9h**	68095-10-3	6-OCH_3	180–181 (EtOH) lit.[12] 178	83	1710 1683	2.32 (3 H, s, $COCH_3$), 3.91 (3 H, s, OCH_3), 7.08 (2 H, s, CH_2), 6.73 (1 H, d of d, J = 9 Hz, J = 2 Hz, C_5–H), 7.63 (1 H, d, J = 9 Hz, C_4–H), 8.03 (1 H, br s, C_7–H)	$C_{11}H_{11}NO_3$
7i	5-OCH_3	R[b]	15 min	**9i**	62486-04-8	5-OCH_3	184–187 dec (CH_2Cl_2–EtOH) lit.[12] 170	64	1718 1677	2.28 (3 H, s, $COCH_3$), 3.82 (3 H, s, OCH_3), 4.27 (2 H, s, CH_2), 7.1–7.3 (2 H, m, C_4–H and C_6–H), 8.42 (1 H, d, J = 8 Hz, C_7–H)	$C_{11}H_{11}NO_3$
7j	6-OCH_3	I	2 h	**9j**	68095-13-6	4-OCH_3	148–150 (CH_2Cl_2–EtOH)	73	1713 1688	2.30 (3 H, s, $COCH_3$), 3.92 (3 H, s, OCH_3), 4.22 (2 H, s, CH_2), 6.60 (1 H, d, J = 9 Hz, C_5–H), 7.52 (1 H, t, J = 9 Hz, C_6–H), 8.03 (1 H, d, J = 9 Hz, C_7–H)	$C_{11}H_{11}NO_3$
7k	4,5-$(OCH_3)_2$	I	1 h	**9k**	68438-41-5	5,6-$(OCH_3)_2$	236–238 (95% EtOH)	56	1704 1675	2.30 (3 H, s, $COCH_3$), 3.88 (3 H, s, OCH_3), 4.00 (3 H, s, OCH_3), 4.25 (2 H, s, CH_2), 7.08 (1 H, s, C_4–H), 8.12 (1 H, s, C_7–H)	$C_{12}H_{13}NO_4$
7l	4-CH_3–5-OCH_3	I	40 min	**9l**	68438-42-6	5-OCH_3–6-CH_3	198–203 (ether–petroleum ether)	44[e]	1715[f]	2.32 (6 H, s, $COCH_3$ + C_6–CH_3), 3.85 (3 H, s, –OCH_3), 4.28 (2 H, s, –CH_2–), 7.08 (1 H, s, C_4–H), 8.36 (1 H, s, C_7–H)	$C_{12}H_{13}NO_3$
8a	H	R	2.5 h	**10a**	68095-12-5	H	85–86 (CH_2Cl_2–*n*-hexane)	81	1715 1601	4.51 (2 H, g, $^5J_{FH}$ = 1 Hz, CH_2), 7.38–8.61 (4 H, m, arom. H)	$C_{10}H_6NO_2F_3$
8b	3-Cl					7-Cl		*d*			
8c	4-Cl	R	2 h	**10c**	68095-17-0	6-Cl	157–158 (CH_2Cl_2–*n*-hexane)	76	1733 1715	4.53 (2 H, q, $^5J_{FH}$ = 1 Hz, CH_2), 7.34 (1 H, d of d, J = 8 Hz, J = 2 Hz, C_5–H), 7.77 (1 H, d, J = 8 Hz, C_4–H), 8.45 (1 H, d, J = 2 Hz, C_7–H)	$C_{10}H_5NO_2ClF_3$
8d	5-Cl	R	3 h	**10d**	68095-15-8	5-Cl	146–148 (CH_2Cl_2–*n*-hexane)	52	1734 1719	4.54 (2 H, q, $^5J_{FH}$ = 1 Hz, CH_2), 7.6–8.6 (3 H, m, arom. H)	$C_{10}H_5NO_2ClF_3$
8e	6-Cl	R	30 min	**10e**	68095-11-4	4-Cl	157–158 (benzene–*n*-hexane)	88	1719	4.53 (2 H, q, $^5J_{FH}$ = 1 Hz, CH_2), 7.27 (1 H, d of d, J = 8 Hz, J = 1 Hz, C_5–H), 7.63 (1 H, t, J = 8 Hz, C_6–H), 8.46 (1 H, d of d, J = 8 Hz, J = 1 Hz, C_7–H)	$C_{10}H_5NO_2ClF_3$

