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A STUDY OF CERTAIN ASPECTS OF THE VON BRAUN REACTION

by
Richard David Carlson

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in the
University of Michigan
1959

Doctoral Committee:

Professor Wyman R. Vaughan, Chairman
Professor Frederick F. Blicke
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Assistant Professor Bruno Jaselskis
Professor Peter A. S. Smith

ACKNOWLEDGEMENT

The author wishes to express his sincere appreciation to Dr. Wyman R. Vaughan who suggested the problem, and without whose kind and thoughtful assistance this work would neither have been begun nor completed.

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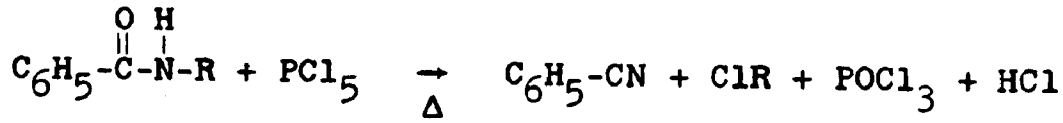
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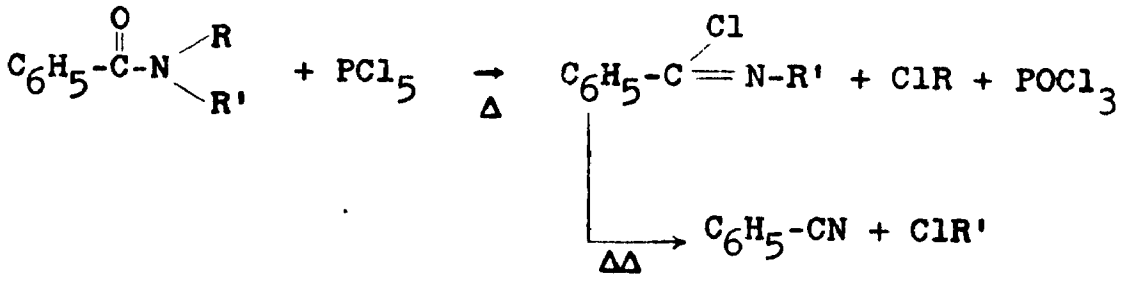
HISTORICAL BACKGROUND

The von Braun Reaction

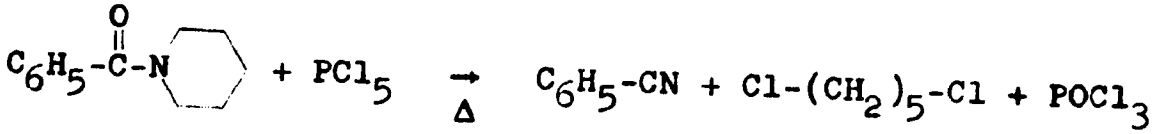
The formation of an alkyl halide and benzonitrile by heating an N-substituted benzamide with phosphorus pentachloride or pentabromide is known as the von Braun reaction.[1]



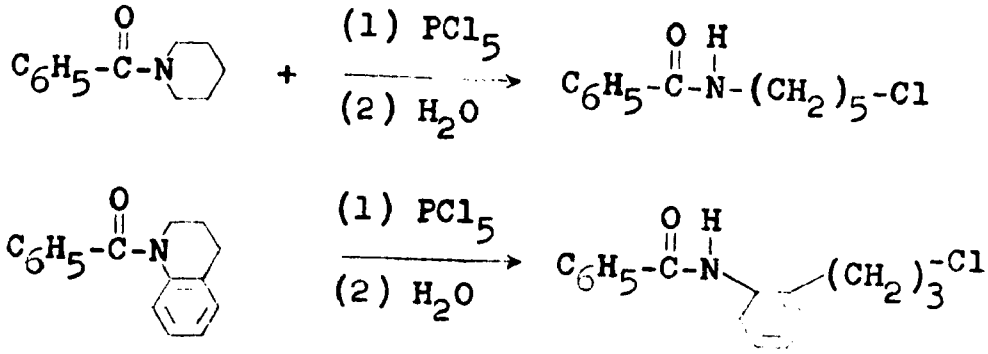
The reaction was first observed by von Pechmann[2] in 1900. He found that when N-methylbenzamide was heated with an equimolar amount of phosphorus pentachloride and the resulting mixture distilled at atmospheric pressure, benzonitrile and methyl chloride were obtained. The reaction was confirmed in 1903 by Ley and Holzweissig[3] who found that benzonitrile and benzyl chloride were produced when N-benzylbenzamide was treated with phosphorus pentachloride. In 1904, von Braun[4] demonstrated that benzamides and naphthamides of secondary amines would also undergo the reaction, eliminating one alkyl group with moderate heating and the second with distillation at atmospheric pressure.



If the second substituent of the nitrogen was aromatic, the imidyl chloride produced was stable to heat and the aromatic chloride was not produced. von Braun[5] also showed that benzamides of cyclic amines would undergo the reaction with a phosphorus pentahalide to give the open chain dihalide.



This reaction could also be interrupted at the halfway point[6].



von Braun and Weismantel[7] studied the ease of elimination of the hydrocarbon portion of secondary amines by stopping the reaction of the benzamides of these amines with phosphorus pentachloride at the halfway point. They found that the hydrocarbon radicals, $PhCH_2$, Me, Et, Pr and Bu were eliminated competitively as the alkyl chloride in the order given. von Braun, Kuhn and Weismantel[8] found that p-chlorobenzyl chloride was eliminated in preference to the p-bromo compound and that p-bromobenzyl chloride was eliminated in preference to p-iodobenzyl chloride. These same workers also found that p-chlorobenzyl chloride was

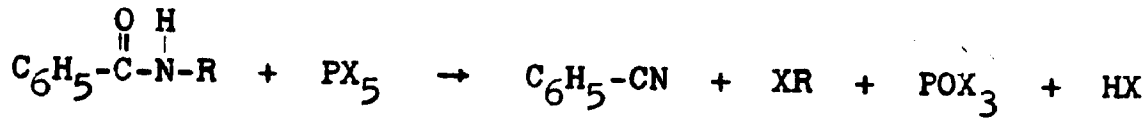
eliminated in preference to either m-chloro or o-chlorobenzyl chloride.

von Braun and Irmisch[9] found that phosphorus pentabromide need not be used for the preparation of alkyl bromides. In their hands the benzamide of heptadecylamine gave a 60% yield of heptadecyl bromide when treated with an equimolar mixture of phosphorus pentachloride and bromine. The yield was increased to 73% when pure phosphorus pentabromide was used.

Leonard and Nommensen[10] studied the reaction in 1949. These workers reported that the yield of halide decreased with an increase in hindrance at the α_N-carbon, but that there was a negligible influence of hindrance at the carbonyl carbon. They also reported predominant inversion at the asymmetric α_N-carbon of N-benzoyl-s-butylamine. The following tables contain many of the von Braun reactions which have been run.

TABLE I

von Braun Reactions of Monosubstituted Benzamides



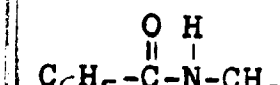
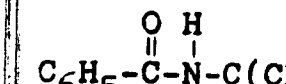
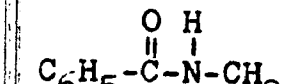
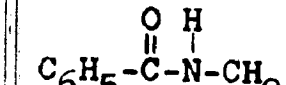
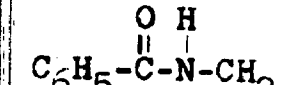
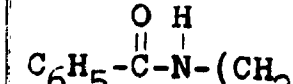
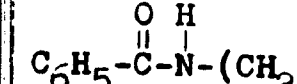
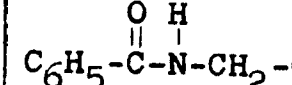
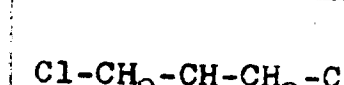
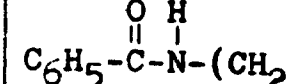
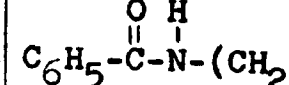
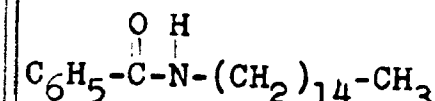
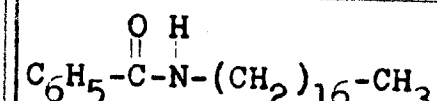
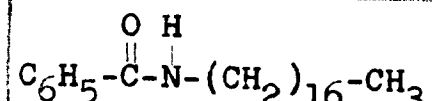
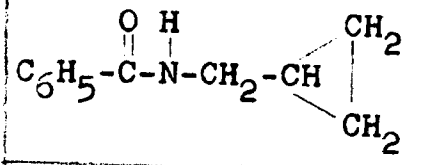
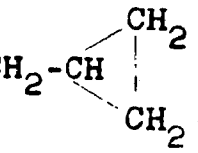
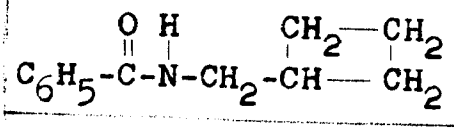
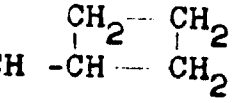
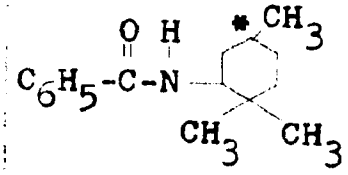
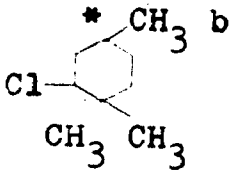
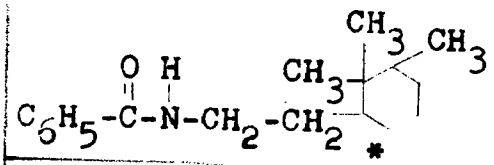
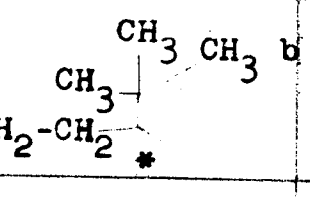
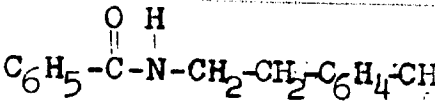
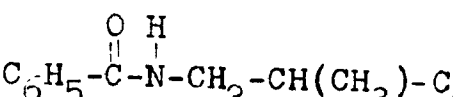
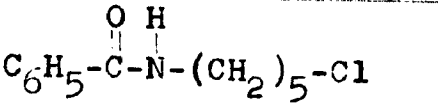
Amide	X	Product	% Yield	Ref.
	Cl	$Cl-CH_3$	-	2
	Cl	$C_6H_5-CN + ClC(CH_3)_3$[a]	-	11
	Cl	$Cl-CH_2-C_6H_5$	-	3
	Cl	$Cl-CH_2-\alpha-C_{10}H_7$	65-70	12
	Br	$Br-CH_2-\alpha-C_{10}H_7$	-	12
	Cl	$Cl(CH_2)_4-C_6H_5$	75	13
	Cl	$Cl(CH_2)_5-C_6H_5$	73-75	13,14
	Cl		25	15
	Cl	$Cl-(CH_2)_5CN$	-	16
	Br	$Br-(CH_2)_8CH_3$	70	14

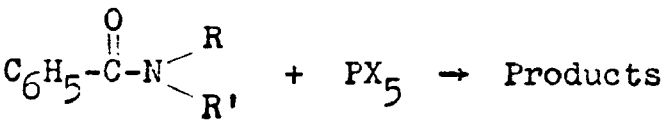
TABLE I (continued

Amide	X	Product	% Yield	Ref.
	Cl	$Cl-(CH_2)_{14}-CH_3$	-	14
	Br	$Br-(CH_2)_{16}-CH_3$	73	9
	Cl	$Cl-(CH_2)_{16}-CH_3$	50	14
	Br		30	17
	Br		31	17
	Cl	 b	40	18
	Cl	 b	50	18
 (m)	Cl	$Cl-CH_2-CH_2-C_6H_4-CH_3$ (m)	50	19
	Cl	$Cl-CH_2-CH(CH_3)-C_6H_5$	25	19
	Cl	$Cl-(CH_2)_5-Cl$	70-80	6

a. The chloride was not isolated.
b. Optically active at the site indicated.

TABLE II

von Braun Reactions of N,N-Disubstituted Aromatic Amides



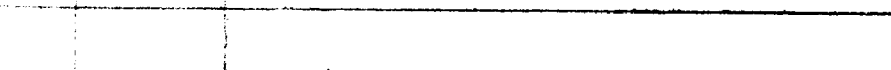
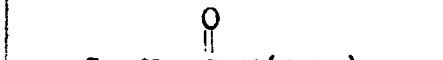
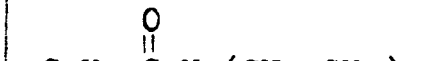
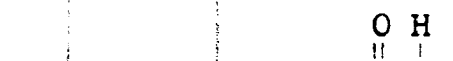
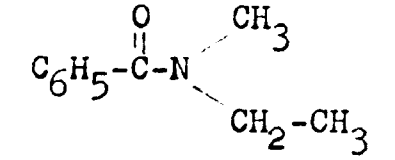
Amide	X	Product	% Yield	Ref.
	Cl		70-80	4
	Cl		quant.	4
	Cl		-	4
	Cl		-	4
	Cl		-	4
	Cl		-	7

TABLE II continued

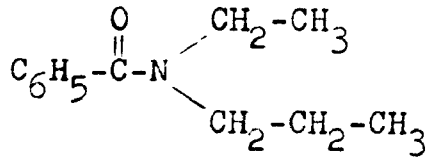
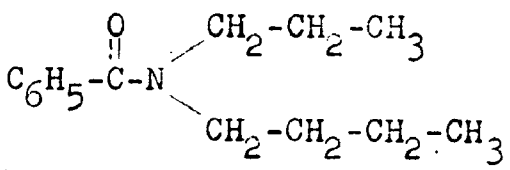
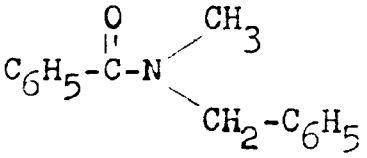
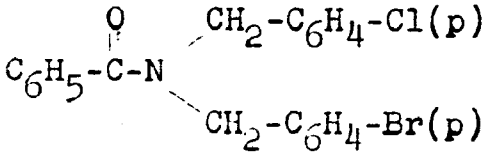
Amide	X	Product	% Yield	Ref.
	Cl	$Cl-CH_2-CH_3$	-	7
	Cl	$Cl-CH_2-CH_2-CH_3$	-	7
	Cl	$Cl-CH_2-CH_2-C_6H_4-NO_2(p)$	-	20
	Cl	$Cl-CH_2-C_6H_5$	-	7
	Cl	$Cl-CH_2-C_6H_4-Cl(p)$	-	8

TABLE II continued

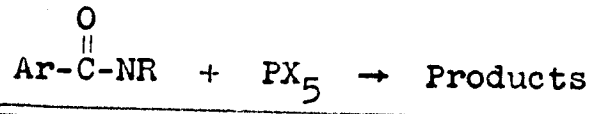
Amides	X	Product	% Yield	Ref.
$C_6H_5-C(=O)-N(CH_2-C_6H_4-Br(p))(CH_2-C_6H_4-I(p))$	Cl	$Cl-CH_2-C_6H_4-Br(p)$	-	8
$C_6H_5-C(=O)-N(CH_2-C_6H_4-Cl(m))(CH_2-C_6H_4-Cl(p))$	Cl	$Cl-CH_2-C_6H_4-Cl(p)$	-	8
$C_6H_5-C(=O)-N(CH_2-C_6H_4-Cl(p))(CH_2-C_6H_4-Cl(o))$	Cl	$Cl-CH_2-C_6H_4-Cl(p)$	-	8
$C_6H_5-C(=O)-N(CH_2-C_6H_4-Cl(o))(CH_2-C_6H_4-Cl(m))$	Cl	$Cl-CH_2-C_6H_4-Cl(o)$ + $Cl-CH_2-C_6H_4-Cl(m)$	-	8
$C_6H_5-C(=O)-N-[CH_2-C_6H_4-Cl(m)]$	Cl	$Cl-CH_2-C_6H_4-Cl(m)$	60	8

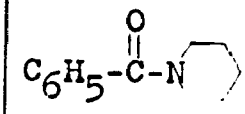
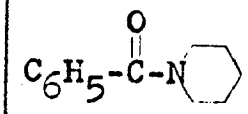
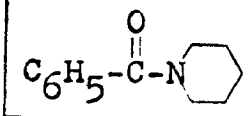
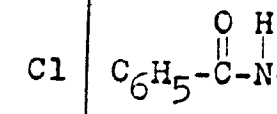
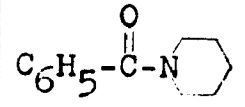
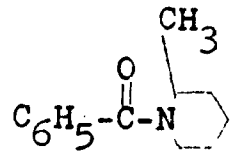
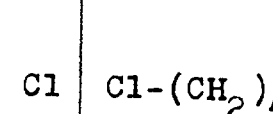
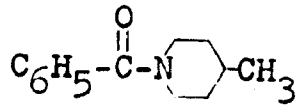
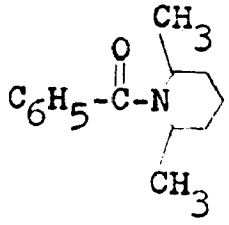
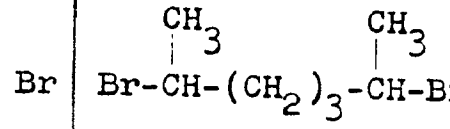
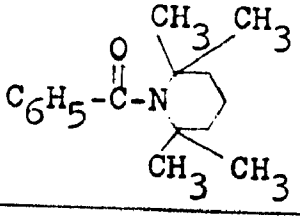
TABLE II continued

Amides	X	Product	% Yield	Ref.
$C_6H_5-\overset{O}{\overset{\|}{C}}-N(CH_2-\alpha-C_{10}H_7)_2$	Cl	$Cl-CH_2-\alpha-C_{10}H_7$	65-70	12
$C_6H_5-\overset{O}{\overset{\|}{C}}-\overset{CH_3}{\overset{\|}{N}}-C_6H_5$	Cl	$C_6H_5-\overset{Cl}{\overset{\|}{C}}=N-C_6H_5$	-	4
$C_6H_5-\overset{O}{\overset{\|}{C}}-N(CH_2-C_6H_5)(C_6H_5)$	Cl	$Cl-CH_2-C_6H_5$ + $C_6H_5-\overset{Cl}{\overset{\|}{C}}=N-C_6H_5$	90	4

TABLE III

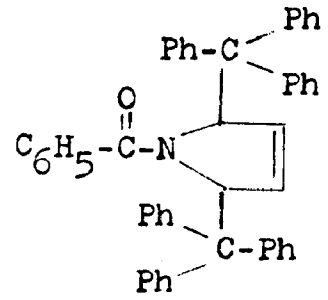
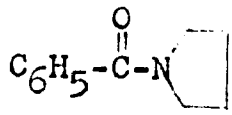
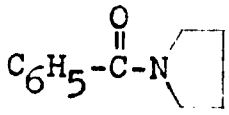
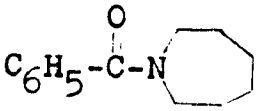
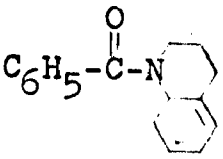
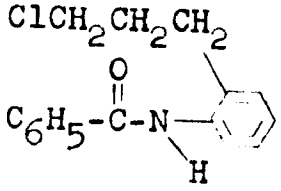
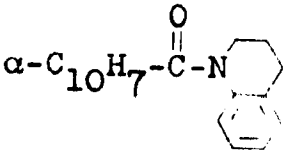
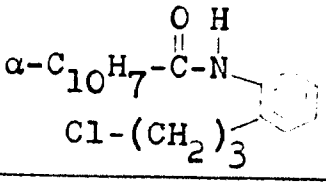
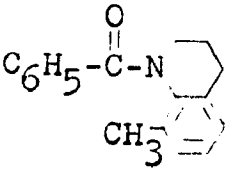
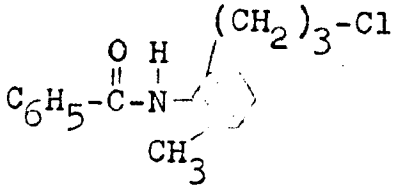
von Braun Reactions of Aromatic Amides of Cyclic Amines



Amide	X	Product	% Yield	Ref.
	Br	$Br-(CH_2)_5-Br$	65-78	5 21 22
	Cl	$Cl-(CH_2)_5-Cl$	70-80	6
	Cl		-	6
	a	$Br-(CH_2)_5-Br$	50	9
	Cl		-	23
	Br	$(Br-CH_2-CH_2)_2-CH-CH_3$	65	24
	Br		19	10
	Br	———	0	10

a. An equimolar mixture of PCl_3 and Br_2 was used.

TABLE III continued

Amide	X	Product	% Yield	Ref.
	Br	$Ph_3C-CH(Br)-CH(Br)-CH(Br)-CH(Br)-CPh_3$	15	25
	Br	$Br-(CH_2)_4-Br$	70	26
	Cl	$Cl(CH_2)_4-Cl$	70	26
	Cl[b]	$Cl(CH_2)_6-Cl$	65	27
	Cl		50-60	6
	Cl		40-50	28
	Cl		-	19

b. The product was isolated as the diphenyl ether.

TABLE III continued

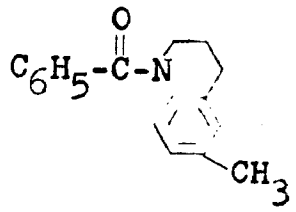
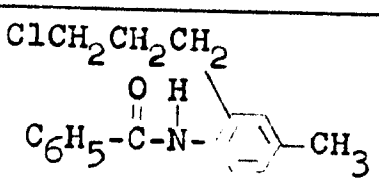
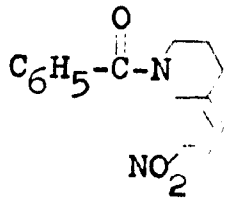
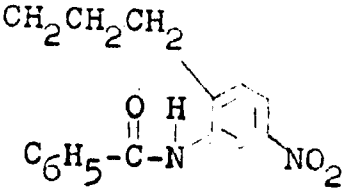
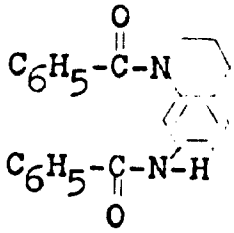
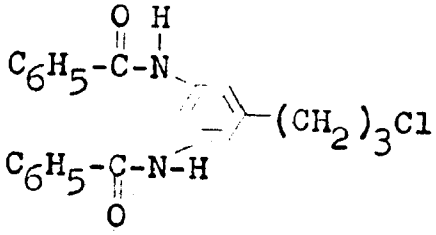
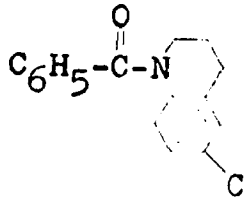
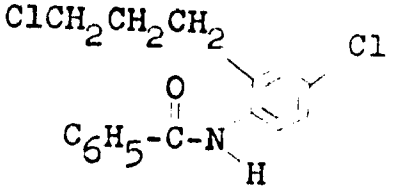
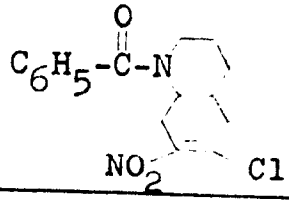
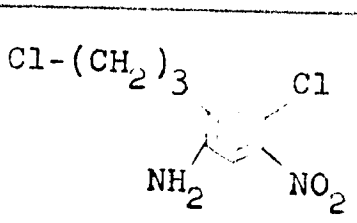
Amide	X	Product	% Yield	Ref.
	Cl		60	19
	Cl		65	29
	Cl		—	29
	Cl		50-65	29
	Cl		50	29

TABLE III continued

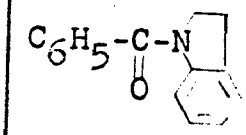
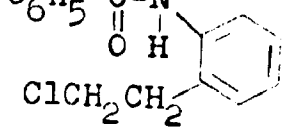
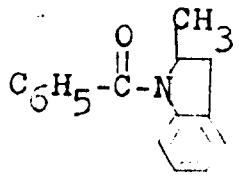
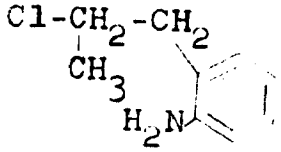
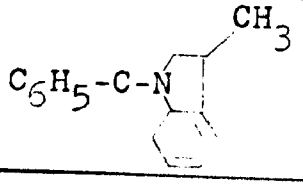
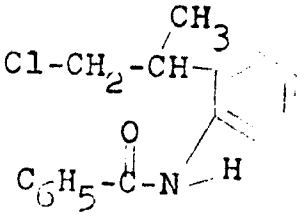
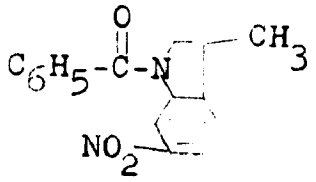
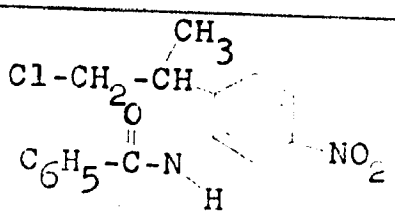
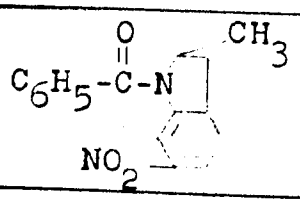
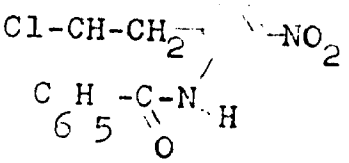
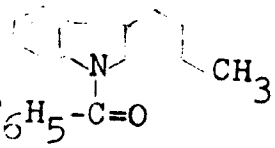
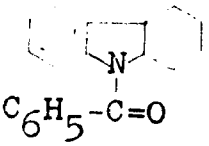
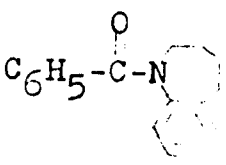
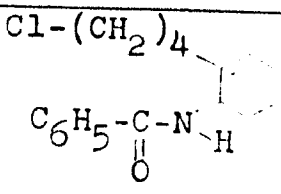
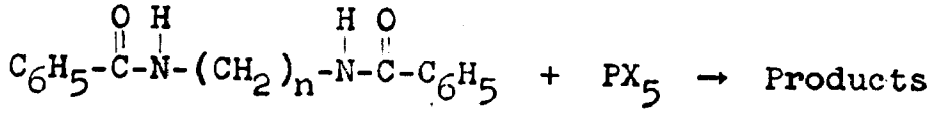
Amide	X	Product	% Yield	Ref.
	Cl		30	30
	Cl		30-40	31
	Cl		50	32
	Cl		75	29
	Cl		65	29
	Cl	(p)CH_3-C_6H_4-(o)C_6H_4-NH-CO-C_6H_5	20-25	33
	Cl	C_6H_5-(o)C_6H_4-NH-CO-C_6H_5	20-25	33
	Cl		quant.	34

