Relative Migratory Aptitudes in the Rearrangement of N,N-Dichlorocarbinamines by Aluminum Chloride[1]

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Rearrangement of a series of N,N-dichlorocarbinamines ($R^1R^2R^3CNCl_2$) at low temperatures with aluminum chloride in methylene chloride, followed by acid hydrolysis, produced carbonyl and amine products in moderate to high yields. The following relative migratory aptitudes were determined: phenyl, 18; *sec*-butyl, 2.4; benzyl, 1.8; *n*-butyl, 1.0; hydrogen, 0.09; methyl, 0.05. These values compare reasonably well with migratory aptitudes observed in the Schmidt and Baeyer–Villiger rearrangements which appear to proceed by concerted processes. Further support for synchronous loss of chloride ion and 1,2 alkyl shift is provided by the low degree of hydrogen migration, indicating the importance of a trans migratory requirement.

Most of the previous work on rearrangement of N,N-dihaloamines by aluminum chloride comprised bi-[5] or tricyclic systems.[6,7] We recently reported[8] the rearrangement of N,N-dichlorotri-*n*-butylcarbinamine, which yielded, after acid hydrolysis, di-*n*-butyl ketone and *n*-butylamine. Migration appeared to involve electron-deficient nitrogen. The present study was concerned with obtaining relative migratory aptitudes for various types of alkyl groups, hydrogen, and phenyl, with the aim of elucidating additional aspects of the reaction mechanism. Useful comparisons are made with related systems entailing 1,2 shifts from carbon to nitrogen, carbon to oxygen, and carbon to carbon.

Results and Discussion

Preparation of Starting Materials.—All the amines except di-*n*-butylcarbinamine were prepared by means of the Ritter reaction or Hofmann degradation as described in the earlier paper.[8] $(n\text{-Bu})_2CHNH_2$ was obtained from reduction of di-*n*-butylketoxime with sodium in ethanol. Acetylation of tri-*n*-butylcarbinamine, followed by $LiAlH_4$ reduction, provided N-ethyltri-*n*-butylcarbinamine. N,N-Dichloroamines **2**–**8** were synthesized by the previous procedure.[8] Treatment of the amine with N-chlorosuccinimide was used to generate N-chloro-N-ethyltri-*n*-butylcarbinamine. Yields of products are calculated[8] on the basis of N-monochloroamine as the impurity in crude N,N-dichloroamine.

Rearrangement.—Rearrangement of the N,N-dichlorocarbinamines by aluminum chloride, followed by acid hydrolysis, generally yielded a mixture of two carbonyl compounds, two alkyl amines, recovered parent amine, and intractable material (Table I). The best procedure developed in the previous work[8] was employed in the majority of runs. Rearrangement of $(n\text{-Bu})_2(sec\text{-Bu})CNCl_2$ (**2**) was studied under a variety of conditions. Little change in yield was noted for those reactions in which the amount of solvent was reduced by one third, reaction time was decreased from 90 to 30 min, temperature was in the range of 0 to −50°, or the solvent was methylene chloride or chloroform. A significant feature is the similarity of the ratios, di-*n*-butyl ketone:*n*-butyl-*sec*-butyl ketone and *sec*-butylamine:*n*-butylamine. The figures, which are an index of the relative migratory aptitudes, were 2.2–2.6:1, after statistical correction, over the range of conditions indicated in Table I. The observed relative migratory aptitudes for all groups studied are included in Table II. Ferric chloride, a relatively weak Lewis acid, gave only low yields of rearranged products, emphasizing the role of the catalyst.

In the case of $(Me)_2$-*n*-$BuCNCl_2$ (**3**), since the desired basic products were not separable from a side product, yields could not be ascertained. This problem was circumvented by utilizing the di-*n*-butylmethyl compound, **4**, for determining the migratory aptitude of the methyl group. Although rearrangement of **4** proceeded cleanly, the per cent conversion was somewhat lower than for the cases already discussed. Even when a longer reaction time was employed, the yield of rearrangement products was not appreciably improved. The trimethyl compound, **5**, behaved sluggishly, producing only low yields of acetone and methylamine. Surprisingly (see below), $(n\text{-Bu})_2CHNCl_2$ (**6**) gave very little di-*n*-butyl ketone, which would result from either hydrogen migration or proton elimination. The major product, valeraldehyde, was obtained in conjunction with minor amounts (2–12%) of 2-chloro- and 2,2-dichlorovaleraldehyde. This type of side reaction was also noted in our earlier work.[8] Since both of these compounds are unreported, independent syntheses were carried out for positive identification. 2-Chlorovaleraldehyde was prepared by chlorination of valeraldehyde. Hydride reduction of 2,2-dichlorovaleryl chloride provided the dichloroaldehyde in low yield accompanied by an appreciable amount of material which appeared to be 2,2-dichloro-1-pentanol. Rearrangement of $(n\text{-Bu})_2PhCH_2CNCl_2$ (**7**) was complicated by the aromatic nucleus. Relatively large amounts of tar were formed, and the variation in yields from run to run suggested undesirable side reactions, either during rearrangement or work-up. Thus, the figures for migratory aptitudes from this compound are somewhat less reliable.

With $(n\text{-Bu})_2PhCNCl_2$ (**8**) the reproducibility of yield data and other evidence lead us to believe that one or more competing reactions were taking place