[a] I, ice-cooling. [b] R, room temperature. [c] All products gave satisfactory elemental analyses (C ±0.3, H ±0.2, N ±0.2, Cl ±0.3, F ±0.2). [d] No reaction. [e] Over-all yield based on 41. [f] In Nujol.

4-Methoxy-2-amino-α-chloroacetophenone (4j), 6-Methoxy-2-amino-α-chloroacetophenone (4k), and Corresponding *N*-Acetyl Derivatives 7h and 7j. Estimation of the yield of **4j** and **4k** by GLC. The basic fraction obtained after hydrolysis by 2 N hydrochloric acid was dissolved in benzene and passed through an alumina layer to remove a polar fraction. The concentrated benzene eluate was analyzed by GLC. Column, 2 m, 1% OV-1; column temp, 180 °C; carrier gas, N_2, 1.4 kg/cm^2; retention time, **4k** (2.4 min) and **4j** (3.8 min).

Separation of 4j and 4k by Conversion into Their *N*-Acetyl Derivatives 7h and 7j (Run 6). The neutral fraction (5.43 g) containing **4j** and **4k** in a ratio of 38:28 (comparison of the methylene protons at δ 4.57 and 4.74) was acetylated and purified as described for **4g** and **4h.** The eluate with dichloromethane was concentrated and recrystallized giving **7h** (3.15 g). The concentrated mother liquor was recrystallized giving **7j** (608 mg). **7h** and **7j** were deacetylated as described for **4e** and **4f** giving **4j** and **4k,** respectively.

Separation of 4j and 4k by Thin-Layer Chromatography (TLC) (Run 3). The basic fraction (613 mg) was purified successively on TLC (topless method, *n*-hexane–benzene 2:1 and 1:1, developed for 30 h) giving **4j** (389 mg) and **4k** (151 mg) in the order of decreasing polarity.

Preparation of Indoles (5) from 2-Amino-α-chloroacetophenones (4) (General Procedure for Table IV Experiments). To a stirred solution of 2-amino-α-chloroacetophenone (**4,** 1 mmol) in dioxane (5 mL) containing water (0.5 mL) was added sodium borohydride (1.1 mmol) and the solution was refluxed for the period indicated in Table IV. After removal of the solvent, water was added and the mixture was extracted with dichloromethane. The extract was dissolved in benzene and passed through a silica gel layer (ca. 2 g) to remove a polar fraction. The eluate with benzene was concentrated giving indole (**5**) (one spot, on TLC, dichloromethane).

6-Methoxyindole (5h) by Lithium Aluminum Hydride Reduction. To a stirred solution of 5-methoxy-2-amino-α-chloroacetophenone (**4h,** 200 mg, 1 mmol) in dry ether (8 mL) was added lithium aluminum hydride (40 mg, 1.1. mmol) and the mixture was refluxed for 2 h. After cooling, excess hydride was decomposed with ethyl acetate. Water was added to the mixture, which next was extracted with ether. The extract (142 mg) was dissolved in benzene and petroleum ether (1:1) and passed through a silica gel layer (1.5 g). The eluate with the solvent (60 mL) was concentrated to give **5h** (58 mg).