TABLE IV

von Braun Reactions of N,N'-Dibenzamides of Diamines



$$C_6H_5\text{-}\overset{\overset{O}{\|}}{C}\text{-}\overset{\overset{H}{|}}{N}\text{-}(CH_2)_n\text{-}\overset{\overset{H}{|}}{N}\text{-}\overset{\overset{O}{\|}}{C}\text{-}C_6H_5 + PX_5 \rightarrow \text{Products}$$

Amide	X	Product	% Yield	Ref.
n = 2	Cl	$Cl\text{-}CH_2\text{-}CH_2\text{-}Cl$	-	35
n = 4	Br	$Br(CH_2)_4Br$	70	36
n = 5	Cl	$Cl(CH_2)_5Cl$	60	35
n = 5	Cl	$Cl(CH_2)_5NH_2$	25	35
n = 6	Cl	$Cl(CH_2)_6Cl$	60	35
n = 6	Cl	$Cl(CH_2)_6NH_2$	25	35
n = 6	Br	$Br(CH_2)_6Br$	-	37
n = 7	Cl	$Cl(CH_2)_7Cl$	60	35
n = 7	Cl	$Cl(CH_2)_7NH_2$	25	35
n = 7	Br	$Br(CH_2)_7Br$	-	37
n = 7	Cl	$C_6H_5\text{-}\overset{\overset{O}{\|}}{C}\text{-}\overset{\overset{H}{|}}{N}\text{-}(CH_2)_7Cl$	40	38
n = 8	Br	$Br(CH_2)_8Br$	74	39
n = 8	Cl	$C_6H_5\text{-}\overset{\overset{O}{\|}}{C}\text{-}\overset{\overset{H}{|}}{N}(CH_2)_8Cl$	30	38

TABLE IV continued

Amide	X	Product	% Yield	Ref.
n = 9	Cl	$Cl(CH_2)_9Cl$	60	40
n = 9	Cl	$C_6H_5-\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{\|}{N}}(CH_2)_9Cl$	-	40
n = 11	Cl	$Cl(CH_2)_{11}Cl$	55	40
n = 12	Cl	$Cl(CH_2)_{12}Cl$	60	14
n = 12	Cl	$C_6H_5-\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{\|}{N}}(CH_2)_{12}-Cl$	30	38
$C_6H_5\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{\|}{N}}CH_2\overset{CH_3}{\overset{\|}{C}}HCH_2CH_2\overset{H}{\overset{\|}{N}}-\overset{O}{\overset{\|}{C}}C_6H_5$	Cl	$ClCH_2\overset{CH_3}{\overset{\|}{C}}HCH_2CH_2Cl$	28	41
$C_6H_5\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{\|}{N}}CH_2\overset{CH_3}{\overset{\|}{C}}HCH_2CH_2\overset{H}{\overset{\|}{N}}-\overset{O}{\overset{\|}{C}}C_6H_5$	Br	$BrCH_2\overset{CH_3}{\overset{\|}{C}}HCH_2CH_2Cl$	40	41

Classification of N-Substituted Amides by Their Reaction with Phosphorus Pentahalides and the Stability of the Corresponding Imidyl Halides Towards Heat

von Pechmann[2], Ley and Holzweissig[3], and von Braun[4] all believed that the reaction proceeded through an imidyl halide. In fact, the reaction was discovered by von Pechmann in an attempt to prepare N-methylbenzimidyl chloride. (The fully aromatic imidyl halides,

$$Ar\text{-}\overset{Cl(Br)}{\overset{|}{C}}{=}N\text{-}Ar\ ,$$

had been known for some time[42] prior to the discovery that those with an alkyl substituent on the nitrogen decomposed with heat into the halide and aromatic nitrile.)

von Braun extended the investigation of imidyl halides to those derived from non-aromatic amides, and as a result of his work N-substituted amides can be divided into a number of groups on the basis of their reactions with phosphorus pentahalides and the stability of the corresponding imidyl halides towards heat.

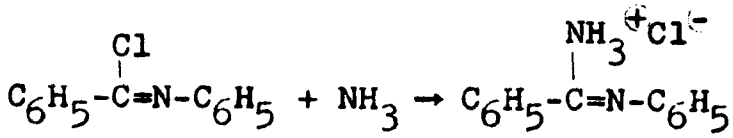
Amides of Type I: $Ar\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{H}{\overset{|}{N}}\text{-}Ar$.

These afford the most stable type of imidyl halide which can be prepared in nearly quantitative yields[42,43] by the reaction of N-aryl derivatives of aromatic amides with a phosphorus pentahalide. They are stable enough to be distilled at atmospheric pressure.

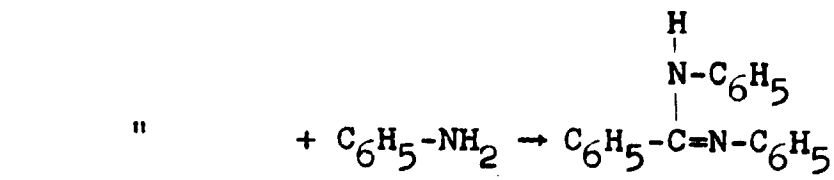
These compounds give the starting amide when treated with water (as do all types of imidyl halides) and they undergo a large variety of nucleophilic substitution reactions, some of which are shown in Chart I.

Chart I

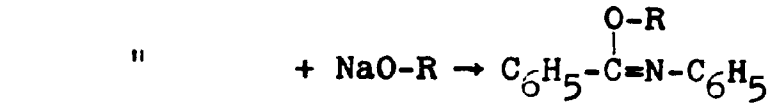
Reactions of N-Phenylbenzimidyl Chlorides



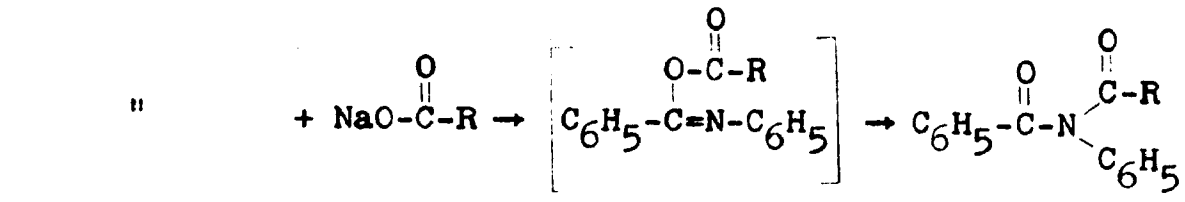
(1) (ref. 1,4)



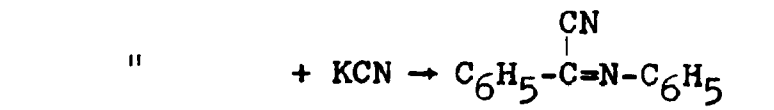
(2) (ref. 45,46)



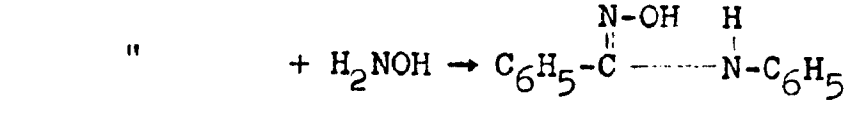
(3) (ref. 47)



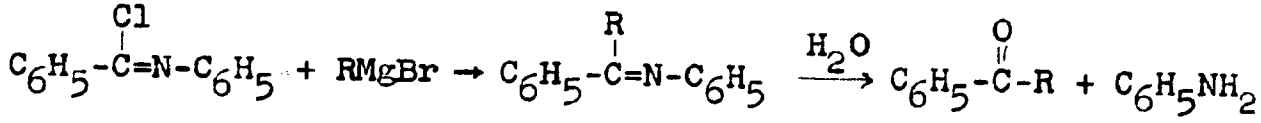
(4) (ref. 43,48)



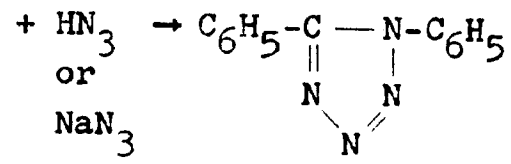
(5) (ref. 43)



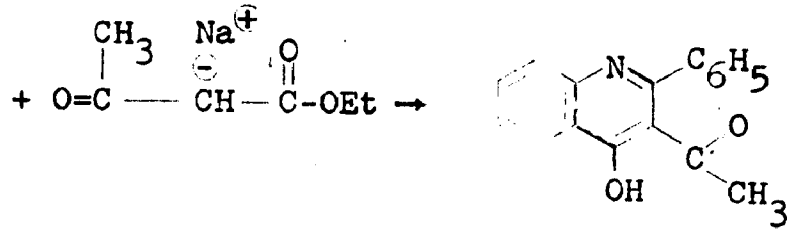
(6) (ref. 49)



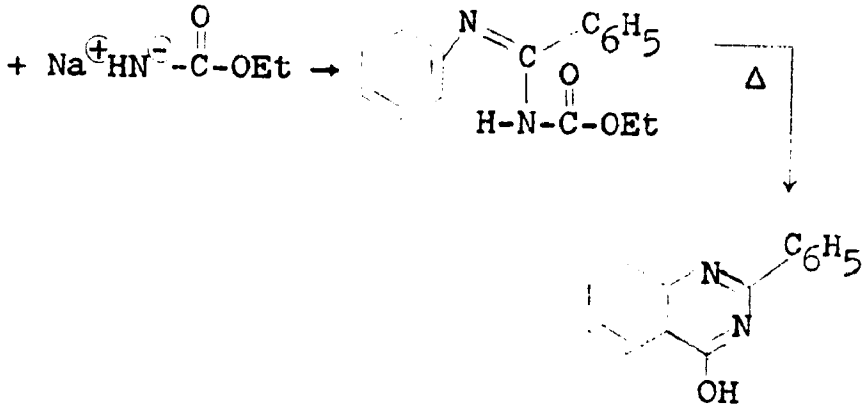
(7) (ref. 50)



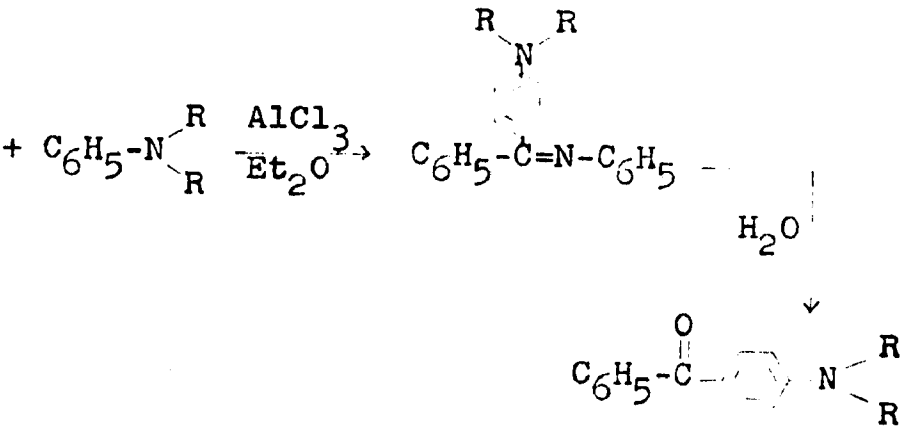
(8) (ref. 51,52)



(9) (ref. 53)



(10) (ref. 54)



(11) (ref. 55)

Amides of Type Ib: $Ar-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-R$.

This type of amide gives rise to the von Braun reaction and has already been partially discussed. The imidyl halides formed from this type of amide can be isolated, but not with the ease of those of type Ia. They can be distilled, but only at reduced pressure, and this becomes more difficult the higher the boiling point of the imidyl halide in question[56]. Imidyl halides of this type are decomposed by heat into the von Braun reaction products, aronitrile and alkyl halide[57].

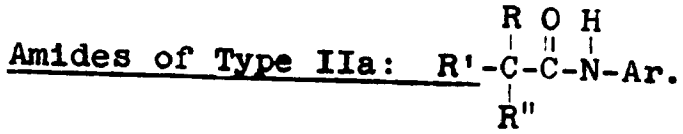
$$Ar-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-R \;+\; PCl_5 \rightarrow Ar-\overset{\overset{Cl}{|}}{C}=N-R \xrightarrow[\Delta]{} ArCN + ClR$$

Amides of Type Ic: $Ar-\overset{\overset{O}{\|}}{C}-N\begin{matrix}R\\R'\end{matrix}$.

This type of amide can be further divided into two types, one in which both R and R' are alkyl groups, and a second in which R is an alkyl group and R' is an aryl group. The first two steps in the reaction of these amides with a phosphorus pentahalide, as postulated by von Braun[4,7,57], are the same:

$$Ar-\overset{\overset{O}{\|}}{C}-N\begin{matrix}R\\R'\end{matrix} + PCl_5 \rightarrow Ar-\overset{\overset{Cl}{|}}{\underset{\underset{Cl}{|}}{C}}-N\begin{matrix}R\\R'\end{matrix} + POCl_3 \xrightarrow[\Delta]{} Ar-\overset{\overset{Cl}{|}}{C}=N-R' + ClR$$

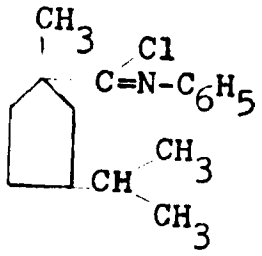
If R' is an alkyl group, the imidyl halide is of type Ib and as such will decompose with heat into the aronitrile and the alkyl halide. If R' is an aryl group, the imidyl halide will be of type Ia, and as such is stable to heat. Amides in which the nitrogen atom is a member of a ring behave in an analogous manner[6,22].



Amides of Type IIa: R'-C(R")-C(=O)-N(H)-Ar.

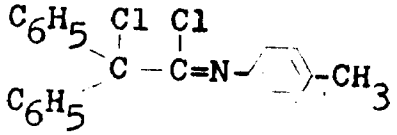
This type of amide has not received much attention, but it is here assumed that the imidyl halide derived from this type amide would have about the same stability towards heat as those of type Ia.

von Braun, Jostes and Munch[58] reported the preparation of the imidyl chloride of N-phenylfencholamide,

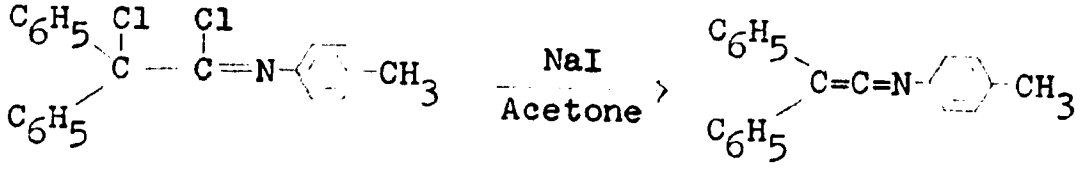


in nearly quantitative yield by heating the amide with phosphorus pentachloride.

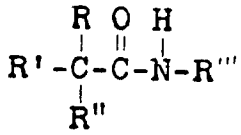
Stevens and French[59] treated N-(p-tolyl)-α-chlorodiphenylacetamide with an equimolar amount of phosphorus pentachloride and obtained the expected imidyl chloride,



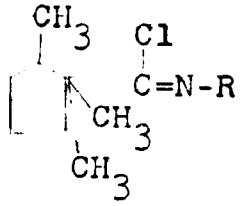
in 87% yield as a solid of m.p. 88.5-90.0°. These workers then treated their α-chloroimidyl chloride with sodium iodide in acetone solution and obtained diphenyl-ketene-p-tolylimine.



Amides of Type IIb:

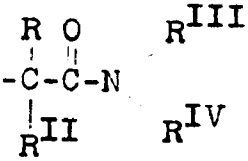


This type of amide gives rise to imidyl chlorides that are as stable or even more so than those derived from aromatic acids. Thus, the imidyl chloride derived from N-methylfencholamide is quite stable, while the imidyl chlorides of N-substituted campholamides



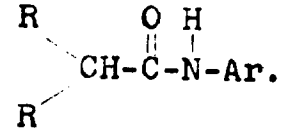
when refluxed for some time and distilled at atmospheric pressure, give campholonitrile and the alkyl chloride[60]. The imidyl chloride from the reaction of N-ethyl-α-chloroisobutyramide and phosphorus pentachloride can be distilled at atmospheric pressure (b.p. 160°) with no decomposition[61].

Amides of Type IIc:

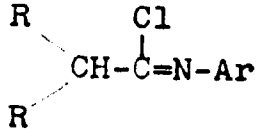


This type of amide apparently does not react with

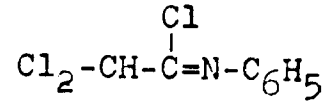
phosphorus pentachloride, von Braun and Heymons[60] reported that N,N-diethyltrichloroacetamide and N,N-diethylcamphol-amide did not react with phosphorus pentachloride even under prolonged heating on a steam bath.

<u>Amides of Type IIIa</u>: 

This type of amide reacts with an equivalent amount of phosphorus pentachloride to give the corresponding imidyl chloride,

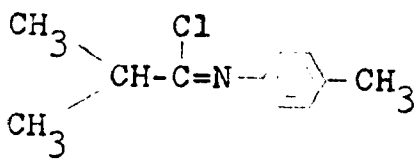


which can be distilled at reduced pressure with very little decomposition. von Braun, Jostes and Munch[58] treated α,α-dichloroacetanilide with one equivalent of phosphorus pentachloride and obtained the expected imidyl chloride,

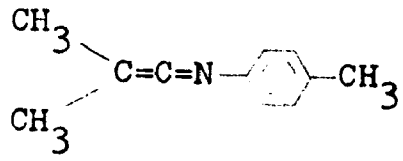


They reported that this compound is relatively stable to heat. The same results were obtained with the N-p-tolyl compound.

Stevens and French[62] reported that the reaction of N-(p-tolyl)-isobutyramide with one equivalent of phosphorus pentachloride gave them the corresponding imidyl chloride,

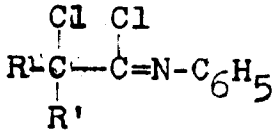


b.p. 80-85°/0.8 mm., in 82.5% yield. These workers then dehydrohalogenated this compound with triethylamine in toluene solution to obtain the ketenimine,

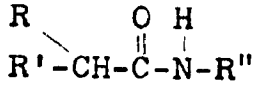


in 66.3% yield.

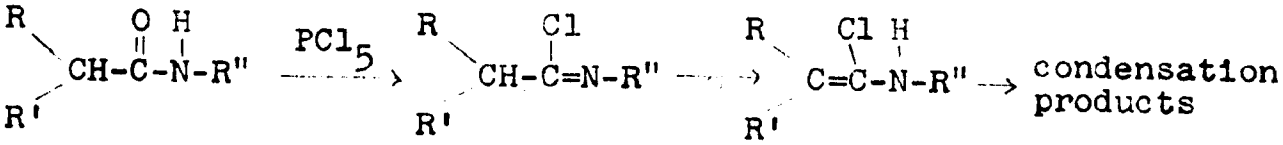
Both groups of workers cited reported that an excess of phosphorus pentachloride produces an α-chloroimidyl chloride of type IIa,



Amides of Type IIIb:

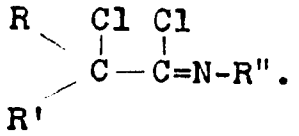


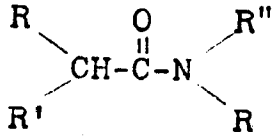
This type of amide reacts with one equivalent of phosphorus pentachloride to produce the expected imidyl halide, but von Braun[63], in a summary of some of his work, reported that imidyl chlorides of this type are quite unstable and usually cannot be distilled. He reported that this instability is a result of the presence of the alpha hydrogen, which undergoes an intramolecular shift to the nitrogen atom; and the newly formed product undergoes condensation reactions through the reactive N-H bond.



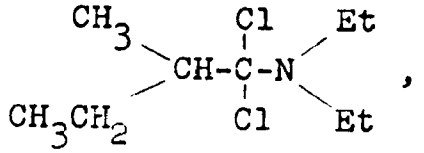
However, Stevens and French[62] reported that the imidyl chloride derived from N-(n-butyl)-α-ethylcaproamide was prepared by reaction of the amide with an equivalent amount of phosphorus pentachloride and was purified by distillation (b.p. 72-76°/0.7 mm.).

Both groups of workers reported that more than an equivalent amount of phosphorus pentachloride resulted in chlorination of the alpha position of the amide to give imidyl chlorides of type IIb,

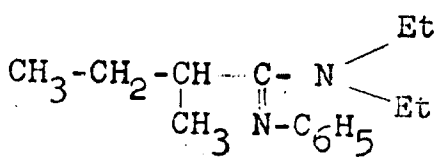


Amides of Type IIIc: 

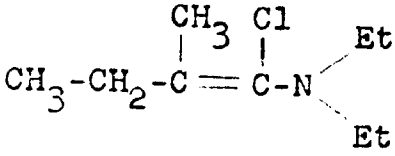
von Braun and Heymons[60] reported that N,N-diethyl-α-methylbutyramide reacted with phosphorus pentachloride to produce an unstable amide chloride,



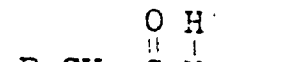
which reacts with water to give the original amide and energetically with aniline to give an amidine,



They reported that on standing the amide chloride loses the elements of hydrogen chloride, rather than an alkyl chloride, to give



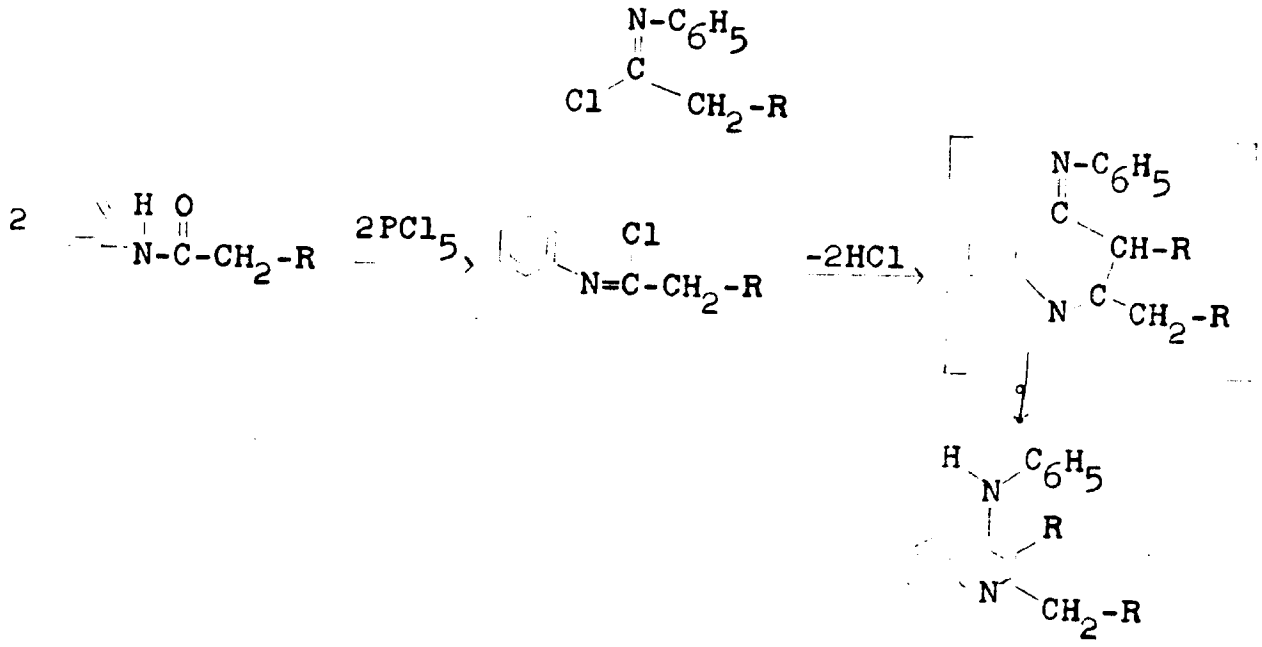
This latter compound is reported to be relatively stable towards water.

Amides of Type IVa: 

The imidyl chlorides derived from this type of amide are reported by von Braun and Silbermann[64] to be so unstable that only those in which the N-aryl group has an ortho substituent have been isolated. von Braun and Rudolph[65] later prepared other imidyl chlorides of this type. The following is a list of percentage yields of undecomposed imidyl chlorides obtained from the reaction of various substituted α-chloroacetanilides with an equivalent amount of phosphorus pentachloride: o-MeO, trace; o-Me, 55; o-Cl, 65; o-Br, 70; o-F, 80; m-Me, 0; m-Cl, 35; m-F, 60; p-Me, 0; and p-Cl, trace.