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TABLE I

REARRANGEMENT OF *N,N*-DICHLOROCARBINAMINES BY ALUMINUM CHLORIDE

	$R^1R^2R^3CNCl_2$						Product, % yield[a]					
Registry no.	R^1	R^2	R^3		Temp, °C	Time, min	R^1R^2CO	R^1R^3CO	R^1NH_2	R^3NH_2	Recovered parent amine[b]	Residue[c]
35329-67-0	*n*-Bu	*n*-Bu	*n*-Bu	1[j]	−30	45	95		92		3	3
35329-68-1	*n*-Bu	*n*-Bu	*sec*-Bu	2	0	90	49	43	43	49	10	7
	n-Bu	*n*-Bu	*sec*-Bu	2[d]	−30	90	54	43	46	51	9	5
	n-Bu	*n*-Bu	*sec*-Bu	2	−30	90	59	47	47	59	4	2
	n-Bu	*n*-Bu	*sec*-Bu	2	−50	90	56	44	44	56	7	5
	n-Bu	*n*-Bu	*sec*-Bu	2	−30	30	57	38	41	54	9	8
	n-Bu	*n*-Bu	*sec*-Bu	2[e]	−30	90	13	11	11	13	39	9
	n-Bu	*n*-Bu	*sec*-Bu	2[f]	−30	90	52	40	41	50	13	9
41718-24-5	Me	Me	*n*-Bu	3	−30	90	7	42				
41718-25-6	*n*-Bu	*n*-Bu	Me	4	−30	90	4	75	71	2	12	<1
	n-Bu	*n*-Bu	Me	4	−30	150	1	81	78	2	9	2
	n-Bu	*n*-Bu	Me	4	−30	90	1	73	81	2	16	3
2156-72-1	Me	Me	Me	5	−30	90	32		45		26	2
	Me	Me	Me	5	−30	180	38		35		14	1
41718-27-8	*n*-Bu	*n*-Bu	H	6	−30	90	2	53[g]	55		9	2
	n-Bu	*n*-Bu	H	6	−30	150	2	47[g]	63		12	2
41718-28-9	*n*-Bu	*n*-Bu	$PhCH_2$	7	−50	30	28	40	42	24	19	20
	n-Bu	*n*-Bu	$PhCH_2$	7	−50	30	29	31	23	12	6	43
	n-Bu	*n*-Bu	$PhCH_2$	7	−50	30	25	24	24	33	17	17
41718-29-0	*n*-Bu	*n*-Bu	Ph	8	−40	45	36	1	4	36	11	24
	n-Bu	*n*-Bu	Ph	8	−40	30	36	1	5	42	12	17
	n-Bu	*n*-Bu	*n*-Bu	9[h,i]	0	180	70		71		20	2
	n-Bu	*n*-Bu	*n*-Bu	9[h,i]	0	180	67		68		26	2

[a] Based on $RNCl_2$. [b] Crude, based on starting amine. [c] Per cent of crude product. [d] 60 ml of solvent. [e] $FeCl_3$ catalyst. [f] $CHCl_3$ solvent. [g] Contained minor amounts of 2-chloro- and 2,2-dichlorovaleraldehyde. [h] *N*-Ethyl; monochloro derivative. [i] The procedure in ref 7 was followed except that the reaction mixture was steam distilled for 7 hr. [j] Reference 8.

TABLE II

RELATIVE MIGRATORY APTITUDES

	Relative migratory aptitudes	
R	Range	Average
Ph	17–18	18
sec-Bu	2.2–2.6	2.4
$PhCH_2$	1.0–3.0	1.8
n-Bu		1.0
H	0.08–0.10	0.09
Me	0.03–0.09	0.05

which did not affect the rearrangement. Glpc revealed numerous minor products in the neutral fraction. The major component from the side reactions was shown to be 4-phenyl-5-nonanone by comparison with authentic material prepared by propylation of 1-phenyl-2-hexanone. To avoid uncertainty concerning identification, the isomer, 5-phenyl-4-nonanone, was also synthesized. Although nmr and glpc data did not permit differentiation, the ir spectra indicated that no more than 20% of the latter isomer could have been present. Mechanistically, any proposal must be highly tentative because of the paucity of experimental evidence. One possibility entails ionization[9] to $(n\text{-Bu})_2PhC^+(Cl_2NAlCl_3)^-$, followed by synchronous 1,2 shift of hydride and phenyl with the gegenion remaining at the original cationic site. Alternatively, 1,3 hydride shift[10] to electron-deficient nitrogen may take place.

N-Chloro-*N*-ethyltri-*n*-butylcarbinamine (**9**) was more reluctant to rearrange, giving only about 70% of rearranged product after 3 hr. The increased basicity of the nitrogen, due to replacement of chlorine by the ethyl group, would promote greater complexation of aluminum chloride with nitrogen, thus retarding rearrangement. Furthermore, increased steric resistance to either approach of a catalyst molecule or migration of an alkyl group, and the reduced statistical factor resulting from the availability of only one chlorine atom, would also retard rearrangement. Previously, *N*-chloro-*N*-ethyl-1-aminoadamantane[7] was found to rearrange to the extent of only 65%, whereas the *N,N*-dichloro derivative gave 79% of rearranged product.[6] Hydrolysis of the rearranged product from **9** was effected only after 7 hr of steam distillation, whereas 1–2 hr was sufficient with the other compounds studied. The slowness of hydrolysis may result from diminished solubility owing to increased molecular weight, and reduced hydrogen bonding capability for $(n\text{-Bu})_2CClNEtBu\text{-}n$ because of absence of the NH group.

The indicated scheme,[8] with **2** as an example, depicts the proposed course of reaction (eq 1). Removal of chloride ion by aluminum chloride and migration of either a *sec*-butyl (path a) or *n*-butyl (path b) group would occur readily to give the corresponding tertiary carbonium ion, **11a** or **11b**, which is stabilized by the two alkyl groups and the neighboring nitrogen. Combination with chloride ion provides the α-chloro-*N*-chloroamines **12a** and **12b**. Treatment with acid effects hydrolysis to the corresponding carbinolamines, **13a** and **13b**, which decompose to ketone and primary amine.

