melting (mp 263–265°) had an infrared spectrum identical with that of authentic material and λ_{max} 282 mμ (ε 14,700).

C.—Attempted preparation of **8** by treating 6-chloro-16α,-17α-(dimethylmethylenedioxy)-1,4,6-pregnatriene-3,20-dione[6] (**9**) with dimethylsulfoxonium methylide gave a mixture which even after extensive column and thin layer chromatography could not be resolved.

1α,2α-Methylene-16α,17α-(dimethylmethylenedioxy)-4-pregnene-3,20-dione (16). A.—A solution of 30 mg of 1α,2α-methylene-16α,17α-(dimethylmethylenedioxy)-4,6-pregnadiene-3,20-dione (**4**) in 5 ml of methanol was added to a hydrogen-saturated suspension of 10 mg of 5% palladium on charcoal in 5 ml of methanol containing 4 mg of potassium hydroxide. The mixture was stirred at room temperature in an atmosphere of hydrogen, and after 1 equiv of hydrogen was absorbed, the catalyst was filtered, the solution was neutralized with glacial acetic acid, and the solvent was evaporated. The residue was dissolved in chloroform, and the chloroform solution was washed with water, dried, and evaporated. Recrystallization of the resulting material from methanol gave 11 mg of 1α,2α-methylene-16α,17α-(dimethylmethylenedioxy)-4-pregnene-3,20-dione (**16**): mp 252–253°; $[\alpha]_D$ +266°; λ_{max} 5.85, 6.03 (br) μ; λ_{max} 240 mμ (ε 12,500); nmr τ 9.33 (18-H, s), 8.71 (19-H, s), 4.97 (16β-H, d, J = 4 cps), 4.46 (4-H, s).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 76.37; H, 8.49.

B.—The preparation of **16** by the reaction of 16α,17α-(dimethylmethylenedioxy)-1,4-pregnadiene-3,20-dione[6] (**13**) with a fivefold excess of dimethylsulfoxonium methylide was attempted. Analysis of the crude reaction product by vapor phase chromatography[24] showed that there was 65% starting material and 25% of a material whose retention time was identical with that of **16** in the mixture. The remaining material was present in minor peaks.

1α,2α-Methylene-16α,17α-(dimethylmethylenedioxy)-5β-pregnane-3,20-dione (17).—A solution of 104 mg of 1α,2α-methylene-16α,17α-(dimethylmethylenedioxy)-4,6-pregnadiene-3,20-dione (**4**) in 20 ml of absolute ethanol containing 200 mg of potassium hydroxide and 25 mg of 10% palladium on charcoal was hydrogenated at room temperature until uptake of hydrogen ceased (3 hr). The solution was filtered, acidified with glacial acetic acid, and evaporated. The residue was taken up in ethyl acetate which was washed with saturated salt solution, dried, and evaporated to give 101 mg of material. Two recrystallizations from methanol gave 23 mg of (**17**), mp 182–186°, and no selective absorption in the ultraviolet. The analytical sample had mp 188–190°; $[\alpha]_{589}$ +94°, $[\alpha]_{578}$ +100°, $[\alpha]_{546}$ +179°, $[\alpha]_{436}$ +214°, $[\alpha]_{365}$ +442°; ORD[28] (methanol) $[\alpha]_{350}$ +531°, $[\alpha]_{325}$ +1460°, $[\alpha]_{307}$ ±0°, $[\alpha]_{290}$ −2130° (trough), $[\alpha]_{268}$ ±0°, $[\alpha]_{260}$ +850°; λ_{max} 5.84 (sh), 5.89 μ; nmr τ 9.37 (18-H, s), 8.75 (19-H, s), 4.99 (16β-H, d, J = 4.5 cps).

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.83; H, 9.04.

6α,7α-Methylene-16α,17α-(dimethylmethylenedioxy)-4-pregnene-3,20-dione (15).—A solution of 387 mg of 16α,17α-(dimethylmethylenedioxy)-4,6-pregnadiene-3,20-dione[6] (**14**) in 25 ml of dimethyl sulfoxide containing 5 mmoles of dimethylsulfoxonium methylide was stirred for 23 hr. After work-up as described above 364 mg of an oil was obtained. Thin layer chromatography (neutral alumina, activity V) using hexane–chloroform (1:4) as the developing solvent and eluting the ultraviolet absorbing band with ethyl acetate gave 284 mg of crystalline material. Recrystallization from methanol afforded 69 mg of **15**, mp 200–203°. The analytical sample had mp 207–209°; $[\alpha]_D$ −83°; λ_{max} 5.85, 6.0 (br), 6.26 μ; λ_{max} 267 mμ (ε 16,600); nmr τ 9.38 (18-H, s), 8.91 (19-H, s), 4.97 (16β-H, br), 4.00 (4-H, s).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.45; H, 8.63.