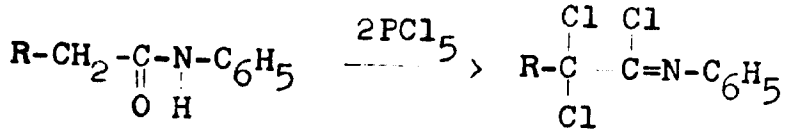
These imidyl chlorides were stable for a long time in the cold, but rapidly thickened to bright yellow compounds with loss of hydrogen chloride when warmed. After investigation of these decomposition products, von Braun, Heymons, and Schnitzspahn[66] found that they were quinoline derivatives, and reported that the reaction of amides of type IVa

with phosphorus pentachloride is a good synthetic route to quinolines. von Braun, Heymons and Manz[67] developed this route further and reported that the quinoline results from a dimerization of two molecules of imidyl chloride with the loss of two molecules of hydrogen chloride.



The quinolines in which R=Cl, Me, Ph, Pr, and C_5H_{11} have been synthesized by this method in yields large enough to make the route synthetically valuable.

von Braun, Jostes and Munch[58] reported that if excess phosphorus pentachloride was used, chlorination of the alpha position of the amide occurred to produce heat-stable α,α-dichlorinated imidyl chlorides,



These imidyl chlorides can be hydrolyzed to the α,α-dichloro

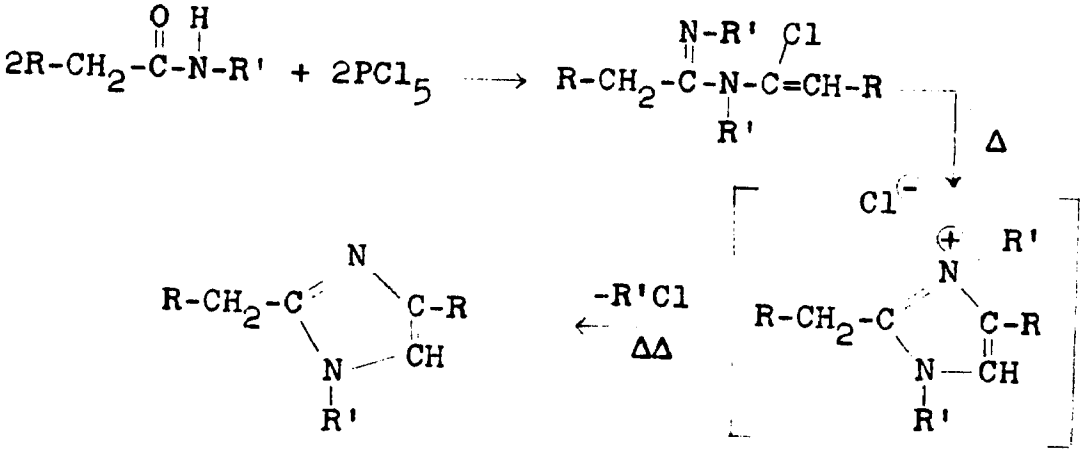
amide, or further, to the α,α-dichloro acid. They reported that imidyl chlorides are more easily chlorinated in the alpha position than the corresponding acid chlorides.

Amides of Type IVb: $R\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{H}{\overset{|}{N}}\text{-}R'$.

This type of amide reacts with one equivalent of phosphorus pentachloride to form very unstable imidyl chlorides. Heymons and Rohland[68] reported that the decomposition of this type of imidyl chloride proceeds in almost quantitative yield to amidines,

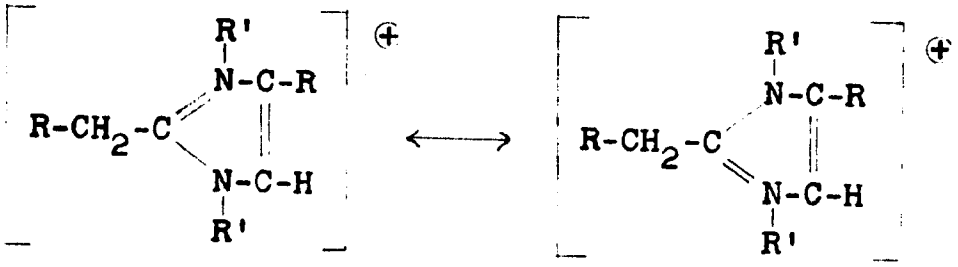
$$R\text{-}CH_2\text{-}\overset{N\text{-}R'}{\overset{\|}{C}}\text{-}\underset{R'}{N}\text{-}\underset{Cl}{C}\text{=}CH\text{-}R$$

They further reported that these amidines are also unstable and with heat give a chloride salt of a tertiary base. With further heating an alkyl chloride is eliminated and a substituted imidazole is formed.

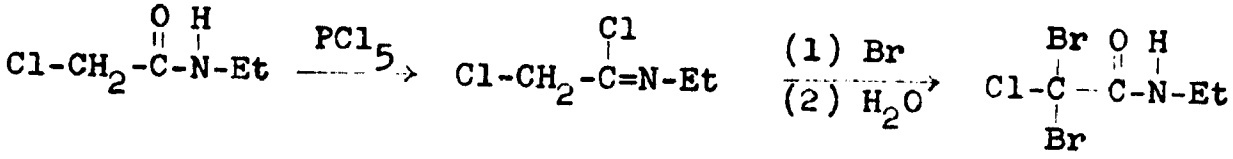


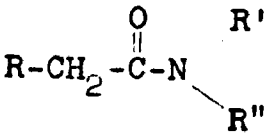
It was not definitely established whether the product was a 1,2,4- or 1,2,5-substituted imidazole; the intermediate

imidazolium salt, represented below, might lose the alkyl group from either nitrogen.

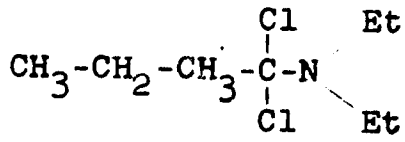


von Braun, Jostes, and Heymons[61] reported that this type of amide can be chlorinated in the α-position by the use of excess phosphorus pentachloride, to give imidyl chlorides of type IIb. These workers also reported that the imidyl chlorides could be brominated in the alpha position with bromine, and hydrolyzed to the α,α-dibromoamide:

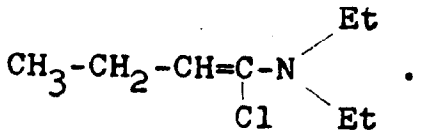


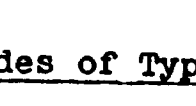
Amides of Type IVc: 

The reaction of this type of amide with phosphorus pentachloride was investigated by von Braun and Heymons[60]. They treated N,N-diethyl-α-chloroacetamide and N,N-diethylbutyramide with phosphorus pentachloride in chloroform solution, and reported that extensive decomposition occurred with the α-chloroacetamide, but was not so pronounced in the butyramide case. The butyramide gave an 80% yield of material which gave a chlorine analysis that suggested that the compound was the amide chloride,



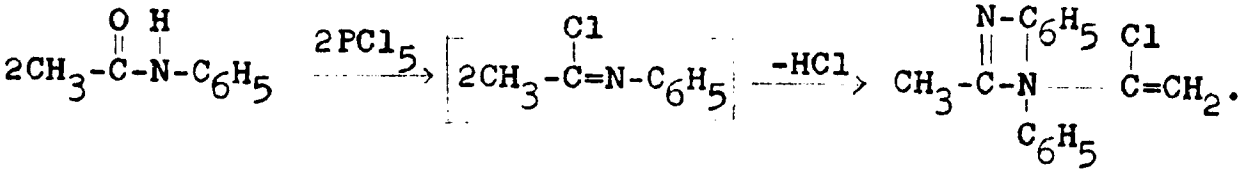
This compound gave the original amide when treated with water or lost hydrogen chloride, when distillation was attempted, to give a compound that analyzed for



Amides of Type Va: 

This type of amide reacts with phosphorus pentachloride to give imidyl chlorides that are so unstable that only a few in which the aryl group is a substituted benzene nucleus have been isolated. von Braun and Silbermann[64], and von Braun and Rudolph[65] reported the isolation of the imidyl chlorides derived from the following substituted acetanilides in the percentage yields given: o-Me, 28; o-Cl, 44; o-Br, 47; o-F, 44; m-F, 27; 2,3-Me_2, 20; and 2-F-3-Me, 20.

von Braun, Jostes and Heymons[61] reported that this type of imidyl chloride dimerizes, with the loss of one molecule of hydrogen chloride, to give chlorovinyl amidines;



Amides of Type Vb: $CH_3-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-R$.

The imidyl chlorides derived from this type of amide have never been isolated. von Braun, Jostes and Heymons[61] reported that with an excess of phosphorus pentachloride, chlorination of the α-position of the amide takes place. They also reported that if the addition of one mole of phosphorus pentachloride was followed by the addition of two moles of bromine and the resulting mixture hydrolyzed with water, the α-α-dibromoamide could be isolated:

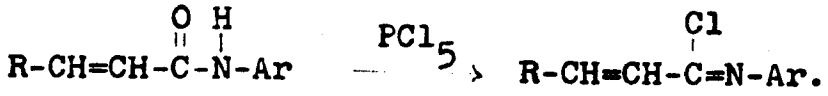
$$CH_3-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-Et \xrightarrow[(3)\ H_2O]{(1)\ PCl_5 \\ (2)\ Br_2} \underset{\underset{Br}{|}}{\overset{\overset{Br}{|}}{CH}}-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-Et$$

Amides of Type VI: $R-CH=CH-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-Ar$.

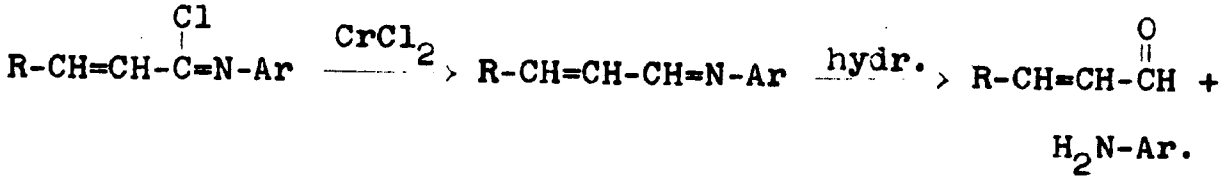
The study of the reaction of this type of amide with phosphorus pentachloride was undertaken by von Braun and his co-workers[63] because it was thought that the intramolecular shift of hydrogen from carbon to nitrogen, which had been encountered in other studies

$$R-CH_2-\overset{\overset{Cl}{|}}{C}=N-R' \longrightarrow R-CH=\overset{\overset{Cl}{|}}{C}-\overset{\overset{H}{|}}{N}-R' ,$$

would not take place. This postulate proved to be correct, and they were able to isolate six different imidyl chlorides from the reaction of this type of amide with phosphorus pentachloride:



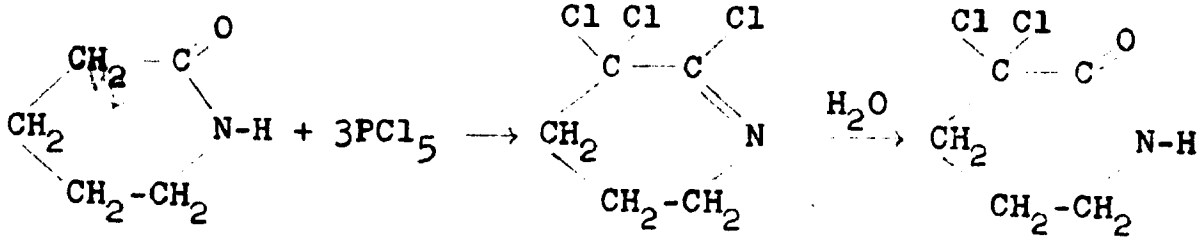
These same workers tried without success to reduce the imidyl chlorides with stannous chloride to the Schiff base, as in the Sonn-Muller reaction. They did find, however, that a specially prepared chromous chloride reagent would effect the desired reduction and allow hydrolysis of the Schiff base to the aldehyde and aromatic amine;



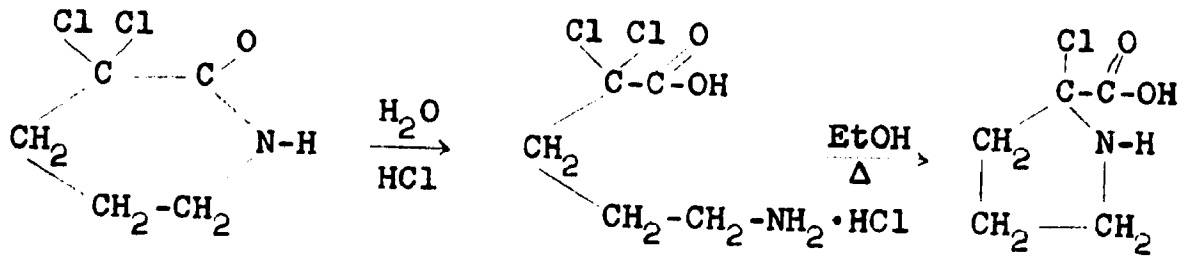
The studies of these workers were extended by von Braun and Rudolph[69], but both sets of workers reported that the yields of aldehydes from the N-aryl amides were less than 50% of the theoretical amount.

Amides of Type VII; Lactams.

von Braun and Heymons[70] studied the reaction of 2-piperidone with phosphorus pentachloride and reported that a heat-stable α,α-dichloroimidyl chloride was produced in 65-70% yield. This imidyl chloride could be hydrolyzed to the α,α-dichlorolactam,

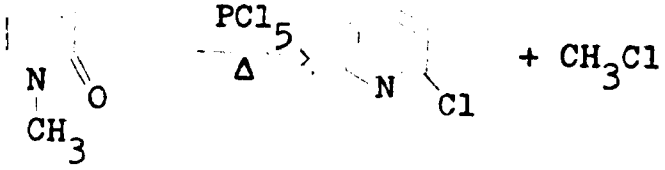


and further hydrolyzed to the δ-amino-α,α-dichloro acid, which underwent cyclization to α-chloroproline when refluxed in ethanol solution;

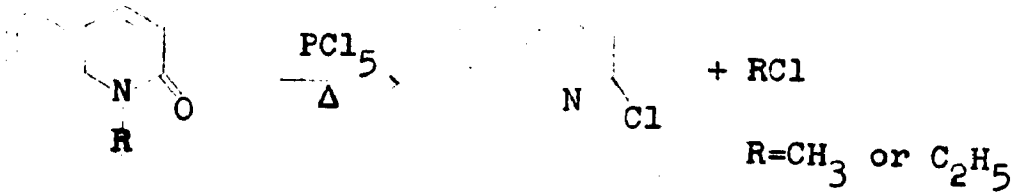


The formation of the α,α-dichloroimidyl chloride of caprolactam followed by hydrolysis to the α,α-dichlorolactam was accomplished in 30-40% overall yield. The reaction of 2-pyrrolidone with phosphorus pentachloride did not go well at all, but the lactam of 6-aminoheptanoic acid gave the α,α-dichlorolactam, through the dichloroimidyl chloride, in 60% yield.

Fischer[71] found that if the lactam was unsaturated and contained an N-methyl group, the N-methyl group was eliminated as methyl chloride and 2-chloropyridine was formed on treatment with phosphorus pentachloride;

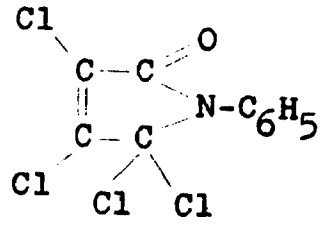


Fischer also found the same type of reaction in the quinoline series;

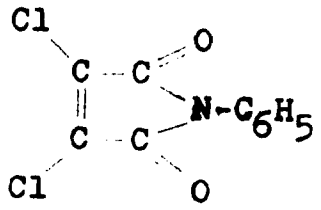


Amides of Type VIII; Imides.

Anschutz[72] and his co-workers have studied the reactions of some cyclic imides with phosphorus pentachloride and have reported that N-phenylsuccinimide gives a mixture of N-phenyltetrachloropyrrole and a compound to which they assigned the structure

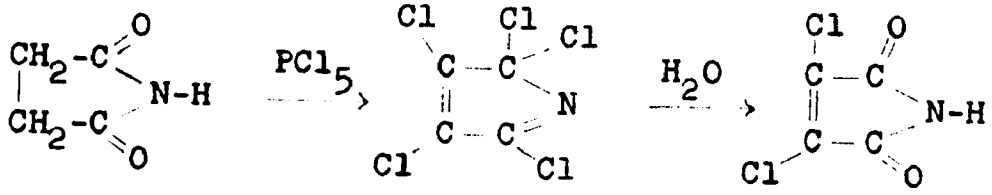


This latter compound gave N-phenyldichloromaleimide,

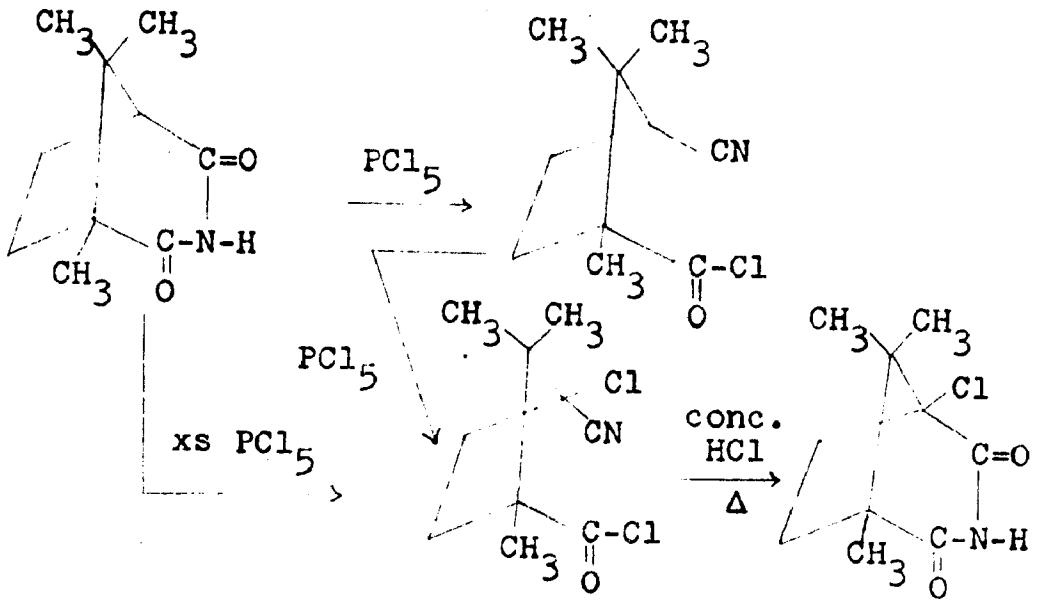


when treated with water.

These same workers found that the unsubstituted imides gave the same type of results. Succinimide, when treated with phosphorus pentachloride and then water, underwent the following reactions:

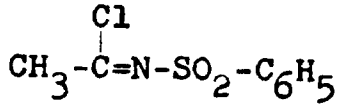


Bredt and Ivanov[73] reported the following reaction of camphorimide;



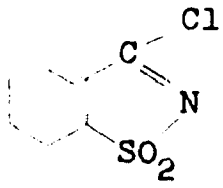
Amides of Type IX: Acylated Sulfonamides.

von Braun[57] in a review of imidyl halides mentioned unpublished work in which it was found that



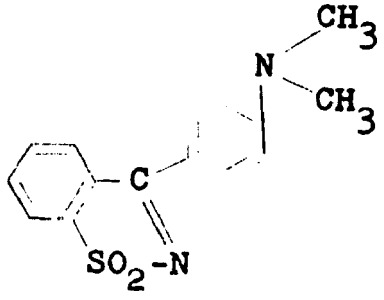
decomposed with heat to give CH_3CN and $ClSO_2-C_6H_5$.

Jesurun[74] reported that saccharin reacted with two equivalents of phosphorus pentachloride to give o-cyanobenzenesulfonyl chloride, which on heating gave the cyclic imidyl chloride,



Fritsch[75] repeated the work of Jesurun, and found that the imidyl chloride would react with dimethylaniline, when

catalyzed by aluminum chloride, to give the Friedel-Crafts type product,



Reaction of Amides with Phosgene.

von Braun and Pinkernelle[76] found that N-methylbenzimidyl chloride was produced from the reaction of N,N-dimethylbenzamide and phosgene, but were persuaded to discontinue the use of phosgene because of its physiological properties.

Reactions of Amides with Thionyl Chloride.

von Braun and Pinkernelle[76] reported that thionyl chloride reacted with N-substituted amides of aromatic acids to give the corresponding imidyl chlorides in nearly quantitative yields. These workers obtained N-phenylbenzimidyl chloride in quantitative yield from the reaction of thionyl chloride with N-phenylbenzamide and with N-methyl-N-phenylbenzamide. They reported further that N-methylbenzamide gave N-methylbenzimidyl chloride and that N,N-diethylbenzamide gave N-ethylbenzimidyl chloride when treated with thionyl chloride.

In this paper von Braun and Pinkernelle stated that

thionyl chloride is a much better reagent for the preparation of imidyl chlorides derived from aromatic acids than phosphorus pentachloride, but does not work well for the preparation of imidyl chlorides derived from non-aromatic acids.

Elpern[77] used thionyl chloride to convert 2-benzamidoethanol to N-(2-chloroethyl)-benzimidyl chloride. This imidyl chloride was treated with hydrazoic acid to give 1-(2-chloroethyl)-5-phenyltetrazole.

STATEMENT OF THE PROBLEM

The von Braun reaction has found only limited use as a synthetic method. It was believed that this was because of the difficulty, often encountered, of separating the alkyl halide produced from the by-products of the reaction, benzonitrile and phosphorus oxyhalide.

The overall objective of this research was to explore the possibility of extending the synthetic value of this reaction. The principal objective was broken down into the following specific objectives.

1.) To explore the use of thionyl chloride as the chloridating agent in place of the phosphorus pentachloride, which gave the troublesome by-product, phosphorus oxychloride.

2.) To explore the use of N-substituted aliphatic amides in place of N-substituted benzamides, which lead to the troublesome by-product, benzonitrile.

3.) To explore the optical course of the reaction in the hope that an optically pure chloride would result from an optically pure amine, if thionyl chloride were used as the chloridating agent.

4.) To attempt to isolate intermediates in the reaction in order to shed more light on its path.

DISCUSSION

The chief difficulty encountered in the von Braun reaction has been isolation of the halide produced. Part of this difficulty arises from the presence of two by-products, the benzonitrile and the phosphorus oxyhalide. When the boiling point of the halide is not sufficiently different from that of benzonitrile (b.p. 191°), the benzonitrile must be removed by chemical means. There have been a number of procedures developed to accomplish this separation[14,21,78], but they all add a complicating factor to the reaction. Not only is the same type of difficulty encountered in the separation of the phosphorus oxyhalide from the product, but the phosphorus oxyhalide becomes an undesirable strong ionizing solvent as it is produced.

It was believed that if this difficulty in the isolation of the halide could be circumvented, the von Braun reaction could be developed and could become a good synthetic route for the conversion of an amine to the corresponding halide.

In recent times, thionyl chloride has been used in many reactions which formerly employed phosphorus pentachloride, and it was thought that the von Braun reaction was another case in which this reagent could be used in place of the more inconvenient and undesirable phosphorus pentachloride. If this reagent could be used as the source of the chlorine, one of the above mentioned problems would be solved. Thionyl chloride should give only gaseous by-products, which would

immediately be removed from the reaction mixture as they are formed:

$$Ar\text{-}\overset{\overset{O}{\|}}{C}\text{-}\overset{\overset{H}{|}}{N}\text{-}R + SOCl_2 \rightarrow ArCN + ClR + SO_2\uparrow + HCl\uparrow.$$

The above reaction was first attempted with N-n-butylbenzamide. The amide was mixed with an equivalent amount of thionyl chloride in the cold, the solution slowly heated and refluxed for four hours. The n-butyl chloride was isolated by distillation from the reaction mixture at atmospheric pressure and, after purification, was obtained in 34% yield. Benzonitrile was obtained as another product of the reaction.

A large amount of the starting amide was found in the residue from the reaction, an indication that either a longer reaction time or a higher ratio of thionyl chloride to amide was needed. Another factor indicated by this reaction was that a solvent would be advantageous, and after a few preliminary trials, it was decided that nitromethane would be a satisfactory solvent.

The reaction was then tried with N-(1-phenylethyl)-benzamide, using a three-to-one mole ratio of thionyl chloride to amide and employing nitromethane as a solvent. After the addition of thionyl chloride to the solution of the amide in nitromethane was complete, the solution was refluxed for three hours. The solvent was then removed by distillation at atmospheric pressure. However, on

distillation of the residue at a reduced pressure, it was found that the 1-phenylethyl chloride could not be separated from the benzonitrile by this method. All of the distillates were recombined and analyzed for carbon, hydrogen and chlorine. The results of this analysis indicated that the chloride had been produced in 80-85% yield.

The reaction of thionyl chloride with the benzamides of benzhydrylamine and α-cyclopentylbenzylamine, under the same conditions as employed for N-(1-phenylethyl)-benzamide, proceeded very smoothly, and the chlorides were easily isolated from the reaction mixture by distillation at reduced pressure.

The chlorides produced from the reaction of thionyl chloride with the benzamides of benzylamine, p-methoxybenzylamine and 1-(p-tolyl)-ethylamine gave some trouble in their separation from benzonitrile, but could be isolated by repeated distillations. The redistillations, of course, lowered the yields of the chlorides.

A further difficulty was encountered in the purification of 1-(p-tolyl)-ethyl chloride, owing to the instability of this compound. This instability will be discussed in a following section of this dissertation.

The chloride could not be isolated from the reaction of thionyl chloride with the benzamide of 1-(p-methoxyphenyl)-ethylamine. This may have been due to the instability of the chloride in the reaction mixture, in view of the apparently similar instability of 1-(p-tolyl)-ethyl chloride.

The results of these experiments are summarized in Table V.

The foregoing reactions of N-substituted benzamides with thionyl chloride demonstrate very clearly that thionyl chloride can be used as a reagent in the von Braun reaction. However, these reactions also illustrate the difficulty encountered in the separation of benzonitrile from some of the chlorides by the most convenient method, distillation.