Although evidence presented thus far strengthens the hypothesis that rearrangement proceeds through formation of electron-deficient nitrogen, the question arises as to whether a discrete nitrenium ion intermediate is involved or a somewhat electron-deficient

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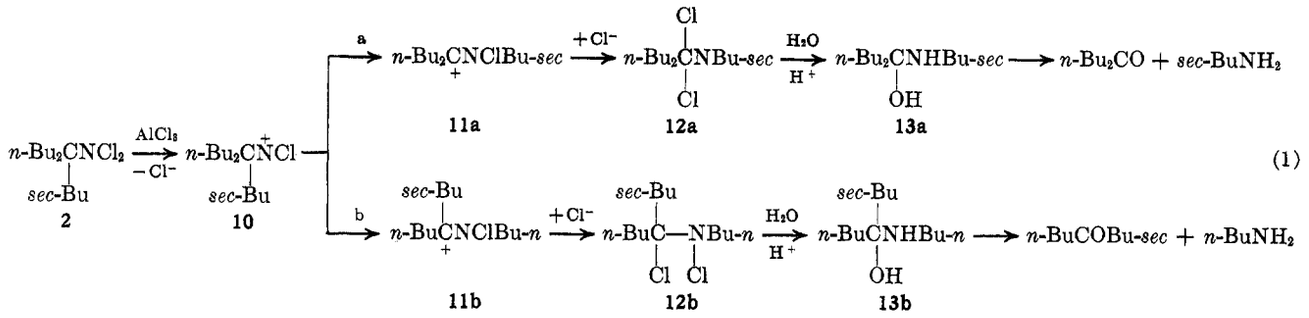

(1)

nitrogen moiety which possesses only transitory existence in a synchronous process. The literature contains examples of carbon to nitrogen migrations which supposedly entail either a concerted process or a two-step pathway with formation of a nitrenium ion. The alternative possibilities will be discussed separately in conjunction with pertinent prior literature. Gassman provided strong evidence[11] for the existence of the nitrenium ion as a distinct entity in either singlet or triplet form. The triplet state on abstraction of hydrogen is converted to the parent amine. In contrast to Gassman's system, most other carbon to nitrogen migrations are postulated to proceed in a concerted fashion. The Schmidt rearrangement comprises a group of reactions resulting from treatment of a carbonyl compound with sodium azide and concentrated acid. A commonly accepted mechanism has been deduced from analogy with the Beckmann rearrangement[12a] and secondary evidence.[12b] In this acid-catalyzed, intramolecular reaction, substituent effects are similar to those in the Hofmann and Lossen processes, and an analogous concerted mechanism is likely.[13] Use of asymmetric ketones enables the detection of a trans-migratory requirement as in the Beckmann reaction. Thus, the tendency for the larger group to migrate in such substrates, *i.e.*, Ph > Me, Et > Me, is a consequence of favored formation of the iminodiazonium ion with the larger group trans.[12c]

There is reason to believe that, in purely aliphatic systems, the iminodiazonium isomers are readily interconverted. As this type of interchange becomes important, so does the role of electronic factors in determining product ratios.[14] Alkyl migration has been shown to be slower than aryl.[15] With phenyl alkyl ketones, the following relative rates of migration of alkyl groups were obtained: methyl, 0.05; ethyl, 0.15; isopropyl, 0.49; *tert*-butyl, 1.0.[16] The group with the largest bulk will migrate preferentially except when electronic effects (chelation or conjugation) come into play.[14]

Another reaction which is relevant to our investigations is the Baeyer–Villiger rearrangement. Mechanistic studies on the oxidation of ketones to esters by peracids suggest that the transformation proceeds in a concerted manner involving a 1,2 shift from carbon to oxygen, with the rate-determining step being the acid-catalyzed decomposition of the peroxy acid–ketone adduct.[17] Several studies have been made to determine the relative migratory aptitudes of alkyl or aryl groups. For example, one group obtained the following sequence: methyl, small; *n*-propyl, 1; isopropyl, 27; benzyl, 19; phenyl, 14; *tert*-butyl, 560.[18]

Although rearrangements which involve 1,2 shift of a saturated alkyl group from carbon to an adjacent, electrophilic carbon are very common, relatively little data are available concerning the effect of structural variation upon migration tendencies. Comparison of intramolecular migratory aptitudes of alkyl groups in the pinacol rearrangement, unlike those for substituted phenyl groups, are unlikely to reflect intrinsic migratory aptitudes because of appreciable variation in the size of the groups. By comparison of absolute rates of migration of different individual groups in the same molecular environment, such as $CH_3CR(OH)C(CH_3)_2^+$, the sequence methyl (1.0), ethyl (17), *tert*-butyl (>4000) has been observed.[19] In carbonium ion rearrangements of bis-*tert*-alkyl ketones,[20,21] recent studies have shown that the relative migratory aptitudes of alkyl groups are a function both of electronic and steric effects (back strain).

It is reasonable to conclude that the rearrangement of *N*,*N*-dichlorocarbinamines proceeds in a concerted manner on the basis of the following evidence. A mechanism involving a free nitrenium ion should be much less susceptible to steric effects than a concerted rearrangement. Since the nitrenium ion would be expected to assume planarity,[22] attack of a migrating group would be possible from two directions, thus decreasing conformational effects. In a concerted rearrangement, on the other hand, much like an internal SN2-type displacement, only the group trans to the leaving chloride is suitably disposed for back-side attack on nitrogen. Since the energetically favored conformation places the bulkiest group as far as possible from the leaving entity (conformers **14** and **15**), the largest substituent will migrate preferentially. The smallest group would be the least likely to migrate on the basis of a trans conformational requirement which places the $AlCl_4^-$ leaving moiety between the more bulky ones (conformer **16**). Hence, evidence for

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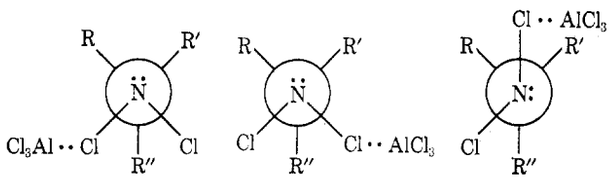

14 15 16

R and R′ > R″

a trans migratory effect weighs against a nitrenium ion intermediate and favors an electron-deficient nitrogen in the transition state.

The relative migratory aptitudes of the groups do not follow the expected order in all cases based on the ability to stabilize an incipient positive charge. Rearrangement of $(n\text{-Bu})_2\text{CHNCl}_2$ (**6**) illustrates the importance of stereochemical effects in this system. In related rearrangements, *e.g.*, Schmidt, Beckmann, and Baeyer–Villiger, hydrogen migration or proton elimination comprises the most important process, with alkyl migration usually accounting for only a minor fraction of the product.[12e] Electronically, hydrogen migration in **6** is favored, since *n*-butyl migration would give a secondary carbonium ion, whereas a tertiary type results from the alternate route. Furthermore, it is expected that hydrogen should stabilize an incipient positive charge during migration better than *n*-butyl. However, since hydrogen, in fact, migrates very little, we are led to rationalize this result on the basis of a compelling trans-migration requirement (see **14** and **15**).