4β,5-Methylene-16α,17α-(dimethylmethylenedioxy)-19-nor-5β-pregnane-3,20-dione (12).—Dimethylsulfoxonium methylide (2.5 mmoles) and 187 mg of 16α,17α-(dimethylmethylenedioxy)-19-nor-4-pregnene-3,20-dione[19] (**11b**) in 6 ml of dimethyl sulfoxide were stirred for 17.5 hr. After work-up, 158 mg of material having no selective absorption in the 220–250-mμ region was obtained. This material was purified by thin layer chromatography on neutral alumina (activity V) using hexane–chloroform (1:4) as the solvent. Elution of the iodine-absorbing band with ethyl acetate gave 95 mg of 4β,5-methylene-16α,17α-(dimethylmethylenedioxy)-19-nor-5β-pregnane-3,20-dione (**12**). Recrystallization from methanol afforded analytically pure material having mp 155–157°; $[\alpha]_{589}$ +81°, $[\alpha]_{578}$ +84°, $[\alpha]_{546}$ +101°, $[\alpha]_{436}$ +228°, $[\alpha]_{365}$ +600°; ORD[28] (methanol) $[\alpha]_{350}$ +1090°, $[\alpha]_{318}$ +2471° (peak) $[\alpha]_{257}$ ±0°, $[\alpha]_{270}$ −3420°; λ_{max} 5.85, 5.95 μ; nmr τ 9.38 (18-H, s), 4.99 (16β-H, d, J = 4 cps).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.50; H, 8.89.

Acknowledgment.—We are grateful to Mr. James W. Brown for technical assistance in preparing the starting materials used in this report. We also thank Mr. Joseph Alicino and his staff for microanalyses, Miss Barbara Keeler for infrared absorption recordings, Dr. A. I. Cohen for nuclear magnetic resonance determination, and Mr. A. Niedermayer for vapor phase chromatograms.

(28) We are grateful to Applied Physics Corp., Monrovia, Calif., for determining these curves on a Cary Model 60 spectropolarimeter.

The Isonitrile–Nitrile Isomerization[1]

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The unimolecular first-order thermal isomerization of isonitriles to nitriles has been investigated in a series of aryl- and alkylisonitriles. Retention of stereochemical integrity at the migrating carbon atom, lack of carbon skeleton rearrangement in the isomerization of cyclobutylisonitrile, and low sensitivity of the reaction rate to variation in *para* substituents in arylisonitriles, all support the view that bond breaking and bond making are essentially synchronous, and that little charge separation develops in the transition state.

The thermal isomerization of isonitriles to nitriles (eq 1) has been known for more than 50 years,[3]

$$R-\overset{+}{N}\equiv\overset{-}{C}: \xrightarrow{\Delta} :N\equiv C-R \qquad (1)$$

but until recently[4] has received scant attention,[5] despite the stoichiometric simplicity of the transformation, and the striking parallel between geometry and bonding in the initial and final states. Rabinovitch and his co-workers have carefully examined the kinetic behavior of *p*-tolylisonitrile[4a] in solution and in

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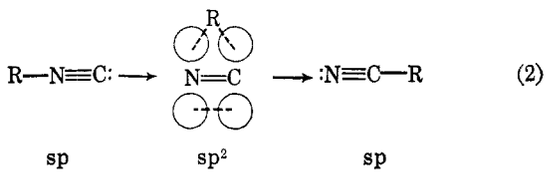
(3) H. Guillemard, *Compt. Rend.*, **144**, 141 (1907).

(4) (a) G. Kohlmaier and B. S. Rabinovitch, *J. Phys. Chem.*, **63**, 1793 (1959); (b) F. W. Schneider and B. S. Rabinovitch, *J. Am. Chem. Soc.*, **84**, 4215 (1962); (c) F. W. Schneider and B. S. Rabinovitch, *ibid.*, **85**, 2365 (1963).

(5) R. A. Ogg, Jr., *J. Chem. Phys.*, **7**, 753 (1939).

the gas phase, and methyl-[4b] and methyl-d_3-isonitriles[4c] in the gas phase, the latter compounds being scrutinized in connection with that author's study of rate processes. Rabinovitch ascertained that the isomerization reaction is unimolecular and first order. The experimental activation energy reported by Rabinovitch for *p*-tolylisonitrile is large (36.8 kcal/mole for solution in Nujol, 33.8 kcal/mole for the gas phase) and for methylisonitrile is even larger (38.4 kcal/mole, over a wide pressure range) over the range 190–220°, suggesting appreciable bond breaking in the transition state. However, the obtention of *p*-toluonitrile as the sole product from *p*-tolylisonitrile rearrangement, free from *m*-toluonitrile implies a continuity in the bond-breaking and bond-making processes. A small, slightly negative entropy of activation further supports this contention, suggesting an increase in bond organization in the activated complex.