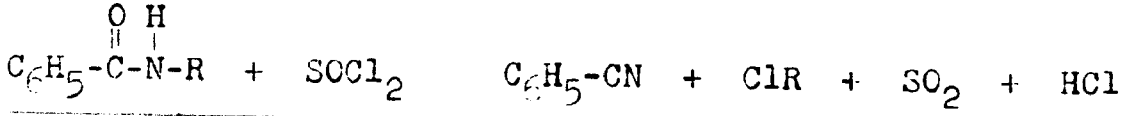
One solution to this difficulty would be judicious choice of an amide which would produce a nitrile with a boiling point very different from that of the expected halide. This could be accomplished by the use of N-substituted benzamides which contained a substituent in the benzene nucleus and which would, therefore, produce a nitrile whose boiling point would be different from that of the expected chloride. For example the ortho-, meta- and para-nitrobenzonitriles are all solids, and the corresponding tolunitriles have boiling points between 205° and 220°.

A similar modification which would circumvent the same problem would be the use of N-substituted amides of aliphatic acids. The lower members of this series would afford nitriles which distill at temperatures much lower than the boiling points of those halides that could not be separated from benzonitrile by distillation.

N-Substituted amides of aliphatic acids have not been used in the von Braun reaction because of side reactions encountered. These side reactions are believed to be due

TABLE V

Reactions of N-Substituted Benzamides with Thionyl Chloride



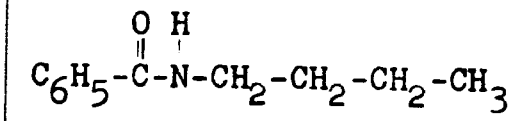
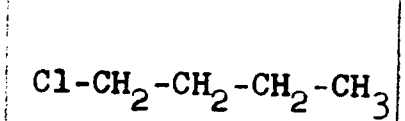
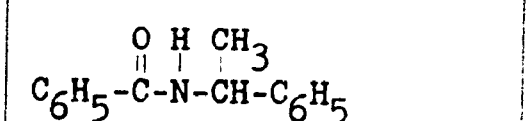
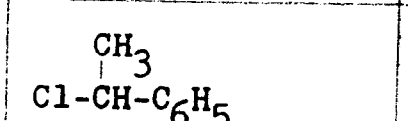
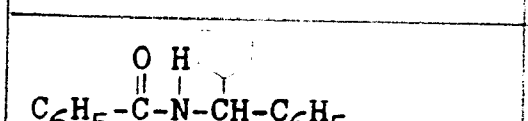
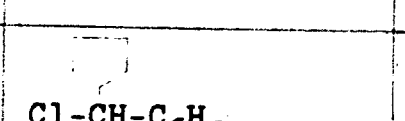
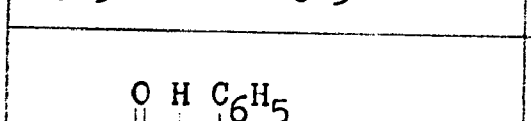
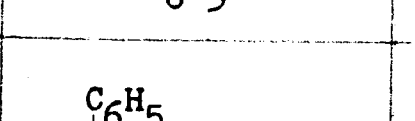
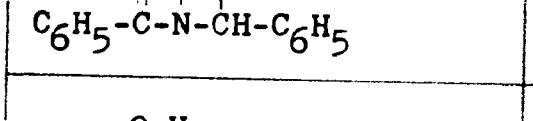
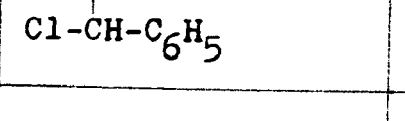
Amide	Chloride	% Yield	Boiling Point Found	Boiling Point Lit.	Refractive Index Found	Refractive Index Lit.	Ref.
		34[a,b]	75-76° / 745 mm	77.3-77.6°	n_D^{25} 1.4012	n_D^{20} 1.4017	79
		80-85[c]	d	—	—	—	—
		80-85	112-114° / 4 mm.	-	n_D^{25} 1.5380	—	—
		80-85	98-100° / 0.5 mm.	96° / 0.2 mm.	$n_D^{25.5}$ 1.5935	n_D^{20} 1.5962	80
		20-50[e]	d	—	—	—	—

TABLE V continued

Amide	Chloride	% Yield	Boiling Point Found	Boiling Point Lit.	Refractive Index Found	Refractive Index Lit.	Ref.
$C_6H_5-\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{\|}{N}}-CH_2-C_6H_4-OCH_3(p)$	$Cl-CH_2-C_6H_4-OCH_3(p)$	40-45	81° / 2.5 mm.	113° / 10.5 mm.	$n_D^{23.5}$ 1.5479	n_D^{20} 1.5491	81
$C_6H_5-\overset{C}{\overset{\|}{C}}-\overset{H}{\overset{\|}{N}}-\overset{CH_3}{\overset{\|}{CH}}-C_6H_4-CH_3(p)$	$Cl-\overset{CH_3}{\overset{\|}{CH}}-C_6H_4-CH_3(p)$	20-35[d]	65-70° / 4-5 mm.	--	$n_D^{25.5}$ 1.5240	—	—
$C_6H_5-\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{\|}{N}}-\overset{CH_3}{\overset{\|}{CH}}-C_6H_4-OCH_3(p)$	$Cl-\overset{CH_3}{\overset{\|}{CH}}-C_6H_4-OCH_3(p)$	0[d]	--	--	---	---	—

a. This reaction was run without a solvent and with only one equivalent of thionyl chloride; in all others nitromethane was used as a solvent, with a 200% excess of thionyl chloride.
b. An appreciable amount of the starting amide was recovered from this reaction.
c. Calculated from analytical data.
d. See the discussion.
e. Estimated.

to the presence of hydrogens attached to the carbon alpha to the carbonyl group. It was thought that the substitution of thionyl chloride for phosphorus pentachloride might minimize these side reactions and allow the use of aliphatic amides in the reaction.

One type of amide, which at first glance appeared to be ideal, is an N-substituted formamide. From the reaction of these amides and thionyl chloride all of the stoichiometric by-products would be gaseous, and thus facilitate isolation of the chloride produced.

$$H\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{H}{\overset{|}{N}}\text{-}R + SOCl_2 \rightarrow HCN + ClR + SO_2 + HCl.$$

The reaction of thionyl chloride with the formamide of n-butylamine was run many times under varied conditions of temperature, solvent, and proportion of reagents, but n-butyl chloride was never isolated in more than trace amounts. The major product was a non-distillable tar, but n-butyl isothiocyanate was isolated in small amounts. This compound was identified by comparison of its infrared spectrum with that of n-butyl isothiocyanate prepared by an independent method, and by analysis. There seems to be no rationale for the direct production of this compound from the reactants.

The reaction of thionyl chloride with the formamide of 2-phenylethylamine produced the same type of results as were obtained from N-n-butylformamide. The expected chloride was never isolated in more than trace amounts.

The reaction of thionyl chloride with the formamide of benzylamine did yield small amounts of benzyl chloride, but again, the major product was a tar which gave off the stench of sulfur-containing compounds when distillation was attempted.

The formamide of 1-phenylethylamine was the only one of the series tried which gave more than trace amounts of the expected halide. With it, thionyl chloride in nitromethane solution produced impure 1-phenylethyl chloride in approximately 50% yields. This chloride contained an impurity which produced sharp bands at 2260 and 820 cm^{-1}. in the infrared spectrum. These bands were not due to hydrogen cyanide (as first suspected), which showed sharp bands at 3220 and 2080 $cm.^{-1}$ when dissolved in an authentic sample of 1-phenylethyl chloride. Furthermore, the impurity was not removed by washing the sample with dilute sodium bicarbonate solution or with dilute hydrochloric acid.

After these more or less discouraging results, it was decided to explore the reaction of N-substituted acetamides with thionyl chloride. These amides should afford acetonitrile as a by-product, the boiling point of which (81°) is low enough to permit isolation by distillation of those chlorides which boil above 100°.

The amide chosen for the initial study was N-(1-phenylethyl)-acetamide, which was refluxed for one hour with a large excess of thionyl chloride. The thionyl chloride was then distilled off at atmospheric pressure, and the residue distilled at a reduced pressure. The yields of redistilled

1-phenylethyl chloride obtained by this procedure were between 20% and 35% of the theoretical amount.

When a 200% excess of thionyl chloride was treated with the amide, dissolved in dioxane, the yields of the chloride were between 15% and 20%. Treating N-(1-phenylethyl)-acetamide, dissolved in cyclohexene, with a 200% excess of thionyl chloride gave the chloride in 15% to 30% yields. The quantity of the chloride produced was increased to 55-65% of the theoretical amount when the amide was dissolved in nitromethane and treated with a 200% excess of thionyl chloride.

The reaction of a 200% excess of thionyl chloride with the acetamide of 2-phenylethylamine was then run in cyclohexene solution and in nitromethane solution. From both cases no pure halide could be obtained, although there was isolated a small amount of a liquid which contained chlorine and whose infrared spectrum corresponded to that expected for 2-phenylethyl chloride.

No pure benzyl chloride was obtained from the reaction of N-benzylacetamide with thionyl chloride in cyclohexene solution. However, from the same reaction in nitromethane solution a product was obtained, with the correct boiling point for benzyl chloride, corresponding to an 8% yield of this compound. The infrared spectrum of this material was nearly identical with that of an authentic sample of benzyl chloride. Preparation of a derivative was attempted, but the experiment failed to yield any isolable product.

Benzhydrylamine was prepared and its N-acetyl derivative treated with thionyl chloride in nitromethane solution to give benzhydryl chloride in 75% to 85% yields. Diphenylcarbinol was prepared from a sample of this chloride by treating its acetone solution with water.

The p-methoxy derivative of benzylamine was prepared and its acetamide treated with thionyl chloride in nitromethane solution to give 40% to 50% yields of p-methoxybenzyl chloride. The physical constants of this halide agreed with the reported values, and it was hydrolyzed to p-methoxybenzyl alcohol, the melting point and infrared spectrum of which were identical with those of an authentic sample of the alcohol.

From these results it appeared that the success of the reaction depended on the stabilization of at least a partial positive charge on the carbon adjacent to the nitrogen and was also promoted by bulk at this position. A compound which would fill both of these requirements is the acetamide of α,α-dimethylbenzylamine. The carbon adjacent to the nitrogen not only has two methyl groups adjacent to it, but is tertiary and also of the benzyl type.

This compound was prepared and allowed to react with thionyl chloride in nitromethane solution, but no α,α-dimethylbenzyl chloride could be isolated. This result may have been due to the instability of the halide in the reaction mixture, or more simply to its instability towards heat. Of course there is also the possibility that an

intermediate decomposed by some other reaction path, causing the tar formation which was observed.

Since the yields of halide were much greater when there was a methoxy group present in the benzene nucleus of N-benzylacetamide it was thought that the acetamide of 1-(p-methoxyphenyl)-ethylamine would give a much higher yield of the corresponding chloride than had been obtained from the acetamide of 1-phenylethylamine. The compound was prepared and subjected to the reaction with thionyl chloride in nitromethane solution, but the results were the same as obtained from the reaction of the acetamide of α,α-dimethylbenzylamine. Only a polymeric-appearing residue remained after removal of the solvent. The causes of the failure of the reaction were most likely the same as suggested for the latter reaction.

The acetamide of 1-(p-nitrophenyl)-ethylamine was prepared by nitration of the acetamide of 1-phenylethylamine and treated with thionyl chloride in nitromethane solution. An attempt was made to distill the residue from the reaction after the solvent had been removed, but no distillate could be collected before the residue charred - the same result as observed from the last two reactions mentioned. However, it does not seem likely that this result occurred for the same reasons as in the other two cases. Although a reference to the expected chloride could not be found in the literature, it is now believed that 1-(p-nitrophenyl)-ethyl chloride would have been a solid if it had been formed.

This conclusion was reached after a comparison of the melting points and boiling points of similar compounds. This would explain why charring occurred before any distillate could be collected.

N-1-(p-Tolyl)-ethylacetamide was prepared and allowed to react with thionyl chloride in nitromethane solution. The yields of 1-(p-tolyl)-ethyl chloride from three separate runs were between 20% and 30% of the theoretical amount. This chloride partially decomposed on redistillation, partially explaining the results obtained from the acetamides of α,α-dimethylbenzylamine and 1-(p-methoxyphenyl)-ethylamine. This decomposition is discussed further in a latter section of this dissertation.

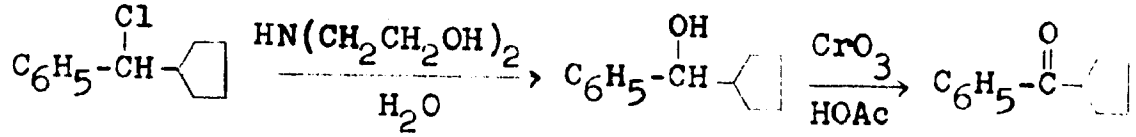
Because of the poor results obtained from the reactions of thionyl chloride with the acetamides of 1-phenylethylamines which contained a para-substituent, a search was made for a benzylamine that would lead to a benzyl type chloride which would be expected to be stable under the reaction conditions. α-Cyclopentylbenzylamine appeared to be a satisfactory choice for many reasons, although neither the properties nor physical constants of the corresponding chloride could be found in the literature.

From work done on the deamination of this amine[82,83], and others[82,84], it was inferred that even if the free carbonium ion (at the benzyl carbon) were formed, no rearrangement should be expected. From work done on dehydration of the corresponding alcohol[85,86], cyclopentylphenylcarbinol,

and an attempted dehydrohalogenation of the chloride[87], it was expected that this dehydrohalogenation would be a minor side reaction under the conditions of the experiment.

Another reason for the choice of this compound is its structural similarity to two of the amines, 1-phenylethylamine and benzhydrylamine, whose acetamides gave good results when treated with thionyl chloride in nitromethane solution. It was thought that the α-cyclopentyl group should not be appreciably different from the α-methyl group in its charge-stabilizing characteristics, and its steric requirements should be very similar to those of the α-phenyl group.

The amine was prepared and its acetamide subjected to the reaction conditions. The yields of redistilled α-cyclopentylbenzyl chloride produced from this reaction were between 75% and 85% of the theoretical amount. The α-cyclopentylbenzyl chloride was identified by C, H and Cl analysis, and by the following reactions:



Thus the results seem to indicate that the chlorides would have been isolated in much higher yields from some of the previous reactions, if the chlorides had been more stable in the reaction medium and more stable to heat on distillation.

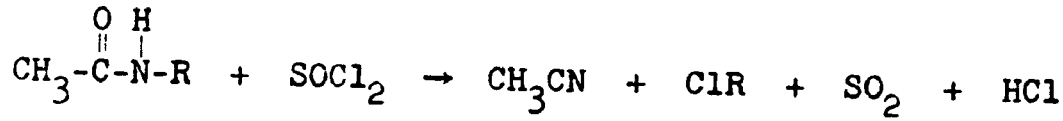
The reaction of the acetamides of cyclohexylamine and t-butylamine with thionyl chloride were run in order to have examples of the reaction of acetamides of amines which were not of the benzyl type. No isolatable cyclohexyl chloride was obtained from the reaction of N-cyclohexylacetamide with thionyl chloride, but t-butyl chloride was obtained from the reaction of the reagent with N-t-butylacetamide. Because of the difficulty encountered in the separation of the excess thionyl chloride from the t-butyl chloride, no accurate yield data can be given; however, it is estimated, from the amount of liquid obtained, that the chloride was produced and distilled from the reaction mixture in 20% to 50% yield. By repeated distillation there was isolated t-butyl chloride whose refractive index and infrared spectrum corresponded reasonably with those of an authentic sample of this halide.

The results summarized in Table VI show that the chloride corresponding to the parent amine is indeed a product of the reaction of thionyl chloride with N-substituted aliphatic amides (at least in some cases), but it was thought desirable to ascertain whether or not the nitrile corresponding to the parent acid is likewise a product of the reaction.

With this objective in mind the low boiling material from the reaction of thionyl chloride with N-(1-phenylethyl)-acetamide in nitromethane solution was fractionated. A fraction was obtained whose infrared spectrum clearly showed

TABLE VI

Reactions of N-Substituted Acetamides with Thionyl Chloride[a,b]



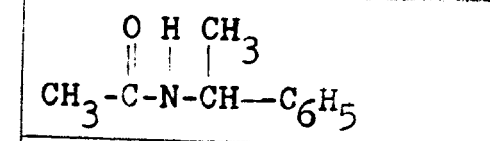
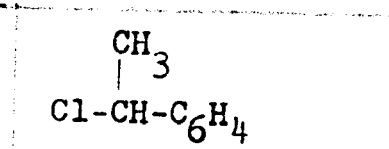
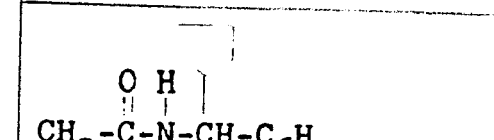
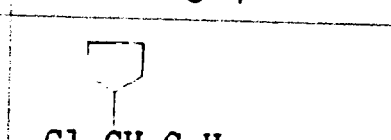
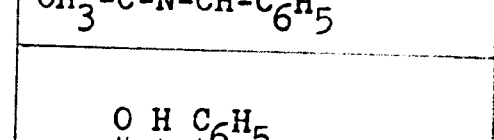
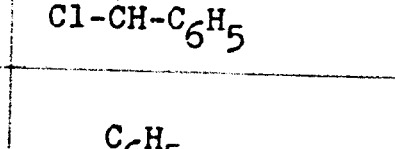
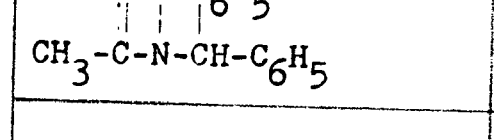
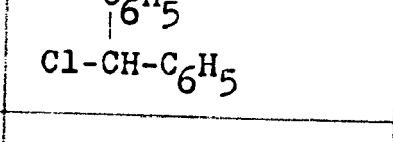
Amide	Chloride	% Yield[c]	Boiling Point Found	Boiling Point Lit.	Refractive Index Found	Refractive Index Lit.	Ref.
		55-65	82-83° / 20 mm.	80-81° / 19 mm.	n_D^{26} 1.5250	n_D^{25} 1.5252	87
		75-85	103-104° / 2-3 mm.	—	$n_D^{24.5}$ 1.5381	—	d
		75-85	111-114° / 1 mm.	96° / 0.2 mm.	—	—	80
		20-30	65° / 2-3 mm.	—	n_D^{24} 1.5240	—	d

TABLE VI continued

Amide	Chloride	% Yield[c]	Boiling Point Found	Boiling Point Lit.	Refractive Index Found	Refractive Index Lit.	Ref.
$CH_3-\overset{O}{\overset{\|}{C}}-\overset{H}{\underset{\|}{N}}-CH_2-C_6H_4-OCH_3(p)$	$Cl-CH_2-C_6H_4-OCH_3(p)$	40-50	85-86° / 3-4 mm.	113° / 10.5 mm.	n_D^{25} 1.5470	n_D^{20} 1.5491	81
$CH_3-\overset{O}{\overset{\|}{C}}-\overset{H}{\underset{\|}{N}}-CH_2-C_6H_5$	$Cl-CH_2-C_6H_5$	10	62-64° / 7-9 mm.	66° / 13.5 mm.	—	—	87
$CH_3-\overset{O}{\overset{\|}{C}}-\overset{H}{\underset{\|}{N}}-\overset{CH_3}{\underset{CH_3}{\overset{\|}{C}}}-CH_3$	$Cl-\overset{CH_3}{\underset{CH_3}{\overset{\|}{C}}}-CH_3$	20-50[e]	48-53° / 740 mm.	53-55° / 760 mm.	—	—	88
$CH_3-\overset{O}{\overset{\|}{C}}-\overset{H}{\underset{\|}{N}}-CH_2-CH_2-C_6H_5$	$Cl-CH_2-CH_2-C_6H_5$	Trace	—	—	—	—	—

a. These reactions were run in nitromethane.
b. Only those acetamides which gave isolatable amounts of the expected chlorides are included.
c. Yields are of redistilled chloride from two or more separate runs, except for the t-butyl case, which was run only once.
d. Structure of the chloride confirmed by C, H, and Cl analysis.
e. Estimated.

the presence of a nitrile, presumably acetonitrile, but it was not isolated in the pure state because of experimental difficulties. Thus, although this indicates that the reaction of N-substituted aliphatic amides with thionyl chloride follows the same path as the reaction of N-substituted benzamides with this reagent, the nitrile band in the infrared spectrum does not definitely demonstrate that the nitrile corresponds to the parent acid and is not altered in some way (e.g., α-chlorinated).

In order to establish the identity of the nitrile an N-substituted amide leading to a nitrile which could be separated more readily from thionyl chloride, nitromethane, the chloride produced, and other by-products present was required. N-(1-Phenylethyl)-butyramide appeared to fill this requirement, and was chosen for study.

Accordingly it was allowed to react with thionyl chloride in nitromethane solution and a surprisingly good yield (75%) of 1-phenylethyl chloride was obtained. The lower boiling material from the reaction was fractionated and n-butyronitrile, contaminated with nitromethane, was isolated. The nitrile was converted to the corresponding amide with basic hydrogen peroxide and was identified as n-butyramide, definitely showing that the nitrile produced in the reaction corresponds to the parent acid and is not chlorinated in the alpha position.

Because a higher yield of chloride was produced from the reaction of N-(1-phenylethyl)-butyramide with thionyl

chloride than had been obtained from the acetamide of the same amine, it was thought desirable to try the reaction on another series of acylated amines. Propionamides were chosen, partly because of the availability of propionic anhydride as an acylating agent, and partly because the expected nitrile, propionitrile, would not interfere with the purification of the halides produced from the amines selected.

The amines selected were those whose acetamides gave yields of the chlorides with thionyl chloride, not in excess of 70%, so that any change in yields would be distinctive in either direction.

The propionamide of 1-phenylethylamine was allowed to react with thionyl chloride in nitromethane solution under the conditions which gave the best yields of halide from the acetamide of this amine. The product was distilled from the reaction mixture under reduced pressure and redistilled to give a 72% yield of 1-phenylethyl chloride. This corresponds to a 10% increase in yield over that obtained from the acetamide.

The same type of results was obtained from the propionamide of p-methoxybenzylamine. Redistilled p-methoxybenzyl chloride was obtained in 64% yield, better than a 10% increase over the yield obtained from the corresponding acetamide.

A similar improvement was observed in the reaction of propionamide of 1-(p-tolyl)-ethylamine and thionyl chloride.

However, an extra band in the infrared spectra of impure samples of the product was noticed: it was a surprisingly strong, sharp band at 1635 $cm.^{-1}$. Traces of it could be found in almost all of the spectra of different fractions of the halide. It was inferred from the intensity of the band in the different fractions that it was due to an impurity of a lower boiling point than the chloride. Also, when a sample of the chloride (whose infrared spectrum showed only a trace of this band) was slowly distilled at a higher pressure, it was observed that the intensity of the band in the infrared spectrum of the distillate was greater than it had been before distillation. The compound that gave rise to this band was isolated and identified as p-methylstyrene, by boiling point, refractive index, and preparation of a dibromide with the correct melting point for p-methylstyrene dibromide.

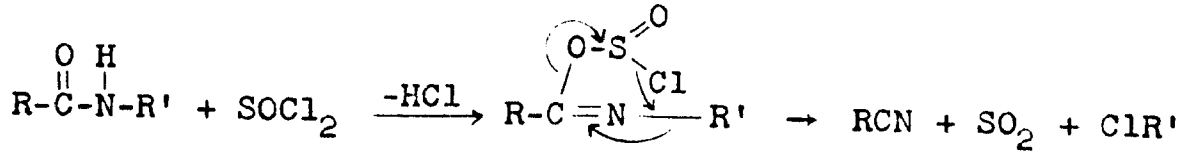
The isolation and identification of p-methylstyrene indicates that a certain percentage of the chloride produced dehydrohalogenated to the olefin when the reaction mixture was heated and during distillation. The isolation of this olefin also lends support to the idea that if the halides were formed from the reactions of the acetamides of α,α-dimethylbenzylamine and 1-(p-methoxyphenyl)-ethylamine with thionyl chloride, isolation from the reaction under the conditions employed would be improbable.

The results obtained from the reactions of thionyl chloride with N-substituted amides prompted a closer

examination of the reaction path by determining the optical course of the reaction.

Leonard and Nommensen[10] have studied the optical course of the reaction of phosphorus pentabromide with the benzamide of (+)s-butylamine. They report that the reaction is accompanied by a "...preponderant inversion of configuration with some racemization." They used optically pure s-butylamine, but the purity of the bromide obtained could not be calculated because the rotation of the optically pure bromide is not known. The bromide obtained by these workers had a specific rotation of -13.52°, while the calculated specific rotation for s-butyl bromide varies from 15.4° to 28.6°, depending on the source of the value[89,90,91]. Using these extreme values, the bromide isolated had a rotation that was from 57% to 87% of the rotation of optically pure s-butyl bromide.

A priori, it seemed that the reaction of an N-substituted amide with thionyl chloride might proceed through the intermediate shown below and lead to optically pure chloride from optically pure amine.



Optically pure (-)1-phenylethylamine was prepared and its acetamide treated with thionyl chloride, using nitromethane as the solvent. When the total time of heating the reaction mixture and the distillation step was about

four hours, the observed rotation of the chloride produced was + 3.7° at room temperature. When the total time was about two hours, the rotation was + 4.31° at room temperature. The chloride with a rotation of + 3.7° was dissolved in 25 ml. of nitromethane and heated at about 100° for approximately two hours, including distillation time. The rotation of the chloride recovered was + 3.59°. A sample of chloride with a rotation of + 3.97° was dissolved in 25 ml. of nitromethane, a 200% excess of thionyl chloride added, and the solution heated for approximately 1.25 hours, after which the rotation of the halide recovered was + 3.87°. The maximum reported experimental rotation for this chloride is 109°[92] at 25°, and it has been calculated[92] that the optically pure chloride should have a rotation of between 126° and 129°. This data indicates that racemization accompanies the reaction and that the halide is not appreciably racemized after being formed.

An investigation of the literature showed that these results should not be surprising if it is assumed that the reaction of thionyl chloride with amides is similar to its reaction with alcohols. Boozer and Lewis[93] have shown that the optical course of the latter reaction is entirely dependent on the solvent and conditions of the reaction. They have shown that the configuration of the product varies from complete retention to complete inversion, depending on the solvent used. Some of their results are reproduced in Table VII.