On the other hand, acid-catalyzed rearrangement of benzyl azide gave approximately equal amounts of hydrogen and phenyl migration (eq 2), whereas with

$$C_6H_5CH_2N_3 \xrightarrow{-N_2} C_6H_5CH{=}NH\ (30\%) + CH_2{=}NC_6H_5\ (30\%) \quad (2)$$

benzhydryl azide only phenyl migration was observed (eq 3). This result was also rationalized on the basis

$$(C_6H_5)_2CHN_3 \xrightarrow{-N_2} C_6H_5CH{=}NC_6H_5\ (90\%) + (C_6H_5)_2C{=}NH\ (0\%) \quad (3)$$

of conformational factors.[12f] In contrast to **6**, *N,N*-dichloroisopropylamine, when treated with aluminum chloride in methylene chloride at −30°, underwent substantial loss of HCl, producing acetone in 42% yield after work-up.[23] In this case, methyl migrates poorly and the difference in size is less, so that proton elimination becomes important.

One would expect the di-*n*-butylmethyl compound (**4**) to show enhanced *n*-butyl migration compared to that in the *n*-butyldimethyl analog (**3**) because of increased "back strain." This is found to be the case, **3** giving a 0.08 ratio of methyl to *n*-butyl migration, whereas values of 0.05–0.06 are observed with **4**. In the di-*n*-butyl–*sec*-butyl case (**2**), both the electronic and steric effects make *sec*-butyl the preferred group for migration. The resulting carbonium ions **11a** and **11b** are of nearly the same stability. A different situation pertains in the case of the di-*n*-butylbenzyl system (**7**), since benzyl migration produces a standard tertiary carbonium ion, whereas rearrangement entailing *n*-butyl affords a phenonium ion. It is difficult to estimate the relative influence of this consideration in relation to steric and electronic factors. Similarly, rearrangement of $(n\text{-Bu})_2\text{PhCNCl}_2$ (**8**) presents two nonequivalent paths, phenyl migration leading to a tertiary ion, while a 1,2 shift of *n*-butyl yields a benzylic cation.

The "back strain" effect also seems to be related to the overall yields of rearranged products (substituents, per cent rearranged product): $(n\text{-Bu})_2$–*sec*-Bu, >95; $(n\text{-Bu})_3$, 95; $(n\text{-Bu})_2\text{Me}$, 80; $(n\text{-Bu})_2\text{H}$, 55; $n\text{-BuMe}_2$, 50; Me_3, 40. The data indicate that smoothness of reaction is favored by crowding at the carbon affixed to nitrogen.

The small differences in relative migratory aptitudes compare favorably with results from the Schmidt rearrangement and correspond fairly closely to those of the Baeyer–Villiger reaction, both of which are believed to proceed in a concerted fashion. However, in these rearrangements, interpretation is complicated by the possible presence of equilibrium steps prior to the transition state and the existence of nonisolable intermediates, which might influence the kinetics of the reaction. In addition, the alkyl group in the Schmidt reaction apparently migrates across a double bond.

If the rearrangement were a two-step process entailing the nitrenium ion as a discrete intermediate, solvent-catalyzed spin inversion of the singlet to the triplet species should give an increased yield of recovered parent amine when solvent was changed from methylene chloride to chloroform, which has enhanced characteristics of a heavy atom solvent. Furthermore, chloroform could also serve as a good hydrogen atom donor. Gassman and coworkers found a 190-fold reduction in the singlet–triplet product ratio when chloroform was added to methanol.[11] However, with chloroform the yield of recovered amine in the case of **2** was only 13% compared with 4–9% in methylene chloride. We cannot be sure if this small increase is real because of our uncertainty concerning the accuracy of the recovered amine data.

There are various possible reasons for the apparent difference in mechanistic detail between Gassman's work and the present study, although both presumably involve electron-deficient nitrogen. Gassman utilized silver salts as catalysts for *N*-chloroamine ionization, whereas we used aluminum chloride. It is reasonable to suppose that the two catalysts might behave somewhat differently in relation to the degree of ionization induced. Also, there may be differences in the role of the gegenion during rearrangement depending upon the type of catalyst.[11] Sasaki and coworkers[24] reported the virtual absence of rearrangement of *N*-chloro-*N*-acetyl-1-adamantylamine in methylene chloride, in contrast with the formation of 47% of rearranged product in carbon tetrachloride. Since Gassman used methanol, some degree of stabilization of the nitrenium ion by the medium through solvation appears likely. Furthermore, the *ab initio* molecular orbital studies on the structure of the nitrenium ion by Lee and Morokuma stressed the importance of the type of substituents on the ground state of the nitrenium ion.[22]

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(24) T. Sasaki, S. Eguchi, T. Kiriyama, and H. Suzuki, *Syn. Commun.*, **1**, 267 (1971).

There was also the indication that, if the nitrenium ion is formed in a ring structure, the singlet state gains in stability. It is noteworthy that the compounds studied by Gassman generally involved cyclic structures.[11,25,26] In the conversion of *N*-chloroazacyclooctane and *N*-chloroazacyclononane to bicyclic amines by exposure to silver ion, apparently homolytic processes are involved, rather than formation of discrete nitrenium ions.[27]

In summary, the low relative migratory aptitudes, the lack of any convincing evidence for singlet–triplet conversion, and the pronounced steric requirements weaken the case for an intermediate nitrenium ion, but are in accord with concerted loss of chloride with alkyl migration, involving a somewhat electron-deficient nitrogen in the transition state.

Experimental Section

Materials.—In general, high purity commercial chemicals were used directly. Toluene was dried over sodium strips; methylene chloride (Aldrich Chemical Co.) was dried at reflux over calcium hydride.