Linear geometry in both the initial[6] and final states[6c] of the rearrangement requires substantial bond rehybridization during the transition state, so that σ-bonding orbitals are available to ensure continuity of bonding during the migration process.



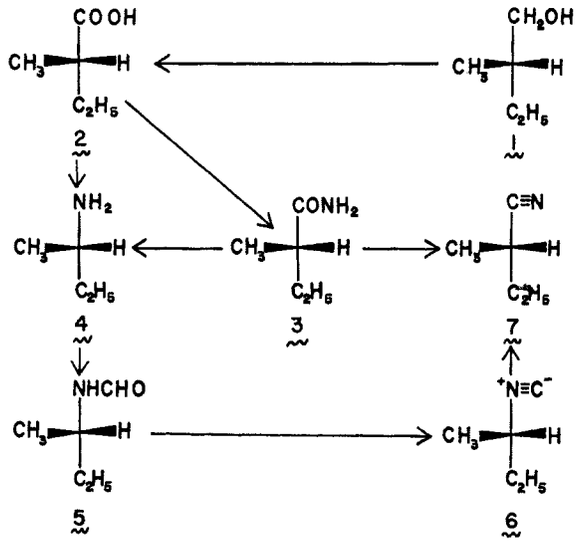
(2)

From the formal similarity between this simple isomerization and the final step of a considerable number of well-studied "saturated rearrangements" to electron-deficient migration termini[7] (*e.g.*, the Hofmann, Curtius, Schmidt, Beckmann, Lossen, and Wolff rearrangements) it occurred to us that the isonitrile–nitrile isomerization reaction might provide an opportunity to examine a reaction which was parallel to the final rearrangement step of saturated rearrangement reactions, but was unencumbered by a sequence of relatively unstable intermediates, or by variations in timing and relative facility for departure of various leaving groups at the migration terminus. These results could prove informative relevant to the nature of the final intermediates in more complex "saturated rearrangement" reactions. To this end, we have examined the stereochemical fate of the migrating group, and the effect of variation in size and electronic nature of the migrating group on the velocity of the reaction.

Results

1. Stereochemistry.—The question of stereochemistry owing to asymmetry at the migrating carbon atom was examined using the conventional technique of a closed synthetic loop that produced known stereospecific results at the asymmetric carbon atom in all steps except that under investigation. The synthetic sequence is shown in Chart I. (−)-*sec*-Butylcarbinol (**1**), isolated from fusel oil, was oxidized to (+)-2-methylbutyric acid (**2**) separately by acidic sodium dichromate or basic potassium permanganate with similar optical results, the latter being slightly more stereospecific (see the Experimental Section). Acid **2** was converted to (+)-*sec*-butylamine (**4**) by two independent routes, directly *via* a Schmidt reaction, and indirectly through 2-methylbutyramide (**3**), *via* a Hofmann reaction. The optical rotation of *sec*-butylamine obtained by both routes was identical within experimental error. The amine was formylated to give (+)-*sec*-butylformamide (**5**) and thence dehydrated to (+)-*sec*-butylisonitrile (**6**). Dehydration of 2-methylbutyramide (**3**) gave (+)-2-methylbutyronitrile (**7**) of the same absolute configuration as isonitrile **6**. The optical purity of isonitrile **6** and nitrile **7** prepared in this manner should be identical, since the only steps which involved bond breaking at the asymmetric carbon (**2** → **4** and **3** → **4**) were well known[8] to proceed with complete retention of configuration at secondary carbon atoms. The possibility that partial racemization could have occurred *via* the α carbanion of isonitrile **6** under the basic conditions employed for its formation was considered very unlikely, because of the weakly basic medium employed, the low temperature, and the immediate removal of the product isonitrile as quickly as it was formed. However, this possibility was not checked by hydrogenation of **6** to **4**.