TABLE VII

Stereochemical Results of the Decomposition of Chlorosulfites* in Various Solvents

$$R\text{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}\text{—}OSOCl \xrightarrow[\Delta]{} R\text{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}\text{—}Cl + \text{Olefin} + SO_2$$

Solvent	R	$[\alpha]_D^{27}$ of Chloride	Optical Purity
Dioxane	n-Propyl	+41.9	98.5%
Ethylene Chloride	Ethyl	+18.5	55
Ethylene bromide	n-Propyl	+16.1	32
Cyclohexanone	Ethyl	-12.2	36
Acetonitrile	Ethyl	-21.6	64
Dioxane 10 M $C_5H_5N \cdot HCl$	Ethyl	-22.7	67
Toluene	Ethyl	-32.0	95

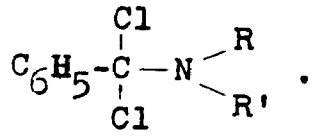
* The chlorosulfites used were derived from dextrorotatory alcohols.

It might be expected that nitromethane would be an intermediate case and lead to almost complete racemization. Unfortunately the reaction could not be studied in a different solvent owing to the low yields of halide obtained.

von Braun believed that the reaction of a phosphorus pentahalide with an N-substituted benzamide proceeded according to the following equation.

$$C_6H_5\text{-}\underset{\displaystyle O}{\underset{\|}{C}}\text{-}\underset{\displaystyle H}{\underset{|}{N}}\text{-}R + PX_5 \xrightarrow{-POX_3} C_6H_5\text{-}\underset{\displaystyle X}{\underset{|}{\overset{\displaystyle X}{\overset{|}{C}}}}\text{-}\underset{\displaystyle H}{\underset{|}{N}}\text{-}R \xrightarrow{-HX} C_6H_5\text{-}\overset{\displaystyle X}{\overset{|}{C}}\text{=}N\text{-}R \rightarrow C_6H_5\text{-}CN + XR$$

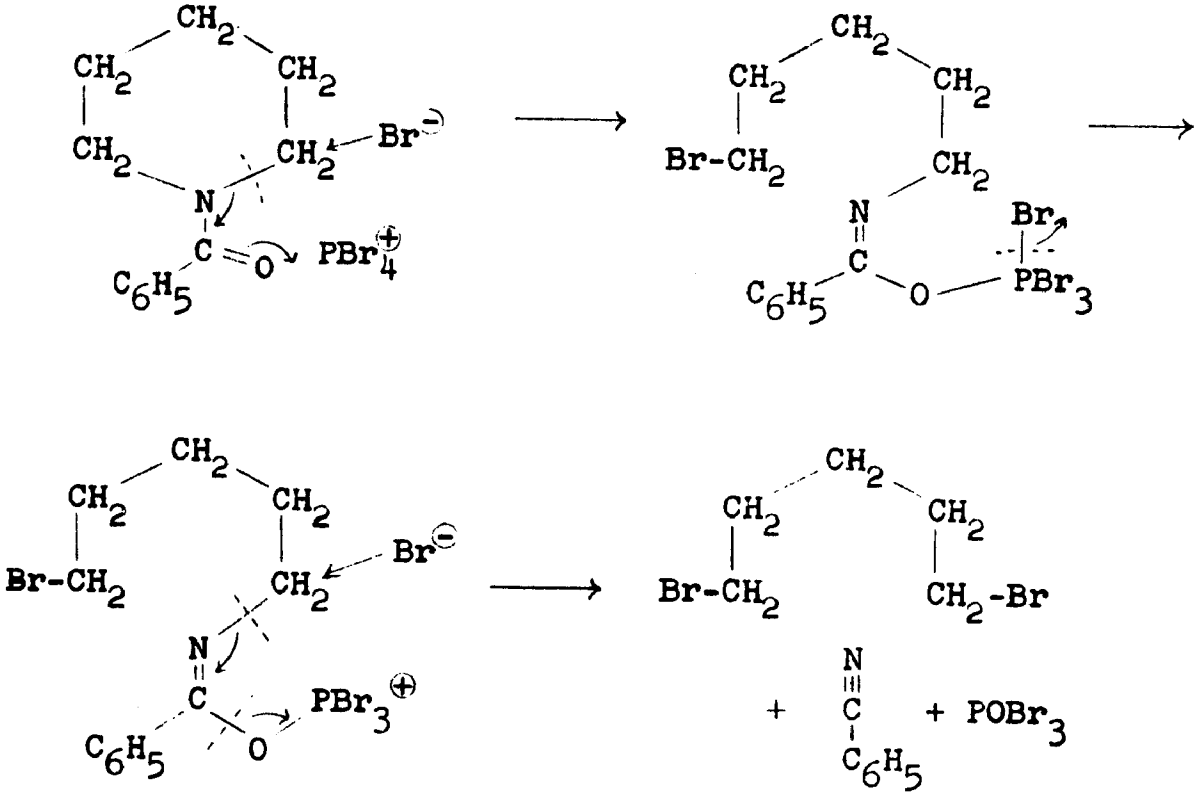
This belief is pointed out in the historical section of this dissertation and in most of von Braun's many papers on the reaction. von Braun and his co-workers substantiate this belief by the isolation of compounds, "amide chlorides", to which they assign the structure,



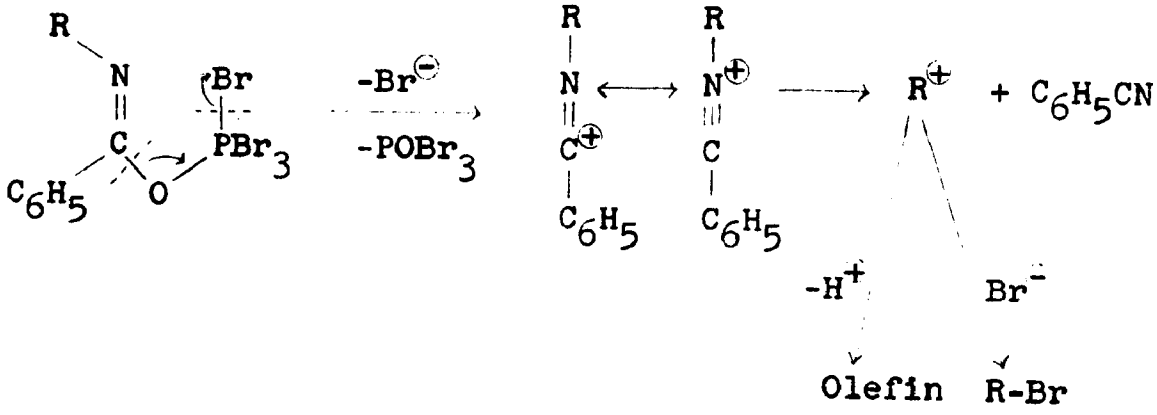
There are also many well substantiated cases of the isolation of imidyl chlorides from the reaction of phosphorus pentachloride with N-substituted benzamides by von Braun and his co-workers, and by other workers. Some of these cases are given in the historical section of this dissertation.

Leonard and Nommensen[10] believe that "... in no case has the existence of such intermediates been definitely established". These workers believe the reaction proceeds by two different paths; a "bimolecular" process when there is no hindrance to rearward attack at the α_N-carbon, and a "unimolecular" process when there is hindrance at this position.

The "bimolecular" process, as visualized by Leonard and Nommensen, is reproduced below.



Their "unimolecular" path of the reaction of phosphorus pentabromide with the benzamide of a hindered amine is as follows:



A selected group of the results of Leonard and Nommensen is given in Table VIII.

TABLE VIII

von Braun Reaction of Amides

N-Benzoyl derivative	Halide produced	% yield
Piperidine	1,5-Dibromopentane	78
2,6-Dimethylpiperidine	2,6-Dibromoheptane	19
2,2,6,6-Tetramethyl-piperidine	---	0
n-Butylamine	n-Butyl bromide	50
s-Butylamine	s-Butyl bromide	61
t-Butylamine	t-Butyl bromide	trace
1-Phenyl-1-aminopropane	α-Bromopropylbenzene	62
1-Phenyl-2-aminopropane	β-Bromopropylbenzene	38
N-Mesitoyl derivative		
s-Butylamine	n-Butyl chloride	54
s-Butylamine	s-Butyl chloride	30
s-Butylamine	s-Butyl bromide	25

The latter workers summarize their experimental results by saying that there is "...(a) decreasing yield of halide with increasing hindrance at the α_N-carbon, (b) predominant inversion of configuration at the asymmetric α_N-carbon of N-benzoyl-s-butylamine, and (c) negligible influence of hindrance at the carbonyl carbon, as indicated in the N-alkylmesitamide series."

In view of the present results and the conflicting beliefs of these two groups of workers it was thought that an attempt to isolate intermediates in the reaction of thionyl chloride with N-substituted amides would be justified.

In the early experiments with the reaction of thionyl chloride with N-substituted acetamides, large amounts of the amine hydrochlorides were found in the residues from the reactions, and it was thought that they arose from hydrolysis of the amides by water present in the solution. Accordingly, to avoid this hydrolysis, an attempt was made to insure anhydrous conditions by adding benzene to the solution of the amide in nitromethane, and distilling the solution until the temperature reached the boiling point of nitromethane.*

It was noticed that when the acetamides were subjected to these conditions a white solid precipitated from the cooled reaction mixture after the thionyl chloride had been added. Thinking that this solid might be an intermediate in the reaction, it was isolated. It contained nitrogen and chlorine, was water-soluble, and gave the starting amide when treated with water in acetone solution. In an attempt to prepare an analytical sample it was discovered that this solid afforded the starting amide when heated in

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* It was later found that the addition of benzene was unnecessary, as nitromethane itself forms an azeotrope with water.

various solvents and also gave the starting amide when a reduced pressure was applied to the solid itself. After further investigation it was found that the same solid was obtained when the acetamide was dissolved in anhydrous benzene and hydrogen chloride gas bubbled into the solution. These data suggest that the solid is the unstable hydrochloride of the amide.

Two experiments were run making use of the supposed amide hydrochlorides. In the first the solid was isolated (from N-benzhydryl acetamide), dissolved in nitromethane and treated with thionyl chloride as usual. In the second, N-(1-phenylethyl)-acetamide in nitromethane was treated with dry hydrogen chloride for one hour, after which, thionyl chloride was added and the reaction continued in the usual manner. In both cases the yield of alkyl halide fell in the same range as that for the normal procedure (i.e., without hydrogen chloride). Thus it appeared that the amide hydrochloride is simply a fortuitous rather than a critical intermediate.

More conclusive evidence that the amide hydrochloride is not an intermediate was obtained by the following procedure. The acetamide of benzhydrylamine was dissolved in a benzene-nitromethane solution and the solution distilled until the boiling point of nitromethane had been reached, cooled, and hydrogen chloride passed into the solution for ten hours. The reaction mixture was then treated in the usual manner but omitting thionyl chloride. After

distillation of the solvent, better than ninety percent of the original amide was recovered, showing that the hydrochloride of the acetamide did not decompose to give the von Braun reaction products under the conditions employed to bring about this reaction.

After reviewing von Braun's work on the preparation of imidyl chlorides, outlined in the historical section of this dissertation, it appeared that no intermediates of this (or similar) type could be isolated from the reaction of N-substituted aliphatic amides. However, it was thought that the reaction of thionyl chloride with N-substituted benzamides should follow the same course as for the other amides, and that there was a higher probability that an intermediate could be isolated from N-substituted benzamides. Accordingly it was decided to verify some of the work of von Braun and Pinkernelle[76].

The reaction of a 200% excess of thionyl chloride with benzanilide proceeded very smoothly to give a good yield of N-phenylbenzimidyl chloride. The identity of this imidyl chloride was established by its boiling point, melting point, and its reaction with aniline to give a compound with the reported melting point of the expected N,N'-diphenylbenzamidine, thus verifying that imidyl chlorides can be prepared with the use of thionyl chloride as the chloridating agent.

Next, thionyl chloride was allowed to react with N-methylbenzamide to give a compound with the reported boiling

point of N-methylbenzimidyl chloride. This compound had no trace of a nitrile band in its infrared spectrum, but when the compound was heated to 150° for eight hours and then distilled at atmospheric pressure, the only distillate collected was almost pure benzonitrile. The residue from this distillation contained the trimer of benzonitrile, cyaphenine. This reaction verifies that benzimidyl chlorides are decomposed by heat into benzonitrile, and presumably an alkyl chloride, although the latter compound was not isolated.

In order to determine whether or not the imidyl chloride could be formed under the conditions of the reactions which produced the alkyl chlorides reported in this dissertation, and further to establish the identity of this postulated imidyl chloride, the experiment was repeated. The same amide was dissolved in nitromethane and treated with thionyl chloride under the conditions which gave the best yields of halides from this type of amide, except that the solvent was removed at water pump pressure, instead of atmospheric pressure, and the residue was not distilled. The infrared spectrum of this residue corresponded very closely to that of the imidyl chloride isolated from the previous reaction. An analysis of this residue showed the presence of chlorine and nitrogen, with only a small trace of sulfur.

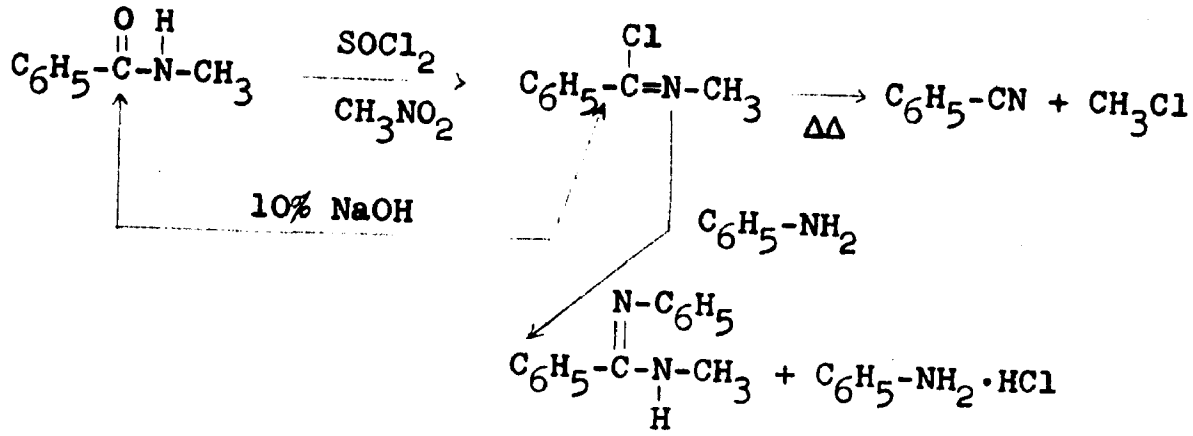
Part of the residue was dissolved in anhydrous ether and treated with an anhydrous ether solution of aniline.

The known N-methyl-N'-phenylbenzamidine was procured and identified by its melting point and the melting point of its picrate.

The second part of the residue from the original reaction was treated with a 10% sodium hydroxide solution until the resulting solution remained basic. The product obtained from this reaction was identified as the starting amide, N-methylbenzamide, by an undepressed mixed melting point with a sample of the original amide, and the fact that its infrared spectrum was superimposable on that of the original amide. These reactions of N-methylbenzimidyl chloride are shown in Chart II.

Chart II

Reactions of N-Methylbenzimidyl Chloride



In order to show definitely that the chloride corresponding to the parent amine was formed on decomposition of an imidyl chloride with heat, the reaction of thionyl chloride and N-benzylbenzamide was run under conditions used for the von Braun reactions, except that the solvent was removed

at water pump pressure. This time the residue was distilled at a low pressure and the distillate divided into five fractions, all of approximately the same boiling point. These fractions were then subjected to the following four reactions.

Part A of the distillate was dissolved in acetone and treated with a small amount of water. The resulting solution was refluxed for three hours and then evaporated. The solid obtained was identified as the starting amide, N-benzylbenzamide, by an undepressed mixed melting point with the starting amide, and the identity of its infrared spectrum with that of the starting amide.

Part B of the distillate was treated with aniline in anhydrous ether solution. The product obtained from this reaction was identified as the known N-benzyl-N'-phenylbenzamidine by its melting point, the melting point of its p-toluensulfonyl derivative, and the similarity of its infrared spectrum to that of the previously obtained, N-methyl-N'-phenylbenzamidine.

Parts C and D of the distillate were combined and distilled at atmospheric pressure to give two main fractions. After redistillations these fractions were identified as benzyl chloride and benzonitrile by their respective boiling points and infrared spectra.

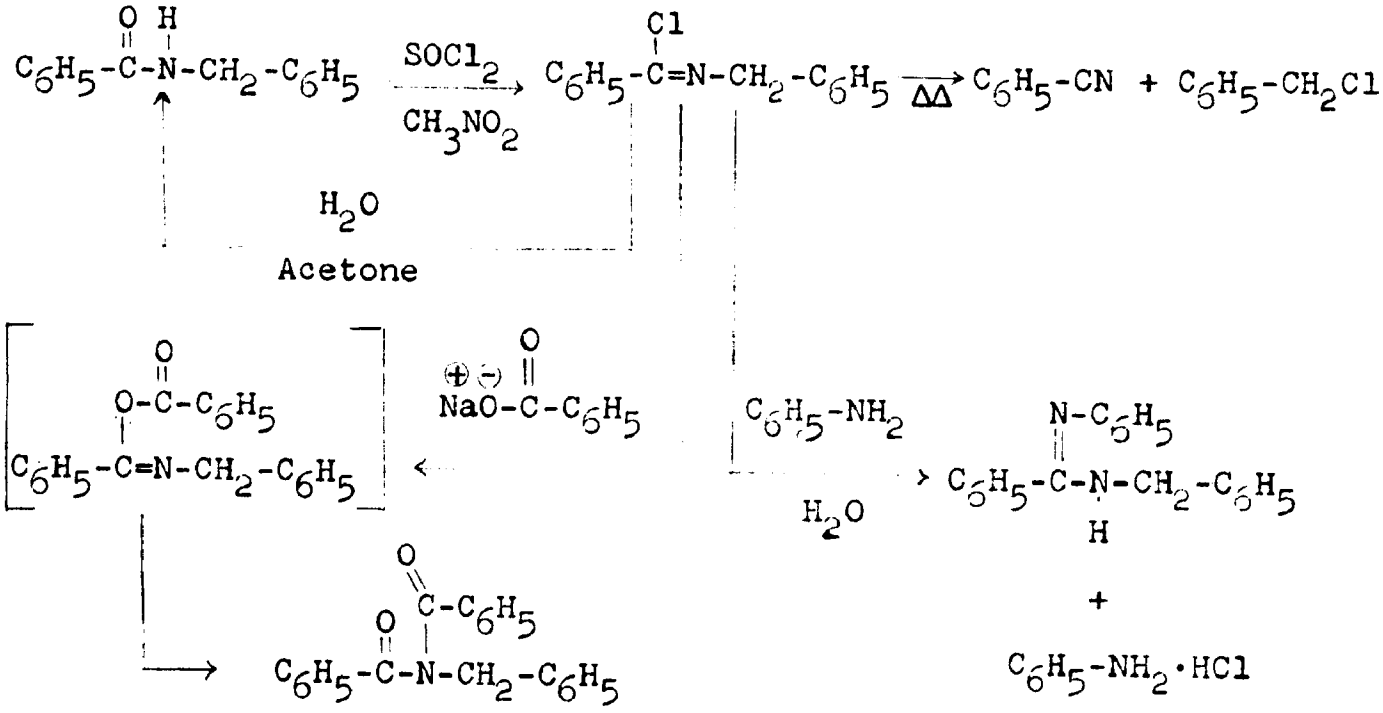
The last part of the distillate, (E), was dissolved in anhydrous ether and intermittently shaken with a saturated, aqueous solution of sodium benzoate for eighteen hours[48].

The product of this reaction was identified as the known N,N-dibenzoyl derivative of benzylamine by its melting point, inspection of its infrared spectrum, and the fact that it depressed the melting point of the original amide.

These reactions of N-benzylbenzimidyl chloride are shown in Chart III.

Chart III

Reactions of N-Benzylbenzimidyl Chloride

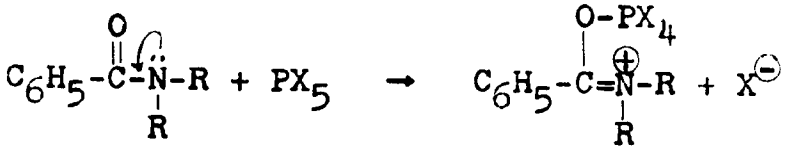


The above reactions show that imidyl chlorides are formed under the same conditions as used for the modified von Braun reactions in this dissertation, and that these imidyl chlorides are decomposed by heat to give the von Braun reaction products. This conclusively shows that at least one path for this reaction involves an imidyl chloride.

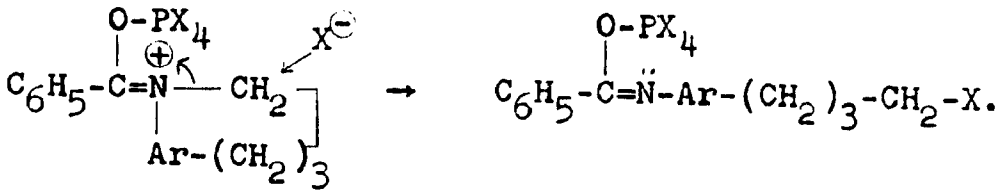
CONCLUSIONS CONCERNING THE NATURE OF THE VON BRAUN REACTION

Although no kinetic data are available, or immediately likely to become available, there is a considerable body of information as to yields of alkyl halides from the von Braun reaction. And while it is seldom safe to infer a mechanism without kinetic information, it is often informative to consider a reaction in mechanistic terms and assume that the yield reflects a kinetic competition between the desired reaction and various undesirable side-reactions.

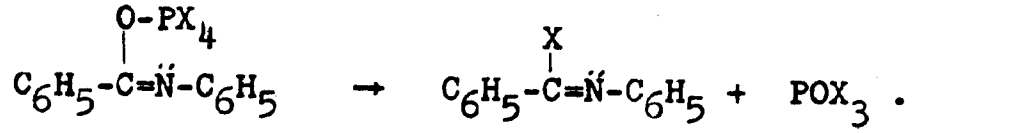
The first question which arises concerns the nature of the initial reaction between the inorganic acid halide and the amide. In the case of N,N-disubstituted benzamides there can be little question that it may be represented by:



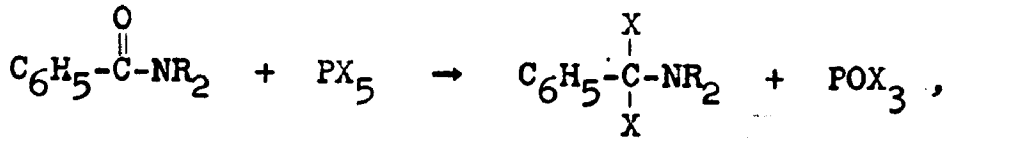
The "ease" (i.e. good yield) with which mono-N-substituted amides plus alkyl halides are produced from such a compound under ideal conditions (cf. Table III, p.13, last cpd.) where a primary alkyl-nitrogen bond is cleaved suggests a typical Sn 2 type reaction (cf. p. 61 and ref. 10):



The isolation of a benzimidyl chloride and benzyl chloride in 90% yield from the reaction of N-benzyl-N-phenylbenzamide with phosphorus pentachloride[4] suggests that the next stage may be represented by:

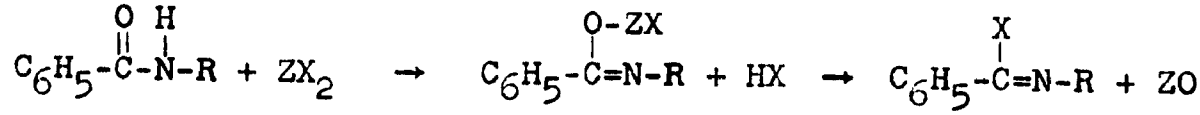


It is not necessary to countenance von Braun's suggestion that the initial reaction is



but there is no evidence available to rule this out entirely.

Where the newly formed intermediate benzimidyl halide is N-alkylated, both von Braun's[57] work and the present investigation have demonstrated subsequent decomposition into an alkyl halide and nitrile; and especially in view of the present work it seems reasonable to propose that for a simple N-alkylbenzamide the initial stages of the reaction with either phosphorus pentahalide (Z = PX_3) or thionyl chloride (Z = SO) proceeds thus:



However, it is possible to consider the essential features of the von Braun reaction in terms of the intermediate benzimidyl ester shown above. It is only reasonable to suppose

that upon the "ionization" (separation into an ion-pair) shown below, the resultant OZX^- will rapidly decompose to X^- and OZ. Reaction conditions (e.g. solvent, temperature) will then govern to what extent X^- combines covalently with the paired cation to give an isolable benzimidyl halide.

The suggestion of Leonard and Nommensen[10] that covalently bonded $-OPX_4$ first loses X^- which then achieves Sn2 type displacement on the α_N-carbon, concerted with cleavage of the carbon-oxygen bond (page 61) is certainly appealing but seems less likely than formation of an ion-pair, for the former reaction path requires a properly oriented collision between two species, which is less likely, if only on probability grounds, than "ionization", which involves simply further polarization of an already highly polarized bond:

$$C_6H_5\text{-}\overset{\overset{O\text{-}ZX}{|}}{C}\text{=}N\text{-}R \rightarrow [C_6H_5\text{-}\overset{\oplus}{C}\text{=}N\text{-}R \longleftrightarrow OZ\text{-}X \rightarrow C_6H_5\text{-}C\text{=}\overset{\oplus}{N}\text{-}R]$$

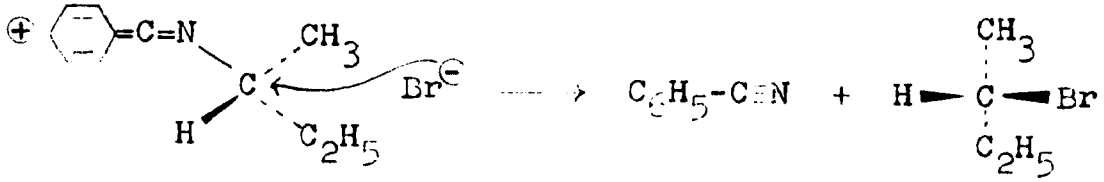
Accordingly let it be assumed that the critical phase of the von Braun reaction involves the ion-pair,

$$R\text{-}\overset{\oplus}{C}\text{=}N\text{-}R' \quad X^{\ominus},$$

either produced directly from the initial imidyl ester as shown above, or by "ionization" of the imidyl halide. The "stability" (i.e. longevity) of the hybrid cation is then one of two important considerations. The other is the

"lability" (scissionability) of the α_N-carbon bond. And it is the relationship between these factors which necessarily determines the course of the reaction. If the cation is long-lived, there will be time for further dissociation between the ions and the consequent possibility that the halide can effect an Sn2 displacement on the α_N-carbon, always providing that this position is accessible to nucleophilic attack on steric grounds and also that the α_N-carbon bond is not prone to rapid rupture. Where observable, this should lead to configurational inversion at the α_N-carbon, and it should be obvious from the character of the two halide ions that bromide will both "ionize" more readily and be a more effective nucleophile than chloride.