Analytical Procedures.—Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer with neat samples and with the 1601.8- and 1028.3-cm^{-1} bands of polystyrene for calibration. Nmr spectra were taken with a Varian Model T-60 (parts per million with tetramethylsilane as internal standard). Gas chromatography was conducted on Varian Aerograph instruments (Hy-Fi 1700 and 1800) by means of the indicated columns (10 ft × 0.25 in.) (column number, packing): (1) 15% Carbowax 20M on Chromosorb W (45/60 mesh); (2) 15% UCON 50HB2000 and 5% NaOH on Chromosorb W, AW-DMCS 45/60 mesh). Quantitative glpc was accomplished by comparison of peak areas of solutions of crude products with those of solutions of authentic materials or of 4-isopropylcyclohexanone as internal standard. Positive chlorine content in solutions of *N*-chloro compounds was determined by standard iodometric titration.[28] Melting and boiling points are uncorrected. Micro-Tech Laboratories, Skokie, Ill., and Baron Consulting Co., Orange, Conn., performed the elemental analyses.

The analysis of basic products involved a modified Kjeldahl procedure,[8] gas chromatography, and quantitative nmr. About 0.1 g of the hydrochloride salt mixture was dissolved in 50% sodium hydroxide and extracted with ether. The ether extract, dried with sodium sulfate, was analyzed by glpc (column 2). For the quantitative nmr analysis, about 0.1 g of the hydrochloride salt mixture was dissolved in D_2O. The signal intensities were compared with those of authentic materials in separate solutions of similar known concentrations.

1-Bromo-2-methylbutane.—An available route (HBr–H_2SO_4)[29a] was used with 2-methyl-1-butanol to yield 59% of bromide, bp 116–118°, $n^{24}D$ 1.4450 (lit.[30] bp 116.5–118°, lit.[31] $n^{20}D$ 1.4452).

3-Methylvaleronitrile.—When a published procedure[29b] was followed with 1-bromo-2-methylbutane, the nitrile was obtained in 61% yield, bp 148–150°, $n^{24}D$ 1.4058 (lit.[32] bp 147–149°, lit.[33] $n^{26}D$ 1.4051).

Di-*n*-butyl-*sec*-butylacetonitrile.—Use of a prior procedure,[34] with 3-methylvaleronitrile gave 85% of product, bp 84–85° (0.15 mm).

Anal. Calcd for $C_{14}H_{27}N$: C, 80.31; H, 13.00. Found: C, 80.53; H, 12.93.

Di-*n*-butyl-*sec*-butylacetamide.—A literature method[34] was used to convert di-*n*-butyl-*sec*-butylacetonitrile to the amide in 87% yield, bp 135–136° (0.3 mm). The distillate slowly solidified to a waxy solid, mp 28–30°.

Anal. Calcd for $C_{14}H_{29}NO$: C, 73.95; H, 12.85; N, 6.16. Found: C, 73.90; H, 12.79; N, 6.10.

Di-*n*-butyl-*sec*-butylcarbinamine.—A known method[35] was used with di-*n*-butyl-*sec*-butylacetamide except that the isocyanate was not isolated. The amine was obtained in 86% yield: bp 75–75.5° (0.28 mm); $n^{25}D$ 1.4474; ir (neat) 3300 (NH), 1615 (NH), 816 (NH), 783, and 732 cm^{-1}; nmr ($CDCl_3$) δ 1.6 (m, 2 H, NH_2, exchangeable with D_2O), 1.27 (m, 14 H, CH_2 + CH), 0.92 (m, 12 H, CH_3).

Anal. Calcd for $C_{13}H_{29}N$: C, 78.31; H, 14.66. Found: C, 78.22; H, 14.75.

The acetamide derivative melted at 62–64°.

Anal. Calcd for $C_{15}H_{31}NO$: C, 74.63; H, 12.94; N, 5.80. Found: C, 74.50; H, 13.31; N, 5.73.

***n*-Butyldimethylcarbinol.**—Use of a prior procedure[36] with *n*-butyl bromide and acetone gave 73% of alcohol, bp 138–142°, $n^{23}D$ 1.4171 (lit.[37] bp 141–142°, lit.[37] $n^{20}D$ 1.4175).

***n*-Butyldimethylcarbinamine.**—A published route[38] was followed with *n*-butyldimethylcarbinol to yield 47% of basic product: bp 125–126° (lit.[39] bp 124–127°); $n^{24}D$ 1.4137; phenylurea mp 119–120° (lit.[40] mp 116–117°); ir (neat) 3200 (NH), 1600 (NH), 1370, 1355, 1180, 830 (NH), 790, 760, and 732 cm^{-1}; nmr (CCl_4) δ 1.27 (m, 6 H, CH_2), 1.02 (m, 9 H, CH_3), 0.87 (2 H, NH_2, exchangeable with D_2O).

Di-*n*-butylmethylcarbinol.—Use of a prior procedure[36] with *n*-butyl bromide and ethyl acetate provided 68% of the alcohol: bp 52–54° (0.15 mm) [lit.[41] bp 86–87° (5 mm)]; $n^{25}D$ 1.4334 (lit.[41] $n^{20}D$ 1.4330); ir (neat) 3300 (OH), 1150 (CO), 1030 (CO), 950, 910, 795, and 735 cm^{-1}; nmr (CCl_4) δ 1.87 (s, 1 H, OH, exchangeable with D_2O), 1.32 (m, 12 H, CH_2), 1.07 (s, 3 H, CH_3COH), 0.92 (m, 6 H, CH_3CH_2).

Di-*n*-butylmethylcarbinamine.—A published procedure[38] was followed with di-*n*-butylmethylcarbinol to yield 67% of basic product: bp 34–35° (0.25 mm); $n^{25}D$ 1.4316; ir (neat) 3250 (NH), 1610 (NH), 1170, 830 (NH), 788, and 732 cm^{-1}; nmr (CCl_4) δ 1.25 (m, 12 H, CH_2), 1.00 (s, 2 H, NH_2, exchangeable with D_2O), 0.95 (m, 9 H, CH_3).

Anal. Calcd for $C_{10}H_{23}N$: C, 76.36; H, 14.74; N, 8.90. Found: C, 76.15; H, 14.52; N, 8.61.

The acetamide derivative melted at 60–61°.

Anal. Calcd for $C_{12}H_{25}NO$: C, 72.30; H, 12.64; N, 7.03. Found: C, 72.56; H, 12.71; N, 7.01.

Di-*n*-butylketoxime.—According to a literature preparation,[42] the oxime was obtained in 88% yield, bp 114–116° (8 mm) [lit.[43] bp 124.5° (15 mm)].