CHART I



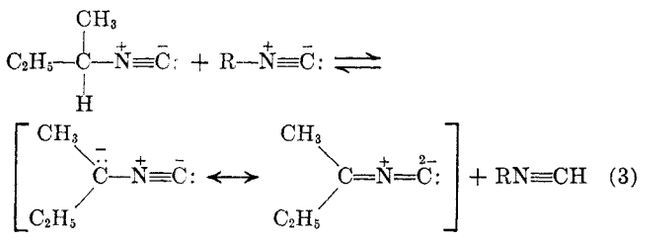
A degassed sample of (+)-*sec*-butylisonitrile was sealed under vacuum in a Pyrex tube and heated at 200.0 ± 0.5° for 24 hr (neat liquid). The nitrile formed by the rearrangement had retained 87% of its optical activity when compared to a sample of (+)-2-methylbutyronitrile prepared by the known stereospecific route. As a control, a sample of (+)-2-methylbutyronitrile (**7**) of known optical purity was subjected to conditions identical with those of the rearrangement in the presence of excess methyl isonitrile. The recovered nitrile had lost 27% of its optical activity, an amount more than sufficient to accommodate the decrease in optical activity observed

(6) (a) B. Bak, L. Hansen Nygaard, and J. Rastrup-Andersen, *J. Mol. Spectry.*, **2**, 54 (1958); (b) M. Kessler, H. Ring, R. Trambarulo, and W. Gardy, *Phys. Rev.*, **79**, 54 (1950); (c) Special Publication No. 11, The Chemical Society, London, 1958, p M128, and Special Publication No. 18, Supplement, The Chemical Society, London, 1965, p M122s.

(7) For reviews and leading references, see (a) P. A. S. Smith, "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 457–528; (b) C. K. Ingold, "Structure and Mechanisms in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapter IX; (c) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 15.

(8) (a) C. L. Arcus and J. Kenyon, *J. Chem. Soc.*, 916 (1939); (b) A. Campbell and J. Kenyon, *ibid.*, 25 (1946).

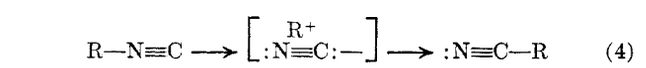
during the thermal isomerization step. It is probable that during the isomerization the unreacted isonitrile acts as a base to remove an α-hydrogen atom from the nitrile to give the carbanion, which may be protonated again nonstereospecifically to give a racemic nitrile (eq 3). Thus, the isonitrile–nitrile rearrangement



(3)

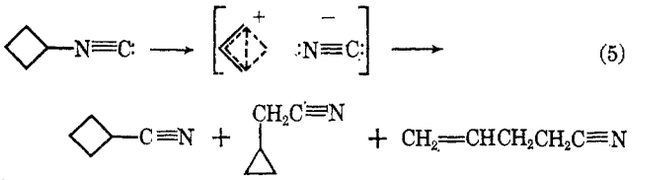
proceeds with the same very high retention of stereochemical integrity at the migrating carbon that characterizes the saturated rearrangement reactions.[7b]

2. Cationic Character in the Migrating Carbon.—If the rearrangement proceeded through a tight ion pair, stereochemical retention of configuration would still be predicted (eq 4), provided that the migrating



(4)

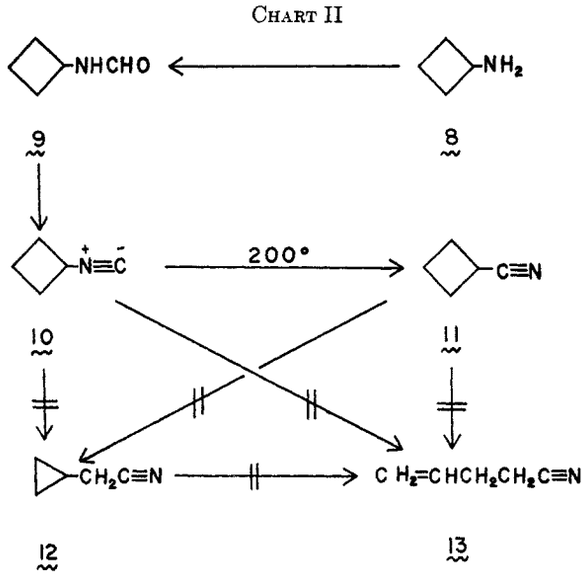
group did not depart from its asymmetric environment. This possibility is consistent with the result obtained from optically active isonitrile, and should be amenable to testing. If R in RNC is a group of demonstrated propensity toward carbon skeleton rearrangement under conditions in which cationic carbon is thought to be involved, then the ion-pair mechanism should lead to carbon skeleton rearrangement. Such a system is the cyclobutyl system,[9a] which yields nearly equivalent amounts of cyclobutyl- and cyclopropylcarbinyl products, together with a small amount of allylcarbinyl product, either upon hydrolysis of the chloride,[9b] acetolysis of the tosylate,[9c] deamination of the amine,[9d] or anodic oxidation of the carboxylic acid.[9e] Even substitution of chloride in cyclobutyl alcohol[9f] using thionyl chloride in the absence of a tertiary amine (the conditions best suited to an S_Ni reaction[9g] yields 69% cyclopropylcarbinyl chloride, 25% cyclobutyl chloride, and 6% allylcarbinyl chloride. If a substantial amount of cationic character developed at migrating carbon during the isonitrile rearrangement, the cyclobutyl group might be expected to undergo carbon skeleton rearrangement during the isomerization process, although it remained closely associated with its counterion and in the optically active case failed to racemize. Chart II depicts the