This situation is realized in the stereochemical studies of the von Braun reaction. (For these and subsequent illustrations, see Table IX). In (+)-N-s.-butylbenzamide the α_N-carbon is secondary, purely alkyl and comparatively accessible to nucleophilic attack (in this instance[10] by bromide), and the cation is resonance-stabilized:



The partial racemization encountered is a consequence of a certain degree of competition from spontaneous "fragmentation"[94].

TABLE IX

Yields of Alkyl Halides from the von Braun Reaction

(references to previous work are given in parentheses)

Alkyl Group	Benzamide	Benzamide	Benzamide	Acetamide	Other
Straight Chain	PCl_5	PBr_5	$SOCl_2$	$SOCl_2$	
$CH_3(CH_2)_3$-		50% (10)	34%[a]		formamide gives trace
$C_6H_5(CH_2)_4$-	75% (13)				
$C_6H_5(CH_2)_5$-	73-5% (13,14)	70% (14)			
$CH_3(CH_2)_8$-		70% (14)			
$CH_3(CH_2)_{16}$-	50% (14)	73% (9)			
-$(CH_2)_4$-	70% (26)	70% (26)			
-$(CH_2)_5$-	70-80% (6)[b]	65-78% (5, 21,22)			
-$(CH_2)_6$-	65% (27)				
-$(CH_2)_2CHCH_3(CH_2)_2$-	65% (24)				
One β_N-Substituent					
-CH_2CH_2-	50% (18)				

TABLE IX continued

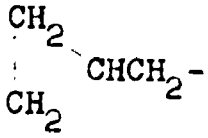
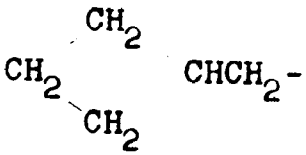
$mCH_3C_6H_4$-CH_2CH_2-	50% (19)			
C_6H_5-CH_2CH_2-			trace	formamide gives trace
Two β_N-Substituents				
		30% (17)		
		31% (17)		
$C_6H_5CH(CH_3)CH_2$-	25% (19)			
$C_6H_5CH_2CH(C_6H_5)CH_2$-	25% (15)			
Three β_N-Substituents				
$(CH_3)_3CCH_2$-		none (10)		

TABLE IX continued

One α_N-Substituent				
$CH_3CH_2CH(CH_3)$-	61%[c] (10)			
$C_6H_5CH_2CH(CH_3)$-	38% (10)			
$-CH(CH_3)(CH_2)_3CH(CH_3)$-	19% (10)			
$[-CH(C[C_6H_5]_3)CHBr]_2$	15% (25)			
Two α_N-Substituents				
$(CH_3)_3C$-	trace (10)	20-50%[d]		
$-C(CH_3)_2(CH_2)_3C(CH_3)_2$-	none (10)			
Benzyl Type				
No Substituents				
$C_6H_5CH_2$-	90% (4)[e]	20-50%[d]	10%	formamide gives trace
$pCH_3OC_6H_4CH_2$-		40-45%	40-50%	propionamide gives 65%
$mClC_6H_4CH_2$-	60% (8)[f]			
α-$C_{10}H_7CH_2$-	65-70% (12)[g]			

TABLE IX continued

One α_N-Substituent				
$C_6H_5CH(CH_3)$-		80-85%	55-65%[h]	formamide gives 50% propionamide: 72% butyramide: 75%
$C_6H_5CH(C_2H_5)$-	62% (10)			
$C_6H_5CH(C_5H_9)$-[i]		80-85%	75-85%	
$C_6H_5CH(C_6H_5)$-		80-85%	75-85%	
$pCH_3C_6H_4CH(CH_3)$-		20-35%[j]	20-30%[j]	propionamide gives 34%[j]

a. Optimum yield probably considerably higher: insufficient thionyl chloride.

b. Same yield obtained from $C_6H_5CONH(CH_2)_5Cl$.

c. "Optical purity" 57-87%.

d. Yield estimated: see experimental.

e. From $C_6H_5CON(C_6H_5)CH_2C_6H_5$.

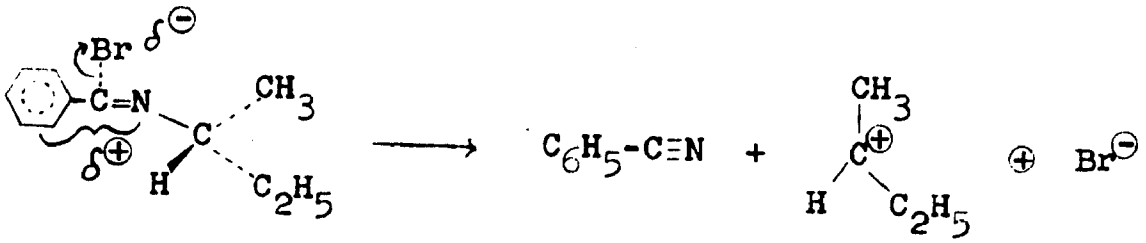
f. From $C_6H_5CON(CH_2C_6H_4mCl)_2$

g. From $C_6H_5CON(\alpha\text{-}C_{10}H_7)_2$ as well as $C_6H_5CONH(\alpha\text{-}C_{10}H_7)$.

h. "Optical purity" 33-34%.

i. Cyclopentyl

j. Appreciable dehydrohalogenation (see experimental). Evidently this, rather than the principal reaction is yield-limiting (cf. $C_6H_5CH(CH_3)$-.



As in the Sn1 reaction the optical properties of the resultant alkyl halide are a function of the longevity of the carbonium ion, i.e. how "far away" it can get from the departing nitrogen before it captures a bromide. It is also obvious that if the carbonium ion can achieve stabilization by deprotonation, an olefin (and/or polymer) will also be produced.

It is clear that if the resultant carbonium ion possesses a high degree of "stability", the spontaneous fragmentation will be a more significant competitor to displacement, and the resultant alkyl halide should be more extensively racemic. This is the case for (-)-N-1-phenylethylbenzamide* from which the alkyl halide has a lower degree of optical purity than in the s.-butyl bromide obtained by Leonard and Nommensen[10]. And if one shortens the life of the original cationic portion of the ion-pair, the probability of fragmentation before displacement should be increased. This, too, is observed: (-)-N-1-phenylethylacetamide affords the corresponding chloride in only 3-4% "optical purity", for the methyl group of the acyl portion of the amide is considerably less effective in "stabilizing"

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* W. R. Vaughan, C. Placeway and W. E. Reusch, unpublished results.

the cation (inductive effect only) than the phenyl group (resonance). Thus the stereochemistry of the von Braun reaction is in accord with the ion-pair hypothesis.

The probability of fragmentation where the α_N-carbon is primary and purely alkyl is vanishingly low. Consequently one should expect satisfactory yields of alkyl halide only when the cation is stabilized and the halide is a good nucleophile. Furthermore the yields should reflect the extent of "stabilization", the nucleophilicity of the halide and the accessibility (i.e. lack of steric hindrance) of the α_N-carbon to nucleophilic attack.

The order of "stabilization" of the cationic member of the ion-pair depends on the acyl substituent of the amide and falls in the order C_6H_5- C_3H_7- C_2H_5- CH_3- H- (resonance for phenyl and inductive effect for the others). Comparative yields for corresponding amides do indeed fall in this order; and the need for accessibility to nucleophilic attack is clearly revealed in a series of N-primary alkylbenzamides with increasing β-substitution.

If the intermediate cation is comparatively stable, i.e. electronically, and not prone to undergo competitive forms of decomposition (see pages 27-30), a benzyl-type carbonium ion should fragment from it (or be displaced) fairly readily. Thus for a series of N-benzyl type benzamides, one should expect fairly constant yields; this is realized. However, where the cation is less effectively stabilized (alkanoamides) the product yield should be

sensitive both to degree of stabilization (as shown above) and the scissionability of the α_N-carbon bond. Increasing bulk adjacent to this bond will have the effect of decreasing its accessibility to nucleophilic attack but at the same time it should assist carbonium ion formation ("B-strain"). Thus in the N-benzyl alkanoamides introduction of an α-substituent or an increase in size of such a substituent should result in improved yields, since the carbonium ion will thus be induced to fragment from the original cation before the latter can undergo undesirable competitive reactions. The series benzyl-, p-methoxybenzyl-, α-methylbenzyl-, α-cyclopentylbenzyl- and benzhydrylacetamides afford the corresponding chlorides in yields increasing in this order, and the last two are indistinguishable, showing that the two groups of comparable bulk but differing electronic character are equally effective.

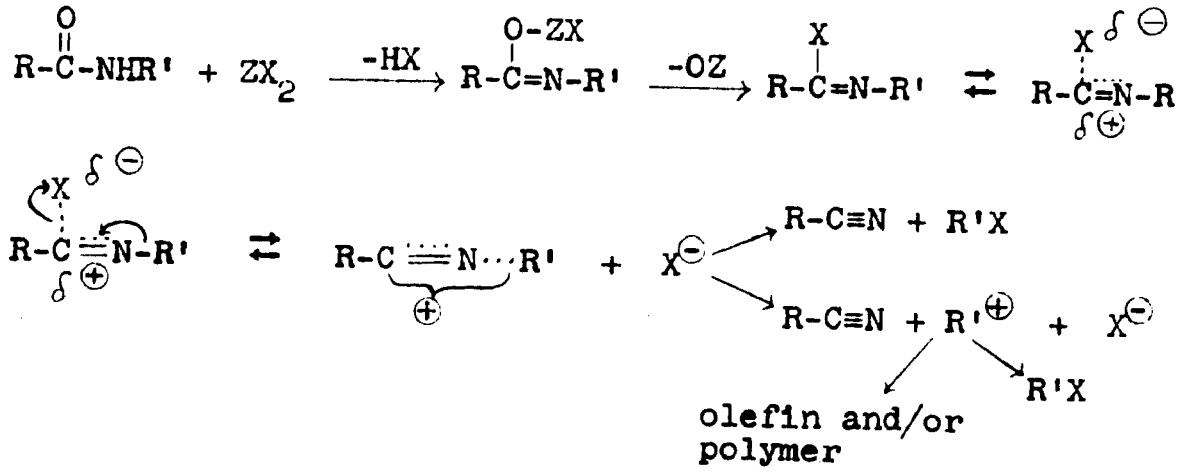
The foregoing observations are in accord with the hypothesis that the probability of fragmentation of a short-lived or "unstable" ion-pair is greater than the probability of displacement of the alkyl group from the cation by halide, for in the latter reaction one would expect increasing bulk to disfavor product formation, and, as noted, the reverse is true.

In conclusion it is clear that in every respect the experimental evidence adduced in the present investigation and by others is in accord with the ion-pair hypothesis for the critical phase of the von Braun reaction. Thus the

mechanistic scheme for the reaction shown in Chart IV may be proposed. It differs somewhat from the earlier suggestion of Leonard and Nommensen[10] in that it incorporates an imidyl halide as a true intermediate, and the two modes of decomposition can be likened to Sn1' and Sn2' reactions for the fragmentation and displacement processes respectively.

Chart IV

Proposed Mechanism of the von Braun Reaction



SUMMARY

The yields of alkyl halide produced in the von Braun reaction will parallel the accessibility to nucleophilic attack at the α_N-carbon for benzamides in which this carbon is primary and purely alkyl; they will parallel the relative stability of the corresponding carbonium ion for amides of benzylamines; and they will parallel the stabilizing character of the radical in the acyl portion of the amide.

Thionyl chloride may be considered the reagent of choice for the von Braun reaction (over phosphorus pentahalide) only if the alkyl group of the amine affords a comparatively stable carbonium ion. Otherwise thionyl chloride should be used only with alkanoamides of amines whose corresponding alkyl halides may be difficultly separable from the usual by-products of the benzamide-phosphorus pentahalide system, benzonitrile and phosphorus oxyhalide.

These statements and recommendations are based on the experimental results of the present and previous investigations of the von Braun reaction, notably by von Braun and by Leonard and Nommensen, and they are in accord with a mechanistic scheme for the reaction in which an ion-pair intermediate is the critical feature.

EXPERIMENTAL[a,b]

N-Alkylformamides.--- The procedure described for N-butylformamide is typical for this series of compounds.

N-Butylformamide.--- The amine (146 g., 2.00 mol.) was cooled to 0° in a 500 ml. three neck flask, and 98% formic acid (101 g.) added dropwise with stirring and cooling. After the addition was complete the solution was allowed to come to room temperature with stirring. The water and excess formic acid were removed by distillation at water pump pressure. The yields of five separate runs were between 85 and 90% of material, b.p. 101-2°/1-2 mm. Blicke and Chi-Sung Lu[95] report 122-3°/16 mm.

N-(1-Phenylethyl)-formamide.--- The amide, after distillation at 155-60°/2-3 mm., solidified to a white solid, m.p. 41-4°. The yields were between 85 and 90%.

Anal. Calcd. for $C_9H_{11}NO$: C,72.45; H,7.43; N,9.39
Found: C,72.58; H,7.52; N,9.46.

N-Benzylformamide.--- The amide was obtained as a white solid, m.p. 60.5-61.5°, after recrystallization from a chloroform-petroleum ether (b.p. 30-40°) mixture. Blicke and Chi-Sung Lu[95] report 60-61°.

N-(2-Phenylethyl)-formamide.--- This amide was prepared according to the method described by Blicke and Chi-Sung Lu[95].

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a. All melting points were determined in open capillaries and are uncorrected.

b. Microanalyses are by the Spang Microanalytical Laboratory, Ann Arbor, Michigan.

The amine (163 g., 1.35 mol.) was cooled to 0° in a 500 ml. three neck flask equipped with a sealed stirrer, reflux condenser and dropping funnel. The exits were protected with calcium chloride drying tubes. Chloral (200 g., 1.35 mol.), obtained by distilling 291 g. of chloral hydrate from an equal weight of conc. sulfuric acid, was added dropwise with rapid stirring and cooling. After the addition was complete the reaction mixture was stirred at room temperature for 2 hr. and then refluxed for 1 hr. The chloroform was removed at water pump pressure and the amide distilled at a lower pressure to give 111 g. (55%) of material, b.p. 162-3°/ 1.5 mm.: Blicke and Chi-Sung Lu[95] report 192-194°/20 mm.

N-Alkylacetamides.--- The procedure for N-1-Phenylethylacetamide is typical for this series of compounds.

N-(1-Phenylethyl)-acetamide.--- The amine (60 g., 0.50 mol.), 25% sodium hydroxide (110 g.) and 150 g. of ice were rapidly stirred in a one-liter Erlenmeyer flask immersed in a methanol-ice bath while 51 ml. (0.55 mol.) of acetic anhydride were added all at once. The resulting mixture was stirred for 1 hr. and then filtered by suction. The white solid was washed with water and sucked dry on the filter. The solid was then dissolved in absolute ethanol and boiled with Norit for 15 min. The Norit was filtered off and water added to the warm (45°) ethanol solution until it started to become cloudy. The solution was allowed to cool slowly to room temperature and them cooled to 0° and filtered.

The solid thus obtained was recrystallized from a benzene-petroleum ether (b.p. 30-60°) mixture. The yields by this procedure ranged between 49 and 65 g. (60-80%) of material, m.p. 75-76°.

Anal. Calcd. for $C_{10}H_{13}NO$: C,73.59; H,8.03; N,8.58
Found: C,73.65; H,7.84; N,8.50.

(-)N-(1-Phenylethyl)-acetamide.--- The distilled 1-phenylethylamine was resolved according to the method of Campbell, Holeston and Kenyon[96] to give the tartrate salt of the (-)isomer. The salt was decomposed with a large excess of 25% sodium hydroxide and the basic solution steam distilled. The amine was extracted from the distillate with benzene, the benzene solution dried over calcium sulfate and the benzene distilled off at atmospheric pressure. The residue was distilled at reduced pressure to give a 14-15% yield of the (-)amine, b.p. 80-83°/24 mm. $\alpha_D^{33°}$ -36.88 (ℓ, 1.0). Campbell, Holeston and Kenyon[96] report b.p. as 73°/14 mm. and α_D^{17} -18.28 (ℓ, 0.5).

The active amine was acetylated by the same procedure used for the d,ℓ compound. This amide was recrystallized from an ethanol-water mixture and from a benzene-petroleum ether (30-60°) mixture to give the (-) amide of m.p. 101.0-102.5°.

N-(2-Phenylethyl)-acetamide.--- The acetylated amine was recrystallized from a benzene-petroleum ether (b.p. 30-60°) mixture and from a chloroform-petroleum ether mixture to give 50-60% yields of amide, m.p. 53-55°. This amide has a

strong tendency to oil out of the solvents used. Carothers and Jones[97] report the m.p. 51-52°.

N-Benzylacetamide.--- The acetylated amine was recrystallized from aqueous ethanol and from a benzene-petroleum ether (b.p. 30-60°) mixture to give 60-80% yields of amide, m.p. 61-63°: Nicholas and Erickson[98] report 61°.

N-Benzhydrylacetamide.--- The acetylated amine was recrystallized from aqueous ethanol and from ethyl acetate to give 50-60% yields of amide, m.p. 147-8°. Exner[99] reports 147°.

N-1-(p-Methoxyphenyl)-ethylacetamide.--- The acetylated amine was recrystallized from aqueous ethanol and from a benzene-petroleum ether (30-60°) mixture to give a 64% yield of material, m.p. 74.0-75.5°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C,68.37; H,7.82; N,7.25
Found: C,68.37; H,7.69; N,7.51.

N-1-(p-Tolyl)-ethylacetamide.--- The acetylated amine was recrystallized from an absolute ethanol-ether mixture and from a benzene-petroleum ether (30-60°) mixture to give 50-60% yields of amide, m.p. 74-75°.

Anal. Calcd. for C $H_{15}NO$: C,74.54; H,8.53; N,7.91
Found: C,74.76; H,8.45; N,8.04.

N-(α-Cyclopentylbenzyl)-acetamide.--- The acetylated amine was recrystallized from aqueous ethanol and from a benzene-petroleum ether (30-60°) mixture to give a 76% yield of amide, m.p. 109-112°: Smith, Baer and Ege[82] report 109-111°.

N-(α,α-Dimethybenzyl)-acetamide.--- The acetylated amine was recrystallized from an absolute ethanol-ether mixture and from ether alone to give a 75% yield of amide, m.p. 103-104°.

Anal. Calcd. for $C_{11}H_{15}NO$: C,74.54; H,8.53; N,7.91
Found: C,74.73; H,8.59; N,7.92.

N-t-Butylacetamide.--- The acetylated amine was recrystallized three times from a benzene-petroleum ether (30-60°) mixture to give a 41% yield of amide, m.p. 97.0-98.5°: Scholl, Weil and Holdermann[100] report 98°.

N-Cyclohexylacetamide.--- The acetylated amine was recrystallized from an ethanol-water mixture and from a benzene-petroleum ether (30-60°) mixture to give a 66% yield of amide, m.p. 104-106°: Baeyer[101] reports 104°.

N-p-Methoxybenzylacetamide.--- (Procedure A)- The amide was prepared by the same acetylation procedure as N-1-Phenylethylacetamide. The product was recrystallized from aqueous ethanol to give a 60% yield of amide, m.p. 94-96°. Exner[99] reports 96°.

(Procedure B)---A solution of 4-methoxybenzonitrile (26.7 g., 0.200 mol.) in 30 ml. of acetic anhydride was added to 0.24 g. of Adams' catalyst in 40 ml. of acetic anhydride. The mixture was subjected to a continuous pressure of 50 lbs. of hydrogen and shaken until no more hydrogen was taken up (48 hr.). The catalyst was filtered off and the filtrate neutralized with 25% sodium hydroxide. The white solid which separated was filtered off and recrystallized from aqueous ethanol. The material thus obtained was

recrystallized twice from a benzene-petroleum ether (30-60°) mixture with a Norit treatment giving 25 g. (70%) of amide, m.p. 95.5-97.0°.

N-1-(p-Nitrophenyl)-ethylacetamide.--- Nitric acid (242 ml., sp.gr. 1.5) was placed in a one liter flask and cooled to -10° with an ice-salt bath and N-1-phenylethyl-acetamide added, with rapid stirring, at such a rate that the temperature of the reaction mixture never rose above 5°. After all the amide had been added the solution was stirred for an additional 25 min. and then diluted with a mixture of ice and water (300 g.) until the solution appeared milky. The solution was then transferred to a three-liter Erlenmeyer flask and neutralized with ammonium hydroxide (sp.gr. 0.9). The product which precipitated from the solution was filtered off and recrystallized twice from aqueous ethanol to give 43 g. (50%) of material, m.p. 122-124°.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C,57.68; H,5.81; N,13.46
Found: C,57.69; H,5.83; N,13.56.

A portion of the amide (0.7 g.) was heated on a steam bath with 2.5 g. of potassium dichromate, 5 ml. conc. sulfuric acid and 15 ml. of water for 1.5 hr. The crystals that separated from the hot solution were filtered off and recrystallized from water to give 4-nitrobenzoic acid, m.p. 239.5-242.5°: Johnson and Guest[102] report 237-238°.

N-Alkylbenzamides.--- The procedure for N-p-methoxybenzylbenzamide is typical for this series of compounds.

N-p-Methoxybenzylbenzamide.--- The amine (36.0 g., 0.263 mol.), 25% sodium hydroxide (60 g.), and 53 g. of ice were rapidly stirred in a 50 ml. Erlenmeyer flask immersed in an ice-salt bath while 34 ml. (0.29 mol.) of benzoyl chloride were added all at once. The resulting mixture was stirred for an hour and filtered by suction. The white solid was washed with water, recrystallized from aqueous ethanol and from a benzene-petroleum ether (30-60°) mixture. This procedure gave 54 g. (85%) of the amide, m.p. 97.5-99.0°.

Anal. Calcd. for $C_{15}H_{15}NO_2$: C,74.70; H,6.27; N,5.81
Found: C,74.77; H,6.39; N,5.66.

N-(1-Phenylethyl)-benzamide.--- The benzoylated amine was recrystallized twice from aqueous ethanol and dried at 80° for 24 hr. giving 60-80% yields of the amide, m.p. 122.5-124.0°.

Anal. Calcd. for $C_{15}H_{15}NO$: C,79.97; H,6.71; N,6.22
Found: C,79.93; H,6.63; N,6.04.

N-Benzhydrylbenzamide.--- The benzoylated amine was recrystallized from 95% ethanol and from absolute ethanol to give a 68% yield of the amide, m.p. 171-172°: Smith and Bergstrom[104] report 170.5-171°.

N-1-(p-Methoxyphenyl)-ethylbenzamide.--- The benzoylated amine was recrystallized from aqueous ethanol and from a benzene-petroleum ether (30-60°) mixture to give a 70% yield of amide, m.p. 121-122°: Ingersoll, Brown, Kim, Beauchamp and Jennings[105] report 117-118°.

N-Benzylbenzamide.--- The benzoylated amine was recrystallized from aqueous ethanol and from a benzene-petroleum ether (30-60°) mixture giving 75-85% yields of amide, m.p. 104.8-105.8°: Beckmann[106] reports 105°.

N-(α-Cyclopentylbenzyl)-benzamide.--- The benzoylated amine was recrystallized twice from 95% ethanol to give a 66% yield of the amide, m.p. 162.5-164.0°: Smith, Baer and Ege[82] report 166-167°.

N-1-(p-Tolyl)-ethylbenzamide.--- The benzoylated amine was recrystallized from aqueous ethanol, with a Norit treatment, and from a benzene-petroleum ether (30-60°) mixture to give a 70% yield of the amide, m.p. 118-119°.

Anal. Calcd. for $C_{16}H_{17}NO$: C,80.30; H,7.16; N,5.85

Found: C,80.03; H,7.02; N,5.75; (Trace of ash.)

Benzanilide.--- The benzoylated amine was recrystallized from absolute ethanol and dried at 80° for 24 hr. to give a 74% yield of the amide m.p. 160-162°: Stephen and Staskun[107] report 161-162°.

N-Methylbenzamide.--- The same procedure was used for the preparation of this benzamide as for N-p-Methoxybenzylbenzamide except that a 40% solution of methylamine in water was used instead of the pure amine. The benzoylated amine was recrystallized from 95% ethanol to give an 86% yield of the amide, m.p. 78-80°. Wheeler[108] reports 82°.

N-n-Butylbenzamide.--- The benzoylated amine was recrystallized from ethanol to give a 70% yield of amide, m.p.

39-41°. Leonard and Nommensen[10] report 41-42°.

N-(1-Phenylethyl)-n-butyramide.--- A mixture of 1-phenylethylamine (64 ml., 0.50 mol.), 25% sodium hydroxide (100 g.) and 100 g. of ice were cooled to below 0° in an ice-salt bath and butyryl chloride (54 g., 0.55 mol.) added all at once with rapid stirring. More ice had to be added to keep the reaction mixture below 0°. The mixture was stirred for an additional 0.5 hr. The product separated as an oil which was extracted with benzene. The benzene extracts were washed with 10% hydrochloric acid, water, 10% sodium hydroxide and finally with water. The benzene was evaporated and the oil, thus obtained, solidified. This material defied all attempts to find a recrystallization procedure. For this reason the amide was distilled at reduced pressure, b.p. 107-108°/0.1 mm. This water-white, viscous oil solidified on standing, but was too wax-like to obtain a definite melting point.