α-Chloromethyl-2-amino-3-chlorobenzyl Alcohol (6, X = 3-Cl). To a stirred solution of 3-chloro-2-amino-α-chloroacetophenone (**4b,** 410 mg, 2 mmol) in methanol (10 mL) containing water (0.5 mL) was added sodium borohydride (29 mg, 0.75 mmol) and the solution was kept for 5 min. Water was added and the solution was extracted with dichloromethane. Concentration of the organic phase gave **6** (X = 3-Cl, 377 mg, 92%, one spot on TLC, dichloromethane): mp 67–68 °C (petroleum ether); IR ($CHCl_3$) ν_{max} 3570, 3470, and 3380 (OH and NH); ^{1}H-NMR ($CDCl_3$ + D_2O) δ 3.85 and 3.88 (2 H, ABX system, J_{AB} = 11 Hz, J_{AX} = 9 Hz, J_{BX} = 4 Hz, CH_2), 4.88 (1 H, q, J_{AX} = 9 Hz, J_{BX} = 4 Hz, CH), 6.63 (1 H, t, J = 8 Hz, C_5-H), 6.99 and 7.25 (2 H, two d of d, J = 8 Hz, J = 2 Hz, C_4–H and C_6–H). Anal. Calcd for $C_8H_9NOCl_2$: C, 46.62; H, 4.40; N, 6.80; Cl, 34.41. Found: C, 46.74; H, 4.47; N, 6.88; Cl, 34.31.

6-Methoxyindole (5h) from 4-Methoxy-2-amino-α-chloroacetophenone (4h) via α-Chloromethyl-2-amino-4-methoxybenzyl Alcohol (6, X = 4-OCH$_3$). To a stirred solution of **4h** (200 mg, 1 mmol) in methanol (6 mL) containing water (0.5 mL) was added sodium borohydride (38 mg, 1 mmol), and the solution was kept for 5 min at room temperature. An aqueous solution of ammonium chloride was added and the solution was extracted with dichloromethane. Concentration of the organic layer gave crystalline **6** (X = 4-OCH$_3$) (205 mg, one spot on TLC (CH_2Cl_2)): IR ($CHCl_3$) ν_{max} = 3570, 3470, and 3380. This was dissolved in dimethylformamide (4 mL) whereupon sodium hydride (50 mg, 50% in oil, 1 mmol) was added under ice-cooling. After stirring for 50 min at room temperature under nitrogen, ice was added and the mixture was extracted with ether. The extract was suspended in petroleum ether and passed through a silica gel layer (1.5 g) to remove a nonpolar fraction. The eluate with benzene (40 mL) was concentrated giving **5h** (69 mg).

2-(Acetylamino)-α-chloroacetophenone (7). 2-Amino-α-chloroacetophenone (**4**) was dissolved in acetic anhydride and the solution was heated at 80–85 °C (bath temperature) for 30 min. After concentration to dryness at reduced pressure, the residue was dissolved in dichloromethane and passed through a silica gel layer to remove a polar fraction. The eluate with dichloromethane was concentrated and recrystallized to give **7.**

2-(Trifluoroacetylamino)-α-chloroacetophenone (8). A solution of 2-amino-α-chloroacetophenone (**4**) in dry benzene containing trifluoroacetic anhydride (1.2 equiv) was allowed to stand for 2 to 5 min at room temperature. After concentration to dryness, the residue was worked up as described for **7.**

1-Acetyl-3-indolinone (9). To a stirred suspension of sodium hydride (1.05 equiv) in monoglyme (5 mL) was added a solution of 2-(acetylamino)-α-chloroacetophenone (**7,** 1 equiv) in the same solvent (5 mL) under ice-cooling. This was stirred for the period given in Table VI. Ice and 2 N hydrochloric acid were added and the mixture was extracted with benzene or dichloromethane. The extract was dissolved in benzene and chromatographed on silica gel (ca. 2 g). The eluate with benzene and dichloromethane (1:1) was collected and concentrated giving **9.**

1-Trifluoroacetyl-3-indolinone (10). To a sitrred solution of a 2-trifluoroacetyl-α-chloroacetophenone (**8,** 1 mmol) in acetonitrile (5 mL) was added potassium carbonate (0.75 mmol) and the mixture was stirred for the period given in Table VI. Water was added and the mixture was extracted with benzene. The extract was dissolved in benzene and chromatographed on silica gel. The eluate with benzene was collected and concentrated giving **10.**

Registry No.—**6** (X = 3-Cl), 68095-31-8; **6** (X = 4-OCH$_3$), 68438-43-7; boron trichloride, 10294-34-5.

References and Notes

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