(5)

(9) (a) R. Breslow, ref 7a, p 260; P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 52, 272, 300; (b) J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc.*, **73**, 2509 (1951); (c) J. D. Roberts and V. C. Chambers, *ibid.*, **73**, 3176 (1951); (d) R. H. Mazur, W. N. White, D. A. Semenov, C. C. Lee, M. S. Silver, and J. D. Roberts, *ibid.*, **81**, 4390 (1959); (e) E. J. Corey, N. L. Bauld, R. T. LaLonde, J. Casanova, Jr., and E. T. Kaiser, *ibid.*, **82**, 2645 (1960); (f) M. C. Caserio, W. H. Graham, and J. D. Roberts, *Tetrahedron*, **11**, 171 (1960); (g) D. J. Cram, *J. Am. Chem. Soc.*, **75**, 332 (1953); C. E. Boozer and E. S. Lewis, *ibid.*, **75**, 3182 (1953).

CHART II



results of this experiment. Cyclobutylisonitrile (**10**) was prepared from cyclobutylamine (**8**) *via* formamide **9**. Thermal isomerization of **10**, when carried out in the liquid phase at 200.0° in an evacuated, sealed tube, failed to show any trace of cyclopropylcarbinyl cyanide (**12**) or 3-butenyl cyanide (**13**), when followed either by the change in its proton resonance spectrum or by isolation of the total nitrile product and vapor phase chromatographic analysis. Under these conditions 0.1% of nitrile could have been detected. The absence of products derived from carbon skeleton rearrangement in this reaction suggests that little charge separation develops in the transition state. Neither cyclopropylcarbinyl cyanide nor 3-butenyl cyanide is converted to cyclobutyl cyanide under the reaction conditions.

In support of this conclusion is the absence of electronic effect on the rate of rearrangement of three *para*-substituted arylisonitriles. These data are shown in Table I. *p*-Chlorophenyl-, phenyl-, and *p*-methoxyphenylisonitriles in diglyme solution were heated under vacuum in sealed nmr tubes at 200.0° and changes in their spectra were observed periodically. Because of significant differences in the chemical shift of aro-

TABLE I

FIRST-ORDER RATE CONSTANTS FOR THE THERMAL ISOMERIZATION OF *para*-SUBSTITUTED ISONITRILES IN DIGLYME AT 200.0 ± 0.5°

G, in G–C₆H₄–N≡C	10^5k_1, sec^{-1}	10^5k_1, av	k_1, rel	σ^a
H	28.8			
H	28.0			
H	26.9			
H	26.8	27.6 ± 0.8	1.13	0.000
Cl	25.1			
Cl	24.3			
Cl	23.9			
Cl	24.3	24.4 ± 0.4	1.00	+0.227
CH_3O	32.5			
CH_3O	31.0			
CH_3O	30.3			
CH_3O	31.7	31.4 ± 0.9	1.29	−0.268

[a] R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 571.

matic protons in the starting material and product, the progress of the reaction could be followed this way. These data obtained from a plot of log [(RNC) + (RCN)]/(RNC) *vs.* time were submitted to least-square analysis to extract the first-order rate constant.[10] The first-order rate constants for thermal rearrangement of these samples fell within 30% of each other, in spite of a variation of 0.495 in the value of the σ constants.[11] A plot of log k *vs.* σ for the data of Table I for these three points failed to give a straight line, but the lack of change of log k with variations of σ suggests that the reaction rate is nearly insensitive to the nature of polar *para* substituents, with a ρ of about -0.12 ± 0.10. This signifies a lack of sensitivity of the reaction rate to electronic effects.

3. Rearrangement of Alkylisonitriles.—The small size and symmetry of the $^{+}N{=}C^{-}$: group should place only minimal steric demands on the migrating group. The results of the previous section suggest that electronic demands in the transition state for the rearrangement are small. In this connection it became interesting to speculate on the primacy of factors which determine the relative migratory rates of a series of alkylisonitriles. It was not clear, *ab initio*, whether the relative migratory rates in such a series would follow the order expected for decreasing bond dissociation energy,[12a] which is Me < Et < Pr-*i* ≈ Bu-*i* < Bu-*t*, which is also the Baker–Nathan order for stabilization of cationic character at the migrating carbon, and which is the order observed for the pinacol rearrangement,[12b] or whether the relative rates would be governed by statistical factors which have led several workers[12c,d] to propose a "ponderal effect" to rationalize the migratory tendencies of alkyl groups in some rearrangement reactions.