Anal. Calcd. for $C_{12}H_{17}NO$: C,75.33; H,8.96; N,7.32

Found: C,75.33; H,8.87; N,7.27.

N-Alkylpropionamides.--- The procedure for N-1-phenylethylpropionamide is typical for this series of compounds.

N-(1-Phenylethyl)-propionamide.--- The amine (60 g., 0.50 mol.), 25% sodium hydroxide (110 g.), and 150 g. of crushed ice were rapidly stirred in a 1-liter Erlenmeyer flask immersed in a methanol-ice bath, while 71.5 g. (0.55 mol.) of propionic anhydride were added all at once. The resulting mixture was rapidly stirred for 1 hr., the solid filtered off, washed with water, and sucked dry. The solid

was recrystallized from an ethanol-water mixture and from a benzene-petroleum ether (30-60°) mixture to give 73 g. (77%) of the amide, m.p. 59.5-61.0°.

Anal. Calcd. for $C_{11}H_{15}NO$: C,74.51; H,8.53; N,7.90
Found: C,74.55; H,8.53; N,8.02.

N-1-(p-Tolyl)-ethylpropionamide.--- The propionylated amine was recrystallized from an ethanol-water mixture and from a benzene-petroleum ether (30-60°) mixture to give a 67% yield of the amide, m.p. 83-84°.

Anal. Calcd. for $C_{12}H_{17}NO$: C,75.35; H,8.96; N,7.32
Found: C,75.28; H,8.86; N,7.22.

N-(p-Methoxybenzyl)-propionamide.--- The propionylated amine was recrystallized twice from an ethanol-water mixture to give a 70% yield of amide, m.p. 88.0-89.5°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C,68.37; H,7.82; N,7.25
Found: C,68.21; H,7.72; N,7.09.

Preparation of Amines.

Anisaldoxime.--- Anisaldehyde (136 g., 1.00 mol.) and hydroxylamine hydrochloride (87.0 g., 1.25 mol.) were added to 150 ml. of water in a one-liter three-neck flask and cooled to 4°. A solution of 66.3 g. of sodium carbonate in 125 ml. of water was added from a dropping funnel at a rapid rate with fast stirring. The temperature of the reaction mixture at the end of the addition was 26°. The mixture was stirred for an additional hour, during which time the temperature rose to 35°. The white solid which had separated

was filtered off, washed thoroughly, and air dried. The product was then recrystallized from a benzene-petroleum ether (30-40°) mixture. Air drying gave 135.5 g. (90%) of the oxime, m.p. 59-62°. Heilbron[109] reports three forms of the oxime, one of which melts at 65°.

p-Methoxybenzylamine.--- (Procedure A) By Reduction of Anisaldoxime.--- Lithium aluminum hydride (28.5 g., 0.750 mol.) was dissolved in a mixture of 300 ml. of anhydrous ether and 200 ml. of anhydrous benzene in a two-liter three-neck flask. Anisaldoxime (75.5 g., 0.500 mol.), dissolved in an anhydrous mixture of 300 ml. of ether and 100 ml. of benzene, was added to the rapidly stirred solution as fast as possible without causing too vigorous reflux. The addition took about 2 hr. The mixture was then maintained at reflux by warming, and the mixture was stirred over night. The flask was then immersed in an ice bath and 57 ml. of water added dropwise, followed by 45.6 ml. of 10% sodium hydroxide. The mixture was again stirred over night at room temperature and then filtered. The solvent was removed by distillation at atmospheric pressure and the residue distilled at water pump pressure to 46 g. (67%) of the amine, b.p. 120-130°/18-30 mm.: Heilbron[110] reports 122-4°/14 mm. The reduction procedure was repeated with a 48 hr. reflux period and the yield was increased to 80%.

(Procedure B) By Reduction of Anisonitrile.--- A solution of anisonitrile (66.5 g., 0.50 mol.) in 500 ml. of anhydrous ether was added dropwise to a stirred mixture of

lithium aluminum hydride (19.14 g., 0.505 mol.) and 500 ml. of anhydrous ether, at such a rate as to maintain a steady reflux. The addition took about 45 min. After the addition was complete the mixture was stirred at room temperature for 2 hr. At the end of this time the mixture was cooled and 19 ml. of water added dropwise, followed by 15.3 ml. of 10% sodium hydroxide. This mixture was stirred over night and then filtered. The filtrate was distilled at water pump pressure to give 36.0 g., (52.5%)* of the amine, b.p. 126-128°/ 16-20 mm.

p-Methoxyacetophenone Ketoxime.--- A mixture of p-methoxyacetophenone (82.5 g., 0.550 mol.), hydroxylamine hydrochloride (60 g., 0.86 mol.), 200 ml. of 95% ethanol, and 40 ml. of water was stirred rapidly in a two-liter three-neck flask while pellet sodium hydroxide (110 g., 275 mol.) was added in small portions. The mixture became warm, but the pellets were added slowly enough to prevent the mixture from reaching reflux temperature. After the addition of sodium hydroxide was complete the mixture was refluxed for 15 min. and then allowed to cool and was poured onto a stirring mixture of 1000 g. of ice and 300 ml. of conc. hydrochloric acid in a three-liter Erlenmeyer flask immersed in an ice-salt bath. The white solid was filtered off by suction and recrystallized from aqueous methanol and from a benzene-petroleum ether (30-60°) mixture to give 65.0 g. (71.5%) of the oxime, m.p. 85-87°: Lyle and Troscianiec[111] report 85-87°.

*It is felt that a higher yield of amine would have been obtained if a longer reaction time had been allowed.

1-(p-Methoxyphenyl)-ethylamine.(Procedure A)-- By Reduction of p-Methoxyacetophenone Ketoxime--- A mixture of 4-methoxyacetophenone ketoxime (64.0 g., 0.388 mol.), Raney nickel (W-2, 6 g.) and 200 ml. of absolute ethanol was placed in a copper lined hydrogenation bomb and subjected to an initial hydrogen pressure of 1100 p.s.i. The bomb was then heated to 100°, with shaking, and this temperature maintained for 1.5 hr. The catalyst was filtered off by suction, the ethanol removed at atmospheric pressure, and the residue distilled at reduced pressure to give 43.8 g. (75.0%) of the amine, b.p. 120-128°/15-25 mm.: Lyle and Troscianiec[111] report 100-101°/9 mm.

(Procedure B) - By Reaction p-Methoxyacetophenone with Urea and Formic Acid.--- A mixture of 4-methoxyacetophenone (90 g., 0.60 mol.), urea (72 g., 1.2 mol.), and 98% formic acid (110 g., 2.35 mol.) was heated under slow distillation conditions to 110-120°, and kept at this temperature for 2 hr. The temperature of the mixture was then raised, and kept between 175-185° for 3.5 hr. The mixture was cooled and transferred to a two-liter flask and a solution of 210 ml. of conc. hydrochloric acid in 210 ml. of water added. This mixture was refluxed for 2 hr. and cooled. A dark red oil remained which was extracted from the acid solution with benzene. The acid solution was made strongly basic with sodium hydroxide and extracted with benzene. The benzene solution was dried with sodium hydroxide and distilled. The fraction boiling at 126°/20 mm. was collected to give 49 g.

(54%) of the amine.

Benzophenone Ketoxime.--- This oxime was prepared from the ketone by the same procedure as used for the preparation of 4-methoxyacetophenone. The product was recrystallized from aqueous methanol and washed with petroleum ether (30-60°) to give an 80% yield of material, m.p. 140-142°: Lachman[112] reports 141-142°.

Benzhydrylamine.--(Procedure A)--By Reduction of Benzophenone Ketoxime.--- A solution of the dried oxime (78.0 g., 0.395 mol.) in 200 ml. of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added dropwise to a rapidly stirred slurry of lithium aluminum hydride (22.5 g., 0.593 mol.) in 300 ml. of tetrahydrofuran (distilled as above). After the addition was complete the mixture was refluxed with stirring for 24 hr. The mixture was cooled and the excess hydride decomposed with 45 ml. of water, followed by 36 ml. of 10% sodium hydroxide. The mixture was then stirred over night and filtered. The solvent was removed under water pump pressure and the residue distilled to give 50.3 g. (70.0%) of the amine, b.p. 180-86°/20-24 mm.: Exner[113] reports 172-174°/20 mm.

(Procedure B)-- By Reaction of Benzophenone with Urea and Formic Acid.--- A mixture of benzophenone (109 g., 0.600 mol.), urea (72 g., 1.2 mol.) and 98% formic acid (110 g., 2.35 mol.) was heated at 110-135° for 2 hr. under slow distillation conditions. Some of the ketone steam-distilled, but it was not replaced. The mixture was then heated to 180°

over a 1.5 hr. period and kept between 180-185° for 3 hr. After the second layer disappeared, the temperature started to rise. The mixture was then cooled and transferred to a two-liter flask, and 210 ml. of conc. hydrochloric acid, diluted with 210 ml. of water, were added and the resulting mixture refluxed for 1.5 hr. The mixture was then cooled and the white solid which separated was filtered by suction and washed with three portions of cold distilled water. After being sucked dry the solid was washed with two portions of ether and one portion of petroleum ether (30-40°) and was air dried to give 103.5 g. (79.0%) of the amine hydrochloride, m.p. 291-293°. Biltz, Seydel and Hamburger-Glaser[114] report 293°.

p-Methylacetophenone Ketoxime.--- A solution of hydroxylamine hydrochloride (76 g., 1.1 mol.) in 92 ml. of water was added to a solution of 4-methylacetophenone (120 g., 0.895 mol.) in 400 ml. of 95% ethanol in a three-liter three-neck flask, and rapidly stirred while a solution of 172 g. of sodium hydroxide in 210 ml. of water was added at such a rate that the solution became hot, but did not reflux. After the addition was complete the resulting mixture was stirred for 36 hr., refluxed for 3.5 hr., and allowed to stand over night. The mixture was then poured onto 1000 g. of ice, and again allowed to stand over night. The solid which had separated was then filtered off by suction, recrystallized from aqueous ethanol and from a benzene-petroleum ether (30-60°) mixture to give 107 g. (82.0%) of the oxime,

m.p. 84-86°. Campbell and McKenna[115] report 85-87°.

1-(p-Tolyl)-ethylamine. - (Procedure A) -- By Reduction of 4-Methylacetophenone.--- The oxime of 4-methylacetophenone was reduced with hydrogen over Raney nickel by the same procedure used for the reduction of 4-methoxyacetophenone ketoxime. The amine (65% yield) boiled at 130°/20 mm.: Lyle and Troscianiec[111] report 82-83°/4 mm.

(Procedure B) -- By Reaction of Methyl p-Tolyl Ketone with Urea and Formic Acid.--- A mixture of methyl p-tolyl ketone (161 g., 1.20 mol.), urea (144 g., 2.40 mol.), and 98% formic acid (220 ml., 4.70 mol.) was heated under slow distillation conditions to 110-130°, and this temperature maintained for 2 hr. The heat was then increased and the temperature slowly rose to 155° over a 1 hr. period. The heat was removed, and the mixture allowed to stand over night. The mixture was then heated to 175-185°, and this temperature maintained for 3 hr. The mixture was cooled, a solution of 200 ml. conc. hydrochloric acid added, and this new mixture refluxed for 1 hr. The mixture was cooled somewhat and extracted with benzene. A solid separated on further cooling. This solid was recrystallized, with difficulty, from an absolute ethanol-ether mixture to give 91 g. (53%) of the amine hydrochloride. The product was converted directly to the acetamide and benzamide.

(Procedure C) -- By Reaction of Methyl p-Tolyl Ketone with Ammonium Formate.--- A mixture of methyl p-tolyl ketone (168 g., 1.25 mol.) and ammonium formate (253 g., 4.01 mol.)

was heated under slow distillation conditions. After 1 hr. of heating, the temperature of the mixture had reached 140°. Heating was continued and a temperature of 185° maintained for 2 hr. The heating was discontinued and the mixture allowed to stand over night. The ketone which had steam distilled was separated and returned to the reaction flask. Heating was renewed and a temperature of 185° maintained for an additional 4 hr. The mixture was cooled to room temperature and extracted with water. The water extracts were extracted with two 30 ml. portions of benzene. The benzene extracts and 150 ml. of conc. hydrochloric acid were added to the non-aqueous layer. The benzene was distilled off and the remaining mixture refluxed for 1.5 hr. The mixture was allowed to stand over night and then extracted with benzene. The acid solution was made strongly basic with 125 g. of sodium hydroxide and steam distilled, keeping the pot level equal to, or below, the starting level. Most of the amine came over in the first liter of distillate. The distillate was extracted with benzene and dried with potassium hydroxide sticks. The benzene solution was decanted from the drying agent and distilled at atmospheric pressure to give 128.3 g. (76.0%) of amine, b.p. 199-201°/740-750 mm.: Smith, Baer and Ege[82] report 188-192°/750 mm.

Cyclopentyl Phenyl Ketone.--- A solution of cyclopentyl bromide (100 g., 0.671 mol.) in 250 ml. of ether was added dropwise, over a 1 hr. period, to a stirred mixture of magnesium turnings (15.4 g., 0.634 g. at.) and 500 ml. of

ether. After the addition was complete the reaction flask was warmed for 20 min. A solution of benzonitrile (61.8 g., 0.600 mol.) in 750 ml. of toluene was added to the rapidly stirred mixture over a 2 hr. period. When the addition of nitrile was complete, the solvent was distilled from the reaction mixture until the distillation temperature reached 108° (about 5 hr.). During this distillation the solution turns from black to a light orange. The orange solution was then refluxed for 10 hr. and cooled to room temperature. A saturated solution of ammonium chloride (400 ml.) was added dropwise and the resulting layers separated. The aqueous layer was extracted with ether and the ether extracts added to the organic layer. The ether was distilled out, 600 ml. of 10% sulfuric acid added to the residue, and this mixture refluxed for 2 hr. The layers were separated, the aqueous layer extracted with a 1:1 benzene-ether solution, and the extract added to the organic layer. The solvents of the organic layer were distilled off at atmospheric pressure and the residue distilled at water pump pressure. The fraction boiling at 147-155°/20 mm. was collected to give 64 g. (61%) of the ketone: Smith, Baer and Ege[82] report 145-146°/15 mm.

α-Cyclopentylbenzylamine.--- A mixture of cyclopentyl phenyl ketone (83.9 g., 0.48 mol.), formamide (90 g., 2.0 mol.), and 10 ml. of 98% formic acid was heated with slow distillation of water formed in the reaction. Formic acid was added whenever a solid collected in the condenser.

After having maintained the reaction temperature between 170-180° for about 5 hr., the heating was discontinued, and the mixture allowed to stand over night. The mixture was again heated and the temperature maintained between 175-180° for 3 hr. A total of 110 ml. of formic acid had been added. The solution was cooled and 100 ml. of conc. hydrochloric acid added. This mixture was then refluxed for 2 hr. On cooling, a white solid separated from the acid solution. This solid was filtered off by suction and washed with benzene. The amine hydrochloride thus obtained, was recrystallized from water and from absolute ethanol to give 68 g. (67%) of product. The amine hydrochloride was converted directly to the acetamide and benzamide.

α-Phenylisobutyronitrile.--- Sodamide was prepared according to the Inorganic Syntheses procedure[116]. Iron (III) nitrate-9-hydrate (1 g.) was added, with stirring, to about one liter of liquid ammonia, followed by the addition of sodium metal (2 g.at.), cut into small chunks under xylene. The sodium was added at such a rate as not to flood the Dry Ice condenser with ammonia. The exits of the apparatus were protected with drying tubes containing barium oxide. After the addition of sodium was complete, two liters of anhydrous ether were added and the mixture allowed to evaporate over night. Phenylacetonitrile was then added dropwise, with stirring, over a 1 hr. period. The mixture was refluxed for 1 hr. and then cooled in an ice bath. A solution of methyl iodide (313 g., 2.20 mol.) in 900 ml.

of anhydrous ether was then added dropwise with continued stirring, and about 500 ml. of additional ether was added to keep the solution fluid. The mixture was stirred in the ice bath for 1.5 hr., refluxed for another 1.5 hr., and let stand at room temperature over night. The mixture was then refluxed for an additional 1.5 hr. and cooled to room temperature. Ethanol (10 ml.) was added, to react with excess sodamide, followed by enough water to dissolve the sodium iodide and the mixture was extracted with ether. The ether extracts were washed with water, a 10% sodium bisulfite solution, again with water, and dried over anhydrous sodium sulfate. The ether was removed at atmospheric pressure and the residue distilled to give 70.5 g. (49.0%) of α-phenylisobutyronitrile, b.p. 84-89°/4-5 mm.: Cope, Foster and Towle[117] report 81-82°/2.2 mm.

α-Phenylisobutyramide.--- The nitrile (70.5 g., 0.486 mol.) was added to 730 g. of 80% sulfuric acid (609 g. of conc. sulfuric acid and 121 g. of ice) in a one-liter flask equipped with a Tantalum Hershberg stirrer and a reflux condenser. The mixture was heated on a steam bath and stirred vigorously for 5.5 hr. The solution was then poured onto ice and diluted with water to effect separation of the amide. The solid was filtered off by suction, washed with water, a 5% sodium carbonate solution, and again with water. The dried amide was recrystallized from absolute ethanol to give 72 g. (90%) of α-phenylisobutyramide, m.p. 157-162°: Cope, Foster and Towle[117] report 160-161.5° for the purified

amide.

2-Amino-2-phenylpropane.--- A solution of sodium hydroxide (117 g., 2.39 mol.) in 975 g. of ice water was placed in a two-liter three-neck flask immersed in an ice-methanol bath. Bromine (46.9 g., 0.293 mol.) was added dropwise, with rapid stirring. The solution was stirred for 15 min., and α-phenylisobutyramide (72 g., 0.441 mol.) was added slowly to the rapidly stirred solution. The mixture was stirred in the cooling bath for 5 hr., then was packed in ice and allowed to come to room temperature over night, with stirring. The mixture was next heated on a steam bath for 1 hr., cooled and extracted with ether. The ether extracts were dried over anhydrous sodium sulfate, filtered, and hydrogen chloride gas was bubbled into the filtrate. The white solid was filtered off and air dried to give 37.4 g. of the amine hydrochloride, m.p. 236-238°: Cope, Foster and Towle[117] report 240-241°. The yield was 74.4% based on unrecovered starting material. Some 23.7 g. of which was isolated by filtration before the ether extraction was made.

Reactions of N-Substituted Formamides with Thionyl Chloride.

N-Butylformamide.--- The N-butylformamide (50.5 g., 0.500 mol.) was placed in a 500 ml. three-neck flask equipped with a stirrer (mercury-seal), reflux condenser, and dropping funnel. The exits were protected with calcium chloride drying tubes. The reaction flask was cooled in an ice bath and the thionyl chloride (75 ml., 1.0 mol.) was added drop-

wise with stirring over a 45 min. period. After the addition of thionyl chloride was complete the dark red solution was stirred in the ice bath for 2 hr., the ice bath removed and the solution stirred over night. The solution was transferred to a 300 ml. flask and slow distillation from an oil bath attempted. An acidic gas was evolved when the bath temperature reached 60°. Only a very small amount of distillate was collected, even though the bath temperature reached 170°. Distillation of the residue was then attempted at water pump pressure. A small fraction of distillate was collected at approximately 70°/40 mm. The residue solidified on cooling to what appeared to be a dark brown polymer. On standing, a white solid separated from the distillate. This solid was filtered off and identified as the hydrochloride of n-butylamine, some of which was also obtained from the walls of the still-head. The filtrate was redistilled, b.p. 170-171°, and identified as n-butyl isothiocyanate.

Anal. Calcd for C_5H_9NS: C,52.12; H,7.87; N,12.16; S,27.83

Found: C,52.22; H,7.92; N,12.25; S,27.55
C,52.25; H,7.81; N,12.14; S,27.62.

This sample was shown by infrared spectra to be identical with a sample prepared by the method of Vaughan, Andersen, Blanchard, McCane and Meyer[118] who report b.p. 165°.

This experiment was repeated using the same conditions, but varying the amount of thionyl chloride. Mole-ratios of thionyl chloride to N-butylformamide of 1:1, 1:0.9, 1:0.8, 1:0.5 and 1:0.25 were used with approximately the same results.

Small amounts of n-butyl chloride, n-butyl isothiocyanate, n-butylamine hydrochloride, starting amide and unidentified products were isolated.

The reaction was repeated using chloroform and then nitromethane as a solvent with a 1:1 ratio of thionyl chloride to amide. The reaction was also repeated using nitromethane as solvent and the reaction temperature maintained between 75 and 90°. The thionyl chloride was added below the surface of the nitromethane solution of the amide, which was kept in this temperature range. The solution was maintained at this temperature with slow distillation for 1.5 hr. and then distillation at a higher temperature was attempted. Once again, the results were the same as above.

N-(1-Phenylethyl)-formamide.--- A solution of N-(1-phenylethyl)-formamide (45 g., 0.30 mol.) in 300 ml. of nitromethane was placed in a one-liter three-neck flask equipped with a stirrer (mercury-seal), reflux condenser, and dropping funnel. The exits were protected with calcium chloride drying tubes. The thionyl chloride (90 ml., 1.2 mol.) was added dropwise with stirring. The solution was stirred at room temperature for 0.5 hr. and then kept at 100° for 4 hr., and allowed to stand at room temperature over night. A gas was evolved at the higher temperature, and the solution became dark red. The solvent was removed at water pump pressure and the residue distilled at a lower pressure to give 21 g. (50%) of 1-phenylethyl chloride, b.p. 70-72°/10-12 mm.; Charlton and Hughes[87] report 80-81°/19 mm. The

infrared spectrum of this product was identical with that of an authentic sample of 1-phenylethyl chloride except for the presence of bands at 2260 and 820 cm^{-1}. These bands were not due to hydrogen cyanide which was found to give bands at 3220 and 2080 $cm.^{-1}$ when dissolved in an authentic sample of the chloride.

N-(2-Phenylethyl)-formamide.--- A solution of N-2-phenylethylformamide in nitromethane was treated with thionyl chloride under conditions identical to those used with the 1-phenylethyl isomer, but only traces of 2-phenylethyl chloride could be identified (infrared spectrum) in the products of the reaction. The major product was a nondistillable tar, along with small amounts of 2-phenylethylamine hydrochloride and the starting amide.

N-Benzylformamide.--- A solution of N-benzylformamide in nitromethane was treated with thionyl chloride under the same conditions as used for N-1-phenylethylformamide. A small amount of benzyl chloride was identified as a product of the reaction, but again the major product was a non-distillable tar.

Reactions of N-Substituted Acetamides with Thionyl Chloride

N-(1-Phenylethyl)-acetamide.-(Procedure A)--- A solution of N-(1-phenylethyl)-acetamide (48.8 g., 0.300 mol.) in 500 ml. of cyclohexene was stirred rapidly while thionyl chloride (75 ml., 1.0 mol.) was added dropwise. The solution was stirred at room temperature for 48 hr. and then refluxed

for 4 hr. The solvent was removed by distillation at atmospheric pressure and the residue distilled at reduced pressure. The fraction boiling at 50-90°/20 mm. was collected and redistilled to give 12 g. (28%) of 1-phenylethyl chloride, b.p. 90-96°/30 mm.

The reaction was repeated with only 2:1 mole ratio of thionyl chloride to amide and a shorter reaction time. The yield under these conditions was reduced to 14%.

(Procedure B).--- The N-(1-phenylethyl)-acetamide (20.4 g., 0.125 mol.) was dissolved in 150 ml. of dioxane and the solution distilled until the distillation temperature remained at 99° for 10 min., and then cooled to room temperature. The thionyl chloride (28.2 g., 0.375 mol.) was added dropwise over a 1 hr. period. During the thionyl chloride addition the solution became warm and colored to a very dark red. The solution was slowly heated to reflux for 1 hr., and then the solvent was removed at atmospheric pressure. The residue was distilled at reduced pressure to give 3.14 g. (17.9%) of yellow colored product. The reaction was repeated twice, but no improvement in yield was noted.

(Procedure C).--- A large excess of thionyl chloride (50 ml., 0.67 mol.) was added to N-(1-phenylethyl)-acetamide (22.3 g., 0.136 mol.) in a 200 ml. flask. The solution darkened within 5 min. and became warm. The solution was refluxed for 1 hr. and the excess thionyl chloride removed by distillation at atmospheric pressure. The residue was then distilled at reduced pressure, b.p. 75-85°/20 mm. This latter

fraction was redistilled to give 5.1 g. (23%) of 1-phenylethyl chloride, b.p. 88-90°/27-30 mm.

The reaction was repeated with cooling the reaction flask during the thionyl chloride addition a 2 hr. reflux period. The yield of redistilled halide, b.p. 65-67°/17 mm., was increased to 35%.

(Procedure D).--- A solution of N-(1-phenylethyl)-acetamide (49 g., 0.30 mol.) in a mixture of 300 ml. of nitromethane and 50 ml. of cyclohexene was rapidly stirred while thionyl chloride (90 ml., 1.2 mol.) was added over a 15 min. period. After the thionyl chloride addition was complete, the solution was stirred at room temperature for 1.5 hr. and then refluxed for 4.5 hr. The solvent was removed at water pump pressure and the residue distilled at reduced pressure. The fraction boiling at 90-93°/13-16 mm. was collected and redistilled, to give 24.6 g. (58.4%) of 1-phenylethyl chloride, b.p. 90°/15 mm.

This latter experiment was repeated up to removal of the solvent. After removal of most of the solvent by distillation at water pump pressure, the residue was extracted with 30-40° petroleum ether. The petroleum ether layer was distilled to give 8 g. (19%) of 1-phenylethyl chloride, b.p. 81-83°/20 mm. The nitromethane layer was then distilled to give 18 g. (43%) of the same chloride, b.p. 79-83°/20 mm.