Di-*n*-butylcarbinamine.—Modification of a published procedure[44] gave 47% of basic product: bp 70–72° (11 mm) [lit.[45] bp 78° (20 mm)]; $n^{24}D$ 1.4273 (lit.[45] $n^{25}D$ 1.4264); ir (neat) 3300 (NH), 1615 (NH), 816 (NH), 778, and 731 cm^{-1}; nmr (CCl_4) δ 1.28 (m, 12 H, CH_2), 0.92 (t, 6 H, CH_3), 2.4–2.9 (m, 1 H, $CHNH_2$).

Di-*n*-butylbenzylcarbinol.—A literature method[36] was used with *n*-butyl bromide and ethyl phenylacetate to give a mixture of the alcohol (65% yield) and olefinic material. A pure sample of the alcohol was obtained by preparative glpc: ir (neat) 3400 (OH), 1610, 1494, 1132, 1080, 1034, 906, 727, and 702 cm^{-1}; nmr (CCl_4) δ 7.18 (s, 5 H, C_6H_5), 2.67 (s, 2 H, $PhCH_2$), 1.33 (m, 12 H, CH_2), 0.92 (m, 6 H, CH_3).

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Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.96; H, 11.08.

Di-*n*-butylbenzylcarbinamine.—The Ritter reaction[33] with crude alcohol was employed to obtain the amine: bp 104–106° (0.25 mm); $n^{24}D$ 1.5036; ir (neat) 3200 (NH), 1595 (NH), 1485, 835 (NH), 725, and 703 cm^{-1}; nmr (CCl_4) δ 7.15 (s, 5 H, C_6H_5), 2.55 (s, 2 H, $PhCH_2$), 1.2–1.7 (m, 12 H, CH_2), 0.92 (m, 6 H, CH_3), 0.67 (s, 2 H, NH_2, exchangeable with D_2O).

Anal. Calcd for $C_{16}H_{27}N$: C, 82.34; H, 11.66; N, 6.00. Found: C, 82.51; H, 11.69; N, 6.00.

The acetamide derivative melted at 106–107°.

Anal. Calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.48; H, 10.87; N, 4.88.

Di-*n*-butylphenylacetonitrile.—A literature procedure[34] was followed except that the reaction mixture was refluxed for 3 days, giving a 73% yield, bp 93–95° (0.18 mm) [lit.[34] bp 135–140° (1.5 mm)].

Di-*n*-butylphenylacetamide.—Conversion of the nitrile to the amide was accomplished *via* a literature method.[34] The crude amide, bp 151–158° (0.05–0.07 mm) [lit.[34] bp 168–170° (0.5 mm)], was used directly in the Hofmann degradation.

Di-*n*-butylphenylcarbinamine.—A previous method[35] was employed except that the isocyanate was not isolated. The amine was obtained in 90% yield: bp 82–84° (0.2 mm); $n^{24}D$ 1.5007; ir (neat) 3200 (NH), 1610, 830 (NH), 770, and 713 cm^{-1}; nmr (CCl_4) δ 7.0–7.5 (m, 5 H, C_6H_5), 1.4–1.9 (m, 4 H, $PhCCH_2$), 1.1–1.4 (m, 8 H, CH_2), 0.83 (t, 6 H, CH_3), 0.83 (s, 2 H, NH_2, exchangeable with D_2O).

Anal. Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.38. Found: C, 81.85; H, 11.69; N, 6.09.

The benzamide derivative melted at 151–152°.

Anal. Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.85; H, 8.74; N, 4.06.

***N*-Acetyltri-*n*-butylcarbinamine.**—A literature procedure[35] was used to produce the acetamide, 89% yield, mp 78–80.5° after recrystallization (lit.[35] mp 80.5–81.5°).

***N*-Ethyltri-*n*-butylcarbinamine.**—A previous method[7] was employed to obtain the amine: 98% yield; bp 86–89° (0.45 mm); $n^{24}D$ 1.4419; ir (neat) 1253, 1159, 1124, 1098, 895, and 729 cm^{-1}; nmr (CCl_4) δ 2.34 (q, 2 H, CH_2CH_2N), 1.17 (m, 18 H, CH_2), 0.88 (m, 12 H, CH_3).

Anal. Calcd for $C_{15}H_{33}N$: C, 79.22; H, 14.63; N, 6.16. Found: C, 79.30; H, 14.56; N, 6.28.

***N*-Chloro-*N*-ethyltri-*n*-butylcarbinamine.**—A mixture of *N*-ethyltri-*n*-butylcarbinamine (5.7 g, 25 mmol) and *N*-chlorosuccinimide (3.6 g, 25 mmol) in 15 ml of ether was stirred at room temperature for 1 hr, cooled, and filtered. After the filtrate was washed with water, it was dried with sodium sulfate, the ether was removed, and the residue was dissolved in methylene chloride. Yields of 95–98% of the *N*-chloroamine were obtained, as indicated by titration for positive chlorine.

***N,N*-Dichloroamines.**—Generally, procedure II of the previous work[8] was followed, providing yields of 92–96%, except in the case of di-*n*-butylbenzylcarbinamine (74–84% yield). Iodometric titration was used for analysis.

Rearrangement of *N,N*-Dichloroamines with Aluminum Chloride.—General procedure C from the earlier report[8] was used except as otherwise noted. In most cases, products were identified by comparison of the ir and nmr spectra and glpc retention times with those of authentic materials.

2-Chlorovaleraldehyde.—A solution of valeraldehyde (10 g, 116 mmol) in 30 ml of methylene chloride in a flask covered with aluminum foil and fitted with a gas-inlet tube was cooled to −15°. Chlorine gas was passed into the solution over a period of 0.5 hr at −15°. The solution was then stirred at −10 to −15° for 5 hr, washed several times with 5% sodium bicarbonate, then with water, and finally dried over sodium sulfate. After removal of solvent, distillation of the residue afforded 7.2 g (49%) of 2-chlorovaleraldehyde: bp 126–130°; 95% pure (glpc); $n^{25}D$ 1.4276 (pure sample); ir (neat) 1725 (C=O), 1050, 892, 762, and 698 cm^{-1}; nmr (CCl_4) δ 9.42 (d, J = 3 Hz, 1 H, CHO), 4.12 (m, 1 H, CHCl), 1.3–2.2 (m, 4 H, CH_2), 0.98 (t, 3 H, CH_3).