The observed first-order reaction rate constants for a series of alkyl isonitriles is shown in Table II. The reactions were conducted in small, sealed tubes at 200.0° with sufficient void to ensure complete vaporization of the liquid at this temperature. Sample tubes were removed at intervals of time, quenched by cooling, and retained until an entire run could be analyzed simultaneously. Analysis was made by the ^1H nmr and by gas–liquid partition chromatography on a column preconditioned by several injections of an isonitrile sample. Satisfactory first-order rate constants were obtained. The columns were calibrated by standard mixtures of the appropriate nitrile and isonitrile. Areas of peaks from duplicate injections were measured with a planimeter and averaged, and rate constants were calculated by least-squares analysis of the data obtained from a plot of log [(RNC) + (RCN)]/(RNC) *vs.* time. The observed rate sequence is inverted from that which might be expected based on bond energies or hyperconjugative stabilization of the transition state, and the reversal in order of the methyl and ethyl entries further complicates the sequence. This could indicate dominance of the activation entropy in determining the rate of the larger members of the series. This point will be developed more fully in the Discussion section of this paper.

TABLE II

FIRST-ORDER RATE CONSTANTS FOR THE GAS-PHASE THERMAL ISOMERIZATION OF ALKYL ISONITRILES AT 200.0 ± 0.5°

R, in R—N≡C	$10^5 k_1$, sec^{-1}	$10^5 k_1$, av	k_1, rel, of [$(CH_3)_3CNC$ = 1]
CH_3	7.75		
	7.15	7.45 ± 0.30	5.6
C_2H_5	10.1		
	10.6	10.4 ± 0.31	7.8
$(CH_3)_2CH$	3.62		
	3.42	3.52 ± 0.10	2.6
$C_2H_5(CH_3)CH$	3.45	3.45	2.6
$(CH_3)_3C$	1.33		
	1.35	1.34 ± 0.01	1.0

Experimental Section

(+)-2-Methylbutyric Acid (2).—(−)-*sec*-Butylcarbinol (1) was isolated from fusel oil by fractionation through a Todd column. The main contaminant in the oil was 3-methyl-1-butanol; the specific rotation of the *sec*-butylcarbinol was −6.0° (*c* 17.1, $CHCl_3$, 24°). The alcohol was oxidized by two procedures, one involving acidic dichromate[13] and the other utilizing basic permanganate[14] as the oxidant.

To a solution of 156 g (0.53 mole) of potassium dichromate in 1980 ml of water was slowly added 210 g of concentrated sulfuric acid. Then 60 g (0.68 mole) of (−)-*sec*-butylcarbinol was added over a 40-min period and the reaction mixture was heated at reflux for 2 hr after the addition was completed. The mixture was then steam distilled and the oily layer of the distillate was decanted. The aqueous phase of the distillate was first saturated with sodium chloride and then extracted four times with ether. The ether extracts were dried over sodium sulfate and the ether was removed on a steam bath. The residue was vacuum distilled to give 26.5 g (38%) of the acid, bp 77–78° (12 mm). A second similar reaction gave 27.5 g (40%) of the optically active acid.

Forty-four grams (0.5 mole) of (−)-*sec*-butylcarbinol was added over a 1-hr period to a solution of 14 g (0.25 mole) of potassium hydroxide, 117 g (0.74 mole) of potassium permanganate, and 2 l. of water. The mixture was stirred at reflux for another hour and then filtered to remove manganese dioxide. The solution was then extracted with ether to remove unreacted alcohol. The aqueous phase was treated with sodium sulfite, then acidified with hydrochloric acid and extracted with four 500-ml portions of ether. The ether extracts were dried over magnesium sulfate, and the ether was removed on a steam bath. The residue was vacuum distilled to give 29.1 g (57%) of the acid, bp 85° (11 mm). The products of three reactions were combined to give 90.2 g of the optically active acid, $[\alpha]^{25}D$ +17.5° (*c* 15, $CHCl_3$) [lit.[13,15] $[\alpha]^{24}D$ +17.5° (neat), $[\alpha]^{21}D$ +19.6 (neat)]. The optically active acid was converted to the methyl ester using 2,2-dimethoxypropane according to the method of Lorette and Brown.[16] Vapor chromatographic analysis (4-m, tricyanoethoxypropane column, 87°, retention volume 1.15×10^3 and 1.23×10^3 cc) of the ester indicated that it consisted of 92% optically active methyl 2-methylbutyrate and 8% inactive methyl 3-methylbutyrate. Thus the acid mixture obtained from the oxidation of the carbinol consisted of 92% 2-methylbutyric acid and 8% 3-methylbutyric acid.