(Procedure E).--- The N-(1-phenylethyl)-acetamide (32.6 g., 0.200 mol.) was dissolved in a mixture of 300 ml. of nitromethane and 50 ml. of benzene. The solution was

distilled until the distillation temperature remained at 99° for 5 min., cooled to room temperature, and anhydrous hydrogen chloride bubbled into the solution for 1 hr. The thionyl chloride (45 ml., 0.60 mol.) was then added dropwise. The reaction mixture was slowly heated to 75° and kept at this temperature for 1 hr. The solution became dark red on heating and a gas was evolved. The solvent was removed at atmospheric pressure and the residue distilled at reduced pressure to give 18.0 g. (64.4%) of crude 1-phenylethyl chloride, b.p. 75-77°/12-13 mm.

(Procedure F).--- The N-(1-phenylethyl)-acetamide (20.5 g., 0.122 mol.) was dissolved in 175 ml. of nitromethane and the solution distilled until the distillation temperature remained at 99° for 5 min. The solution was then cooled to below room temperature and thionyl chloride (27.6 ml., 0.368 mol.) added dropwise. The solution was allowed to stand at room temperature for 1 hr. and then slowly heated to reflux temperature and kept at this temperature for 0.5-1 hr. The solvent was distilled off at atmospheric pressure and the residue distilled at reduced pressure. The fraction boiling at 76-79°/17-18 mm. was collected and redistilled to give 10.4 g. (60.3%) of 1-phenylethyl chloride, b.p. 82-83°/20 mm., n_D^{26} 1.5250: Charlton and Hughes[87] report 80-81°/19 mm., and n_D^{25} 1.5252.

Anal. Calcd. for C_8H_9Cl: C,68.25; H,6.41

Found: C,68.22; H,6.43.

The solvent was redistilled and a nitrile band (2250 cm.$^{-1}$) observed in the infrared spectrum of a fraction, b.p. 75-90°/750 mm.

(-)N-(1-Phenylethyl)-acetamide.--- The amide (20.5 g., 0.125 mol.) was dissolved in 125 ml. of nitromethane and the solution distilled until the distillation temperature had remained at 98° for 5 min. The solution was cooled to room temperature and thionyl chloride (45 g., 0.38 mol.) added by rapid drops. The reaction flask was slowly heated to reflux and this temperature maintained for 1 hr. The excess thionyl chloride and the nitromethane were distilled off at atmospheric pressure. The residue was distilled at reduced pressure to give 10.5 g. (59.5%) of 1-phenylethyl chloride, b.p. 82-83°/18-19 mm., α_D^{25} + 3.7 (ℓ, 1.0)).

It has been calculated[92] that the rotation of optically pure 1-phenylethyl chloride falls between 109 and 129°.

A sample of this chloride (2.45 g., α + 3.97 (ℓ, 1.0)) was dissolved in 25 ml. of nitromethane, 3.2 g. of thionyl chloride added, and the solution refluxed for 1 hr. The chloride, isolated by distillation, had a rotation (+ 3.87) only slightly less than the original sample.

N-Benzylacetamide.--- This amide was treated with thionyl chloride according to procedures D and F. Only traces of benzyl chloride were obtained by procedure D, but an 8% yield of the chloride, b.p. 62-64°/7-9 mm., was obtained by procedure F: Charlton and Hughes[87] report 66°/13.5 mm.

N-(2-Phenylethyl)-acetamide.--- This amide was treated with thionyl chloride according to procedures A, D and F. From all three procedures only traces of the expected chloride could be obtained.

N-Benzhydrylacetamide.--- This amide was treated with thionyl chloride twice according to procedure F. The yields of benzhydryl chloride were between 80 and 85%, b.p. 126-128°/2-3 mm., 111-114°/1 mm.: Gerrard and Shepherd[80] report 96°/0.2 mm.

The chloride obtained was converted to diphenylcarbinol in 70% yield by dissolving the chloride in aqueous acetone, allowing the solution to stand over night, evaporating off the solvent, and recrystallizing the product from aqueous ethanol, m.p. 65-68°: Ward[119] reports 68°.

N-(p-Methoxybenzyl)-acetamide.--- The amide was treated with thionyl chloride twice according to procedure F. The yields of p-methoxybenzyl chloride were between 40 and 50%, b.p. 85-86°/3-4 mm., n_D^{25} 1.5470: Sosa[81] reports 113°/10.5 mm. and n_D^{20} 1.5491.

N-(α,α-Dimethylbenzyl)-acetamide.--- This amide was treated with thionyl chloride according to procedure F, but only a red-brown polymeric material was produced.

N-1-(p-Methoxyphenyl)-ethylacetamide.--- This amide was treated with thionyl chloride according to procedure F, but only a dark brown polymeric material was obtained.

N-Cyclohexylacetamide.--- This amide was treated with thionyl chloride according to procedure F. No cyclohexyl

chloride was isolated.

N-t-Butylacetamide.--- This amide was treated with thionyl chloride according to procedure F. The halide was obtained in what appeared to be a reasonable yield (20-50% est.), but no accurate yield data can be given because of the difficulty encountered in separating the t-butyl chloride from thionyl chloride.

N-1-(p-Tolyl)-ethylacetamide.--- This amide was treated with thionyl chloride three times according to procedure F. The yields of 1-(p-tolyl)-ethyl chloride, b.p. 65°/2-3 mm., n_D^{24} 1.5240, were between 20 and 30%.

Anal. Calcd. for $C_9H_{11}Cl$: C,69.91; H,7.17; Cl,22.93
Found: C,70.04; H,7.25; Cl,22.66.

N-(α-Cyclopentylbenzylacetamide).--- This amide was treated with thionyl chloride according to procedure F to give 75-85% yields of α-cyclopentylbenzyl chloride, b.p. 103-104°/2-3 mm., $n_D^{24.5}$ 1.5381.

Anal. Calcd. for $C_{12}H_{15}Cl$: C,74.01; H,7.77; Cl,18.21
Found: C,74.12; H,7.73; Cl,18.31.

A sample of the chloride produced in the latter reaction (1.40 g., 0.007 mol.) was dissolved in 30 ml. of a 50% aqueous solution of triethanolamine and heated on a steam bath for 48 hr. The resulting solution was extracted with benzene and the benzene extracts washed twice with 10% hydrochloric acid and once with water. The benzene was evaporated in a stream of air on a steam bath to give 1.0 g. of a slightly yellow oil. The oil was dissolved in 2.5 ml.

of glacial acetic acid and this solution added with shaking to a cooled mixture of 0.7 g. (0.007 mol.) of cromic oxide in 2.5 ml. of 80% acetic acid. After standing at room temperature for 48 hr. the reaction mkxture was poured into 10 ml. of ice water and extracted with benzene. The benzene extract was washed twice with 10% sodium bicarbonate solution and once with water. The benzene was removed by evaporation on a steam bath. The infrared spectrum of the resulting oil was identical to that of a previously prepared sample of cyclopentyl phenyl ketone. The 2,4-dinitrophenylhydrazone, prepared in the usual manner, was obtained as bright, orange-yellow crystals, m.p. 142.0-143.5°. Nightingale and Maienthal[83] report 144.5-145.5°.

Reactions of N-Substituted Benzamides with Thionyl Chloride.

N-Butylbenzamide.--- The N-butylbenzamide (50 g., 0.28 mol.) was placed in a 200 ml. three-neck flask equipped with a stirrer, reflux condenser and dropping funnel. The reaction flask was cooled in an ice bath and the thionyl chloride (21 ml., 0.28 mol.) was added dropwise with stirring. After the addition was complete, the mixture was stirred in the ice bath for 1.5 hr. and then allowed to stand over night. The mixture was slowly heated, refluxed for 4 hr., and distilled at atmospheric pressure. Two fractions were collected; fraction A, b.p. 74-75°/740 mm., and fraction B, b.p. 174-183°/740 mm. Fraction A was dissolved in ether and washed with a 10% solution of sodium bicarbonate, the ether layer

dried over anhydrous magnesium sulfate, and distilled to give 8.9 g. (34%) of n-butyl chloride, b.p. 75-76°/745 mm. On distillation of fraction B, benzonitrile, b.p. 185-186°/745 mm., was obtained. The residue from the distillation of the original reaction mixture contained a large amount of the starting amide.

N-(1-Phenylethyl)-benzamide.--- A solution of N-(1-phenylethyl)-benzamide (27.8 g., 0.125 mol.) and 150 ml. of nitromethane was distilled until the distillation temperature remained at 98° for 5 min. and cooled to below room temperature. The thionyl chloride (29 ml., 0.39 mol.) was added dropwise with shaking. After the addition was complete the reaction mixture was allowed to stand at room temperature for 0.5 hr. and then slowly heated to reflux. Reflux was maintained for 3 hr. and then the solution was slowly distilled at atmospheric pressure. After the solvent was removed the residue was distilled at reduced pressure to give 27.4 g. of distillate, b.p. 75-82°/18 mm. This distillate was redistilled and three fractions collected, but the infrared spectrum of all fractions were superimposable. The fractions were again mixed and analyzed. From the percent composition of the mixture it was calculated that 1-phenylethyl chloride was produced by the reaction in 80-85% yield.

N-Benzhydrylbenzamide.--- A solution of N-benzhydrylbenzamide (28.7 g., 0.998 mol.) and 150 ml. of nitromethane was distilled until the distillation temperature remained

at 99° for 10 min. and then cooled to room temperature. The thionyl chloride (25 ml., 0.33 mol.) was added dropwise, and the reaction flask slowly heated and slow reflux maintained for 1 hr. The solvent was then distilled off at atmospheric pressure and the residue distilled at reduced pressure. Fraction A was collected at 75-77°/17mm. and fraction B at 157-167°/17 mm. On redistillation fraction A gave 9.0 g. (87%) of benzonitrile, b.p. 36°/1-1.5 mm. On redistillation fraction B gave 17 g. (85%) of benzhydryl chloride, b.p. 98-100°/0.1 mm., $n_D^{25.5}$ 1.5935: Gerrard and Shepherd[80] report 96°/0.2 mm. and n_D^{20} 1.5962.

N-α-Cyclopentylbenzylbenzamide.--- A solution of N-α-cyclopentylbenzylbenzamide (24.3 g., 0.872 mol.) and 160 ml. of nitromethane was distilled until the distillation temperature remained at 99° for 5 min. and then cooled to room temperature. The thionyl chloride (25 ml., 0.33 mol.) was added dropwise, and the reaction flask slowly heated and reflux maintained for 1.5 hr. The solvent was distilled off at atmospheric pressure and the residue distilled at reduced pressure. Fraction A was collected at 77°/17-18 mm., and fraction B at 145-146°/17 mm. On redistillation of fraction A, 7.25 g. (80.5%) of benzonitrile was obtained, b.p. 42°/2.5 mm. On redistillation fraction B gave 14 g. (82%) of α-cyclopentylbenzyl chloride, b.p. 112-114°/4 mm., n_D^{25} 1.5380.

N-(p-Methoxybenzyl)-benzamide.--- A solution of the amide (30.1 g., 0.125 mol.) in 150 ml. of nitromethane was

distilled until the distillation temperature had remained at 100° for 10 min. The solution was cooled to below room temperature and thionyl chloride (47.5 g., 0.399 mol.) added from a dropping funnel. The solution was allowed to set at room temperature for 1 hr., slowly heated and reflux maintained for 1 hr. The excess thionyl chloride and the nitromethane were removed by distillation at atmospheric pressure and the residue distilled at reduced pressure to give 11.9 g. (92%) of benzonitrile and 8.74 g. (44.9%) of p-methoxybenzyl chloride, b.p. 81°/2.5 mm., $n_D^{23.5}$ 1.5479.

A small amount of this chloride (1.9 g.) was added to a mixture of 25 ml. of anisole and a few crystals of zinc chloride in a flask immersed in an ice bath. The bath was allowed to melt and the mixture allowed to stand at room temperature for 18 hr. with intermittent shaking. The catalyst was filtered off and 25 ml. of ice water added. The layers were separated and the organic layer washed with 10% sodium hydroxide, water, dried over magnesium sulfate, and evaporated to dryness. The solid obtained was recrystallized twice from methanol to give 1.67 g. (58.8%) of 4,4'-dimethoxydiphenylmethane, m.p. 50-51°: Sunagawa[120] reports 51-52°.

N-Benzylbenzamide.--(Procedure A).--- A solution of the amide (26.4 g., 0.125 mol.) was distilled until the distillation temperature had remained at 100° for 10 min. and then cooled to room temperature. The thionyl chloride (49 g., 0.41 mol.) was added from a dropping funnel and the

reaction mixture allowed to set at room temperature for 0.5 hr. The mixture was then slowly heated and reflux maintained for 1 hr. The excess thionyl chloride and the nitromethane were removed by distillation at atmospheric pressure and the residue distilled at reduced pressure. The yield can not be given accurately because of difficulty encountered in the separation of benzonitrile from the benzyl chloride.

N-1-(p-Tolyl)-ethylbenzamide.--- The amide (17.5 g., 0.073 mol.) was dissolved in 125 ml. of nitromethane and the solution distilled until the distillation temperature had remained at 99° for 5 min. The solution was cooled to room temperature and thionyl chloride (36 g., 0.30 mol.) added from a dropping funnel. The reaction mixture was allowed to stand at room temperature for 0.5 hr., slowly heated to reflux and this temperature maintained for 1 hr. The excess thionyl chloride and the nitromethane were removed by distillation at atmospheric pressure and the residue distilled at reduced pressure to give three fractions. These fractions were fractionally distilled to give benzonitrile, b.p. 55-65°/4-5 mm. and 1-(p-tolyl)-ethyl chloride, b.p. 65-70°/4-5 mm., $n_D^{25.5}$ 1.5240. The yields of redistilled chloride were between 20 and 35%.

N-1-(p-Methoxyphenyl)-ethylbenzamide.--- A solution of N-1-(p-methoxyphenyl)-ethylbenzamide. (25.5 g., 0.100 mol.) and 230 ml. of nitromethane was distilled until the distillation temperature remained at 99° for 10 min. and cooled to room temperature. Thionyl chloride (25 ml.,

0.33 mol.) was added dropwise, the solution slowly heated to reflux, and reflux maintained for 1 hr. The solvent was slowly distilled off at atmospheric pressure and the residue distilled at reduced pressure. Only benzonitrile contaminated with a small amount of a chlorine-containing compound (by silver nitrate test), and a dark brown polymeric material was obtained. The experiment was repeated under the same conditions, except that only 170 ml. of nitromethane was used. The same type of polymer and 8.1 g. (79%) of benzonitrile (contaminated with the chlorine containing compound, b.p. 72-82°/60 mm., were obtained as the only products.

Benzanilide.--- The benzanilide (49 g., 0.25 mol.) was placed in a 100 ml. flask and thionyl chloride (56 ml., 0.75 mol.) added. The mixture was allowed to stand at room temperature for 2 hr., heated to 50° for 3 hr. and the excess thionyl chloride removed at water pump pressure. The residue was quickly filtered by suction and distilled at reduced pressure. The material boiling, 175-176°/11-12 mm., solidified in the receiver, m.p. 40-41°, to give 48 g. (89%) of N-phenylbenzimidyl chloride: v. Braun and Pinkernelle[76] report b.p., 174-176°/12 mm. and m.p., 40°.

N,N'-Diphenylbenzamidine was prepared by adding an ether solution of aniline to an ether solution of the imidyl chloride, evaporating off the solvent and recrystallizing the product from aqueous ethanol, m.p. 145.5-146.5°: Chapman[121] reports 146-147°.

N-Methylbenzamide.---(Procedure A).--- The N-methylbenzamide (34 g., 0.25 mol.) was placed in a 100 ml. flask and thionyl chloride (40 ml., 0.53 mol.) added with no apparent reaction. The reaction flask was immersed in a water bath, heated to 45° for 3 hr., then at 80° for 2 hr. and allowed to stand at room temperature over night. The excess thionyl chloride was removed by distillation from an oil bath at atmospheric pressure and the residue distilled at a reduced pressure. The oil bath was never heated to above 105°. The fraction boiling at 78-83°/7-10 mm., was collected and redistilled to give N-methylbenzimidyl chloride, b.p. 88-89°/12 mm: v.Braun and Pinkernelle[76] report 90-93°/13 mm. The infrared spectrum of this product had no trace of a band in the nitrile region. This compound was placed in a 50 ml. flask, equipped with a reflux condenser, the exit protected with a calcium chloride drying tube, and heated to 150° in an oil bath for 8 hr. The material was then distilled at atmospheric pressure to give only one fraction, b.p. 184-186°/750 mm., which was identified as benzonitrile. The residue from this distillation contained a solid which was recrystallized from absolute ethanol, m.p. 230-231°: Cook and Jones[122] report 232° for the trimer of benzonitrile.

(Procedure B).--- A solution of N-methyl benzamide (27 g., 0.20 mol.) in 175 ml. of nitromethane was distilled until the distillation temperature remained at 99° for 10 min. and then cooled to below room temperature. Thionyl

chloride (72 g., 0.61 mol.) was added and the solution heated to a pot temperature of 100° over a 45 min. period. This temperature was maintained for 1 hr. The excess thionyl chloride was removed by distillation at atmospheric pressure and the nitromethane removed at water pump pressure. An elemental analysis of the residue showed only the presence of chlorine and nitrogen. Only a very small trace of sulfur could be found. This residue was divided into two parts.

Part A was dissolved in anhydrous ether and slowly added to an ether solution of aniline. An exothermic reaction took place and a solid precipitated from the reaction mixture. The solid was filtered off, 10% sodium hydroxide added to the solid until the mixture remained definitely basic, and steam distilled to remove aniline. The residue was made homogeneous with absolute ethanol and cooled in an ice bath. The solid which separated was recrystallized twice from an ethanol-water mixture to give N-methyl-N'-phenylbenzamidine, m.p. 135-136°; picrate, m.p. 169-170°: Pyman[123] reports 135-136° and 169-170° respectively.

When the original distillation residue was taken up in anhydrous ether it was noticed that a solid remained. This solid was recrystallized from a chloroform-ether mixture and identified as N-methylbenzamidine hydrochloride, m.p. 224-225°; picrate, m.p. 131-132°: Pyman[123] reports 222-223° and 130-132°, respectively.

Part B. of the residue was treated with 10% sodium hydroxide until the solution was definitely basic, cooled in an ice bath and filtered. The solid obtained was recrystallized twice from an ethanol-ether mixture to give N-methylbenzamide, m.p. 78.5-80.5°. A mixed m.p. with the starting amide of m.p. 78.5-80.0°, was 79-81°. The infrared spectrum of this product was identical with that of the starting amide.

N-Benzylbenzamide.--(Procedure B).--- The amide (21 g., 0.10 mol.) was dissolved in 150 ml. of nitromethane and the solution distilled until the distillation temperature remained at 100° for 10 min. The solution was cooled to below room temperature and thionyl chloride (46 g., 0.38 mol.) added. The reaction mixture was allowed to stand at room temperature and then heated on the steam bath for 1.5 hr. The excess thionyl chloride was distilled off at atmospheric pressure and the nitromethane at water pump pressure from the steam bath. The residue was then distilled at reduced pressure. A forerun and five fractions were collected; A, 120-122°/0.3 mm.; B, 122-128°/0.3 mm.; C, 128°/0.3 mm.; D, 124-128°/0.2-0.3 mm.; and E, 124°/0.2 mm. Lander[124] reports of 80-160°/12 mm. for N-benzylbenzimidyl chloride produced from the reaction of phosphorus pentachloride with N-benzylbenzamide. Lander also reported that his material was not pure, and although the compound had been reported earlier, it had never been isolated in the pure state.

Fraction A (2 g.) was dissolved in 15 ml. of acetone and 5 ml. of water added. The resulting solution was heated on the steam bath for 3 hr., most of the solvent evaporated, and the residue cooled in an ice bath. The solid which separated was recrystallized twice from absolute ethanol to give N-benzylbenzamide, m.p. 104.2-106.2°. When mixed with the starting amide of m.p. 105.5-106.5°, the m.p. was 105.5-107°. The infrared spectrum of this material was identical with that of the starting amide.

Fraction B (1.8 g.) was dissolved in 15 ml. of anhydrous ether and a solution of aniline (1.2 g.) in 15 ml. of anhydrous ether slowly added. The reaction mixture was allowed to set at room temperature for 1 hr. and then warmed on the steam bath. The solid which had separated was filtered off and 10% sodium hydroxide added to this solid until the mixture was definitely basic. This mixture was steam distilled to remove aniline, the residue cooled and the solid which separated filtered off and recrystallized three times from absolute ethanol to give N-benzyl-N'-phenylbenzamidine, m.p. 99.5-100.5°: Strain[125] reports 99-100°.

A small amount of this amidine was treated with p-toluensulfonyl chloride in 10% sodium hydroxide. The solid which separated was filtered off and recrystallized from absolute ethanol and from a chloroform-ether mixture to give the sulfonamide, m.p. 148-149°: Strain[125] reports 148°.

Fractions C and D (5.5 g.) were mixed and distilled at atmospheric pressure. Two fractions were obtained, but

both were a mixture of benzyl chloride and benzonitrile. On redistillation, a fraction b.p. 172-177°, $n_D^{22.8}$ 1.5351, was obtained. Charlton and Hughes[87] report benzyl chloride b.p. 66°/13.5 mm. and n_D^{25} 1.5360. The infrared spectrum of this fraction showed the presence of a small amount of benzonitrile. Another fraction, b.p. 177-180° and $n_D^{22.8}$ 1.5320, was obtained. The infrared spectrum of this fraction corresponded quite well to that of authentic benzonitrile, but the liquid showed the presence of chlorine when treated with silver nitrate.

A solid was isolated from the residue of the original distillation, which when recrystallized from a chloroform-ether mixture was identified as cyaphenine, m.p. 234-236°.

Fraction E (2 g.) was dissolved in 200 ml. of anhydrous ether and intermittently shaken with 25 ml. of a saturated aqueous solution of sodium benzoate for 18 hr. The layers were separated, the ether layer evaporated to dryness, and the residue recrystallized three times from absolute ethanol to give N,N-dibenzoylbenzylamine of m.p. 109-110°: Mumm, Hesse and Volquartz[48] report 108°. When mixed with the starting amide of m.p. 105.5-106.5° the m.p. was 80-100°.

Reaction of an N-Alkylbutyramide with Thionyl Chloride.

N-(1-Phenylethyl)-butyramide.--- The amide (38 g., 0.20 mol.) was dissolved in 200 ml. of nitromethane and the solution distilled until the distillation temperature had remained at 99° for 5 min. The solution was cooled to

below room temperature and thionyl chloride (48 ml., 0.62 mol.) added from a dropping funnel. The reaction mixture was allowed to stand at room temperature for 0.5 hr., slowly heated to reflux and this temperature maintained for 1 hr. The excess thionyl chloride and most of the nitromethane were distilled at atmospheric pressure and the residue distilled at reduced pressure to give two main fractions; A, b.p. 35°/50 mm. and B, b.p. 76°/12 mm. Fraction B was redistilled to give 21 g. (75%) of 1-phenylethyl chloride, b.p. 72°/10 mm.

Fraction A was redistilled to give a fraction which appeared to be mostly butyronitrile from its infrared spectrum. This material was treated with 6% hydrogen peroxide in a basic solution for 4.5 hr. at 60°. The mixture was cooled, neutralized with dilute sulfuric acid, evaporated to dryness, and extracted with chloroform. The chloroform extracts were concentrated and the solid obtained recrystallized from chloroform to give n-butyramide, m.p. 113-114°: McMaster and Noller[126] report 114.6°.

Reactions of N-Substituted Propionamides with Thionyl Chloride.

N-(1-Phenylethyl)-propionamide.--- A solution of the amide (22.1 g., 0.125 mol.) in 150 ml. of nitromethane was distilled until the distillation temperature had remained at 99° for 5 min. The solution was cooled to below room temperature and thionyl chloride (28.2 ml., 0.375 mol.) added from a dropping funnel. The reaction mixture was

allowed to stand at room temperature for 0.5 hr., slowly heated to reflux and this temperature maintained for 1 hr. The excess thionyl chloride and the nitromethane were distilled off at atmospheric pressure and the residue distilled at reduced pressure to give 12.7 g. (72%) of 1-phenylethyl chloride, b.p. 77-79°/17-18 mm., n_D^{22} 1.5269.

N-1-(p-Tolyl)-ethylpropionamide.--- A solution of the amide (30.5 g., 0.159 mol.) in 170 ml. of nitromethane was distilled until the distillation temperature had remained at 100° for 5 min. The solution was cooled to below room temperature and thionyl chloride (36 ml., 0.48 mol.) added from a dropping funnel. The reaction mixture was allowed to stand at room temperature for 0.75 hr., slowly heated to reflux and this temperature maintained for 1 hr. The excess thionyl chloride and the nitromethane were distilled off at atmospheric pressure and the residue distilled at reduced pressure to give 8.32 g. (33.8%) of 1-(p-tolyl)-ethyl chloride, b.p. 67°/3-4 mm. On redistillation the pure chloride, b.p. 88-90°/10-15 mm., n_D^{22} 1.5250 was obtained along with p-methylstyrene, b.p. 60-61°/10-15 mm., n_D^{22} 1.5394; dibromide, m.p. 44.5-45.5°. Schwartzman and Corson[127] report for 4-methylstyrene b.p., 81°/41 mm., n_D^{20} 1.5420 and the dibromide m.p., 44.0-44.5°.

A higher boiling fraction of the original distillation yielded more p-methylstyrene, $n_D^{23.5}$ 1.5401, and impure chloride, on redistillation.

N-(p-Methoxybenzyl)-propionamide.--- A solution of the amide (18.4 g., 0.095 mol.) in 150 ml. of nitromethane was distilled until the distillation temperature had remained at 100° for 5 min. and then cooled to below room temperature. Thionyl chloride (22 ml., 0.29 mol.) was then added from a dropping funnel, the reaction mixture allowed to stand at room temperature for 1 hr., and then slowly heated to reflux temperature. After reflux had been maintained by heating for 1.5 hr., the excess thionyl chloride and the nitromethane were removed by distillation at atmospheric pressure. The residue was distilled at a reduced pressure to give 10.37 g. of product. This material was redistilled to give 9.55 g. (64%) of p-methoxybenzyl chloride, b.p. 82°/2.5 mm. The infrared spectrum of this material is identical with that of a previously prepared and identified sample of the chloride.

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