Anal. Calcd for C_5H_9ClO: C, 49.81; H, 7.52. Found: C, 50.06; H, 7.31.

2,2-Dichlorovaleric Acid.—Procedure B of a literature method[46] provided 73% of 1,2,2-tetrachloropentylphosphorimidic trichloride, bp 109–113° (0.15 mm), $n^{24}D$ 1.5431 [lit.[46] bp 135–136° (3 mm), $n^{20}D$ 1.5450]. Hydrolytic procedure A yielded 76% of 2,2-dichlorovaleric acid: bp 108–110° (6.8 mm); $n^{24}D$ 1.4608 [lit.[46] bp 110–112° (7 mm), $n^{20}D$ 1.4612]; ir (neat) 3600–2200 (COOH), 1725 (C=O), 1265 (CO), 1105, 909, 902, 829, 797, and 756 cm^{-1}; nmr (CCl_4) δ 12.22 (s, 1 H, COOH, exchangeable with D_2O), 2.3–2.7 (m, 2 H, CH_2CCl_2), 1.4–2.1 (m, 2 H, CH_2), 1.03 (t, J = 6.5 Hz, 3 H, CH_3).

2,2-Dichlorovaleryl Chloride.—A mixture of 17.1 g (100 mmol) of 2,2-dichlorovaleric acid and 17.9 g (150 mmol) of thionyl chloride was refluxed for 2 days. After removal of excess thionyl chloride, the residue was distilled to yield 7.8 g (41%) of acid chloride: bp 48–50° (7.5 mm); $n^{24}D$ 1.4586; ir (neat) 1780 (C=O), 1085, 979, 877, 811, 750, and 695 cm^{-1}; nmr (CCl_4) δ 2.3–2.6 (m, 2 H, CH_2CCl_2), 1.3–2.1 (m, 2 H, CH_2), 1.05 (t, J = 6.5 Hz, 3 H, CH_3).

Anal. Calcd for $C_5H_7Cl_3O$: C, 31.70; H, 3.72. Found: C, 31.98; H, 3.86.

2,2-Dichlorovaleraldehyde.—A solution of 2,2-dichlorovaleryl chloride (5.4 g, 28 mmol) in 15 ml of tetrahydrofuran was cooled to −70° under dry nitrogen. Lithium tri-*tert*-butoxyaluminum hydride[47] (7.4 g, 29 mmol) in 20 ml of tetrahydrofuran was added over a period of 4 hr at −70°. The flask was then allowed to warm to room temperature over a period of 1 hr, water was added, the mixture was extracted with ether, and the organic layer was dried with sodium sulfate. The organic phase contained a low yield of aldehyde. Preparative glpc provided a pure sample: ir (neat) 2690 (CHO), 1750 (C=O), 1111, 992, 758, and 688 cm^{-1}; nmr (CCl_4) δ 9.17 (s, 1 H, CHO), 2.1–2.5 (m, 2 H, CCl_2CH_2), 1.4–2.0 (m, 2 H, CH_2), 1.03 (t, 3 H, CH_3).

Anal. Calcd for $C_5H_8Cl_2O$: C, 38.74; H, 5.20. Found: C, 39.01; H, 5.21.

A large amount of material, apparently 2,2-dichloro-1-pentanol, was also present: ir (neat) 3300 (OH), 1250, 1065, 1000, 905, 763, and 704 cm^{-1}; nmr (CCl_4) δ 3.80 (s, 2 H, CH_2OH), 3.0 (s, 1 H, OH, exchangeable with D_2O), 1.9–2.4 (m, 2 H, CCl_2CH_2), 1.3–1.9 (m, 2 H, CH_2), 1.00 (t, 3 H, CH_3).

Anal. Calcd for $C_5H_{10}Cl_2O$: C, 38.24; H, 6.42. Found: C, 38.21; H, 6.49.

4-Phenyl-5-nonanone.—To a solution of 1-phenyl-2-hexanone (1.8 g, 10 mmol) and *n*-propyl bromide (1.2 g, 10 mmol) in 20 ml of dry benzene was added sodium amide (0.4 g, 10 mmol). After the mixture was heated at reflux overnight, water was added, the layers were separated, and the organic phase was dried with sodium sulfate. Removal of solvent and distillation provided 1.1 g (51%) of ketone: bp 87–89° (0.2 mm) [lit.[48] bp 175° (25 mm)]; $n^{23}D$ 1.4923; ir (neat) 1712 (C=O), 1256, 1132, 1044, 751, and 703 cm^{-1}; nmr (CCl_4) δ 7.19 (s, 5 H, C_6H_5), 3.52 (t, 1 H, PhCH), 2.25 (t, 2 H, $COCH_2$), 1.0–2.1 (m, 8 H, CH_2), 0.88 (t, 6 H, CH_3); semicarbazone mp 107–109° (lit.[48] mp 109°).

5-Phenyl-4-nonanone.—To a solution of 1-phenyl-2-pentanone (4.1 g, 25 mmol) and *n*-butyl bromide (4.3 g, 31 mmol) in 40 ml of dry benzene was added sodium amide (1.2 g, 31 mmol). After the mixture was heated at reflux for 30 hr, water was added, the layers were separated, and the organic phase was dried with sodium sulfate. Removal of solvent and distillation provided 3.1 g (57%) of ketone: bp 73–76° (0.08 mm) (lit.[48] bp 275–277°); $n^{24}D$ 1.4930; ir (neat) 1715 (C=O), 1136, 1025, 899, 751, and 705 cm^{-1}; nmr (CCl_4) δ 7.19 (s, 5 H, C_6H_5), 3.50 (t, 1 H, PhCH), 2.25 (t, 2 H, $COCH_2$), 1.1–2.1 (m, 8 H, CH_2), 0.6–1.1 (m, 6 H, CH_3).

Control Experiment for Recovery of Acetone.—A mixture of 1.45 g of acetone, 60 ml of methylene chloride, and 65 ml of 18% hydrochloric acid was distilled under reduced pressure into cold traps (−78°) until a single phase was present in the distilling flask. The mixture in the flask was then steam distilled into a cooled receiver. Glpc analysis of the collected fractions revealed the presence of 1.36 g of acetone (94% recovery).