Optically Active 2-Methylbutyramide (3).—To a solution of 45 g (0.44 mole) of (+)-2-methylbutyric acid and 44.5 g (0.44 mole) of triethylamine in 200 ml of ether cooled to 0° was added 47.5 g (0.44 mole) of ethyl chloroformate dropwise. The mixture was stirred at 0° for 2 hr and the solid was collected on a filter. The ether was removed on a steam bath and the residue was slowly added to cold, concentrated, aqueous ammonia. The

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(11) See Table I, footnote *a*.
(12) (a) T. L. Cottrell, "The Strengths of Chemical Bonds," 2nd ed, Butterworth and Co. (Publishers) Ltd., London, 1958; (b) R. M. Stiles and R. P. Mayer, *J. Am. Chem. Soc.*, **81**, 497 (1959); (c) V. P. de la Mare, L. Fowden, E. D. Hughes, C. K. Ingold, and J. D. H. Mackie, *J. Chem. Soc.*, 3200 (1965); (d) M. Wolfsberg, *Tetrahedron Letters*, 3405 (1964).
(13) M. Kharasch, I. Kuderna, and W. Nudenberg, *J. Org. Chem.*, **19**, 1285 (1954).
(14) F. L. Weissenborn, J. W. Bolger, D. B. Rosen, C. T. Mann, Jr., L. Johnson, and H. L. Holmes, *J. Am. Chem. Soc.*, **76**, 1792 (1954).
(15) A. Kjaer and S. E. Hansen, *Acta Chem. Scand.*, **11**, 898 (1957).
(16) N. B. Lorette and J. H. Brown, Jr., *J. Org. Chem.*, **24**, 261 (1959).

solution was concentrated under vacuum and the solid was collected on a filter. The white solid was recrystallized from ether to give 17 g (38%) of the amide, mp 103–106° uncor (lit.[17] mp 109.2–111°). The literature value is for material of low optical purity.

(+)-*sec*-Butylamine (4).—Forty-five grams (0.28 mole) of bromine was slowly added to a solution of 43.2 g (1.08 moles) of sodium hydroxide in 360 ml of water at 0°. Sixteen grams (0.16 mole) of optically active 2-methylbutyramide was added to the clear, yellow solution. The solution was slowly warmed to 50° and kept at this temperature for 1 hr. Then 50 ml of water was added and the reaction mixture was steam distilled into a slight excess of hydrochloric acid. The acidic steam distillate was evaporated to dryness under vacuum and the white solid was dissolved in 5 ml of water. The solution was made strongly basic with potassium hydroxide and an oily layer then separated. This mixture was fractionally distilled to give 5.9 g (50%) of the amine, bp 61–62.5°, $[\alpha]^{23}D$ +5.2° (*c* 9.3, $CHCl_3$) [lit.[18] $[\alpha]^{20}D$ +7.44° (neat)].

(+)-*sec*-Butylformamide (5).—A solution of 5.44 g (0.074 mole) of (+)-*sec*-butylamine, 10.9 g (0.147 mole) of ethyl formate, and a trace of *p*-toluenesulfonic acid monohydrate was heated at reflux for 16 hr. The excess ethyl formate and ethanol were removed by distillation. Vacuum distillation of the liquid residue gave 6.98 g (93%) of the formamide, bp 60–61° (0.5 mm), $[\alpha]^{23}D$ +15.8° (*c* 15.9, $CHCl_3$) [lit.[19] bp 110–111° (18 mm)].

(+)-*sec*-Butylisonitrile (6).[20]—To a solution of 13.2 g (0.0695 mole) of *p*-toluenesulfonyl chloride in 35.4 g (0.27 mole) of quinoline (distilled from zinc dust) was added very slowly 6.8 g (0.067 mole) of the formamide. The reaction mixture was heated to 65° and the pressure was reduced to 50 mm before the addition was started. The reaction was maintained at these conditions for 2 hr and a colorless liquid (1.65 g, 30%) was collected in a receiver cooled in a Dry Ice–acetone bath. This liquid was found to be 90% *sec*-butylisonitrile and the remainder thought to be inactive isobutylisonitrile by vapor chromatographic analysis. Correcting to 100% purity the following specific rotation was obtained, $[\alpha]^{24}D$ +48.5° (*c* 12.4, $CHCl_3$).