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Registry No.—Aluminum chloride, 7446-70-0; di-*n*-butyl-*sec*-butylacetonitrile, 41718-30-3; 3-methylvaleronitrile, 21101-88-2; di-*n*-butyl-*sec*-butylacetamide, 41718-32-5; di-*n*-butyl-*sec*-butylcarbinamine, 41718-33-6; di-*n*-butyl-*sec*-butylcarbinamine acetamide derivative, 41718-34-7; *n*-butyldimethylcarbinamine, 2626-64-4; *n*-butyldimethylcarbinol, 625-23-0; di-*n*-butylmethylcarbinol, 33933-78-7; *n*-butyl bromide, 109-65-9; ethyl acetate, 141-78-6; di-*n*-butylmethylcarbinamine, 41718-37-0; di-*n*-butylmethylcarbinamine acetamide derivative, 41718-38-1; di-*n*-butylcarbinamine, 2198-45-0; di-*n*-butylbenzylcarbinol, 41718-40-5; ethyl phenylacetate, 101-97-3; di-*n*-butylbenzylcarbinamine, 41718-41-6; di-*n*-butylbenzylcarbinamine acetamide derivative, 41718-42-7; di-*n*-butylphenylacetamide, 41718-43-8; di-*n*-butylphenylcarbinamine, 41718-44-9; di-*n*-butylphenylcarbinamine benzamide derivative, 41718-45-0; *N*-ethyltri-*n*-butylcarbinamine, 41718-46-1; 2-chlorovaleraldehyde, 41718-47-2; valeraldehyde, 110-62-3; methylene chloride, 75-09-2; 2,2-dichlorovaleric acid, 18240-68-1; 1,1,2,2-tetrachloropentylphosphoimidic trichloride, 18240-56-7; 2,2-dichlorovaleryl chloride, 41718-49-4; 2,2-dichlorovaleraldehyde, 41718-50-7; 2,2-dichloro-1-pentanol, 41718-51-8; 4-phenyl-5-nonanone, 41718-52-9; 1-phenyl-2-hexanone, 25870-62-6; *n*-propyl bromide, 106-94-5; 5-phenyl-4-nonanone, 41718-53-0; 1-phenyl-2-pentanone, 6683-92-7.

Nucleophilic Reactions of *N*-Hydroxyimide-*O*-triflates

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Reactions of *N*-hydroxysuccinimide-*O*-triflate (**1**), *N*-hydroxyphthalimide-*O*-triflate (**5**), and *N*-hydroxytetramethylsuccinimide-*O*-triflate (**6**) with various nucleophiles were investigated. Compound **1** reacts with thallous acetate to give *N*-hydroxysuccinimide-*O*-acetate. Sodium thioacetate gives the same product, indicating that the reaction proceeds by initial attack at sulfonate sulfur. Compounds **1** and **5** react with phenoxide and thiophenoxide through attack at imide carbonyl, ring opening, and Lossen rearrangement giving β-alanine and anthranilic acid derivatives, respectively. Compound **6** reacts with phenoxide and thiophenoxide at sulfonate sulfur. In no case was direct nucleophilic displacement at nitrogen or the formation of nitrenium ions indicated.

Nucleophilic substitution reactions at nitrogen are quite rare and the mechanisms are usually in doubt. Although there are several reactions reported in the literature which can be schematically considered nucleophilic displacements at nitrogen, they can be explained by different mechanisms, *e.g.*, nitrene formation, nitrenium ion formation, or addition–elimination.[1-5]

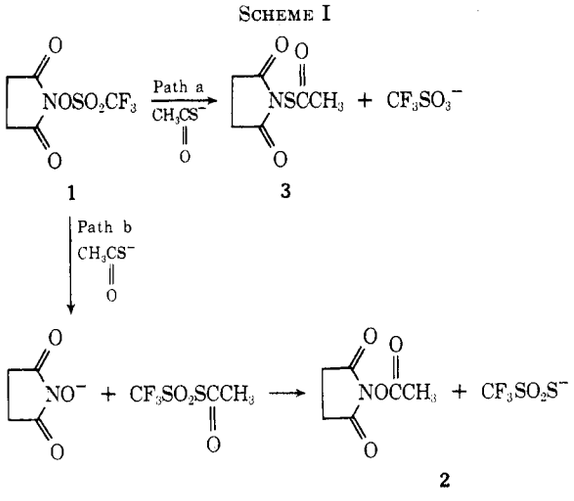
It appeared to us that a compound such as *N*-hydroxysuccinimide-*O*-trifluoromethanesulfonate (triflate)[6] might undergo direct nucleophilic displacement at nitrogen based on the following accounts. First, the group displaced would be triflate anion, considered until recently the most effective leaving group.[7,8] Second, although Gassman and Hartman[9] have shown that the N–O bond in tosyl derivatives of dialkylhydroxylamines is extremely labile, presumably forming nitrenium ion intermediates, related work by Biehler and Fleury[10] showed the proximity of electron-withdrawing groups to stabilize such derivatives.

In an effort to demonstrate the possibility of nucleophilic displacement at nitrogen, the reactivity of compound **1** and two congeners toward nucleophilic reagents was studied.

Results and Discussion

N-Hydroxysuccinimide-*O*-triflate reacted with thallous acetate in dimethylformamide giving a 53% yield of *N*-hydroxysuccinimide-*O*-acetate (**2**). If the reaction occurred by a direct displacement mechanism, it was reasoned that an approach toward the racemization-free formation of peptide active esters might be developed. Compound **2** could have formed from acetate and **1** by two mechanisms, substitution at nitrogen or a double displacement in which carboxylate attacks at sulfonate sulfur giving rise to an activated anhydride which could then acetylate the *N*-hydroxysuccinimidyl anion displaced in the first step. Insight was gained by studying the reaction of sodium thioacetate with **1** under a variety of conditions and solvent media, including dimethylformamide, dimethyl sulfoxide, dimethoxyethane, and methylene chloride. As shown in Scheme I, direct displacement (path a) would give thioacetate **3** whereas double displacement (path

SCHEME I



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