(+)-2-Methylbutyronitrile (7).—To a solution of 2.2 g (0.022 mole) of optically active α-methylbutyramide in 30 ml of anhydrous pyridine, cooled in an ice bath, was slowly added 3.88 g (0.025 mole) of phosphorus oxychloride. The mixture was stirred for 1 hr at 0° and then stirred at room temperature for 2 hr. A few milliliters of water was added cautiously and then reaction mixture was acidified with 2 *N* hydrochloric acid and extracted with four small portions of pentane. The pentane solution was dried over magnesium sulfate and the pentane was removed by slow fractional distillation. The residue was distilled to give 800 mg of a colorless liquid. Correcting to 100% purity for the presence of a small amount of pentane detected by vapor chromatography, the following specific rotation was obtained, $[\alpha]^{22}D$ +37.7° (*c* 17.0, $CHCl_3$). This value of +37.7° for the specific rotation of the nitrile agrees with the value obtained by two other groups[17,21] which converted optically active acid to optically active nitrile. Extrapolation of their results to 100% optical purity (using +19.6° as the specific rotation of optically pure acid)[15] gave values of 37.1 and 38.7° for the specific rotation of 2-methylbutyronitrile, respectively.

Thermal Rearrangement of (+)-*sec*-Butylisonitrile to (+)-2-Methylbutyronitrile at 200.0°.—After being degassed on a high-vacuum line, approximately 0.8 g of the optically active isonitrile was sealed in a glass tube which has been washed with pyridine and dried at 140° under high vacuum. The tube was heated at 200.0° for 24 hr. The liquid, which was dark brown, was added slowly to a mixture of 1 ml of concentrated hydrochloric acid and 10 g of ice in an ice bath and kept at this temperature for 1 hr. The mixture was extracted nine times with 1–2-ml portions of pentane. The pentane solution was dried over calcium hydride and the pentane was removed by fractional distillation to give 0.215 g of colorless liquid. Vapor chromatographic analysis indicated that no isonitrile was present. Correcting to 100% purity for a small amount of pentane detected by vapor phase chromatography, the nitrile had the following rotation: $[\alpha]^{24}D$ +32.4°. It has been reported[21] that the Hofmann rearrangement of α-benzylpropionamide proceeds with 100% retention of configuration. Allowing for this correction it was found that the liquid phase thermal rearrangement of this isonitrile to nitrile proceeds with at least 87% retention of configuration (100)(32.4/37.4)/0.96 = 87%.

Thermal Stability of (+)-2-Methylbutyronitrile (Control).—A sample of the nitrile heated at 200.0° for 18 hr gave the following rotation: $[\alpha]^{28}D$ +37.4° (*c* 15.6, $CHCl_3$). Thus, within experimental error of the measurement, there was no racemization of the nitrile at the temperature of the rearrangement.

Optical Stability of (+)-2-Methylbutyronitrile in The Presence of Methylisonitrile at 200.0° (Control).—A sample of (+)-2-methylbutyronitrile, $[\alpha]^{23}D$ +37.0° (*c* 14.6, $CHCl_3$), and an approximately equal volume of methylisonitrile were sealed under vacuum in a glass tube which had been rinsed with pyridine and dried at 140°. The tube was heated at 200.0° for 20 hr. The volatile portion of the mixture was transferred out of the tube *via* a high-vacuum line. The colorless liquid was subjected to vapor phase chromatography (polypropylene glycol on diatomaceous earth, 100°) and the 2-methylbutyronitrile was collected. It was transferred under high vacuum to separate it from column bleed. The nitrile, $[\alpha]^{24}D$ +28.8° (*c* 12.4, $CHCl_3$), had racemized 27% under conditions of the above reaction. There was no loss of optical activity for the (+)-2-methylbutyronitrile during the purification by vapor phase chromatography.

Cyclobutanecarbonitrile (11).—Cyclobutanecarbonitrile was prepared in a manner similar to that described by Hughes and Roberts.[22] To a flask containing 5.0 g (0.050 mole) of cyclobutanecarboxylic acid (Aldrich Chemical Co.) cooled in an ice bath was slowly added 8.35 g (0.070 mole) of thionyl chloride. The reaction mixture was stirred for 1 hr in an ice bath and then heated for 1 hr at 100°. The thionyl chloride was removed by distillation; the residue was vacuum distilled to give 4.64 g (78%) of colorless liquid, bp 79° (95 mm). The acid chloride (4.6 g, 0.039 mole) was slowly added to a twofold excess of cold, concentrated, aqueous ammonia. The mixture was extracted with four portions of chloroform; the chloroform was removed on a steam bath to give 2.05 g (53%) of a white solid, mp 153.8–155.3° uncor (lit.[23] mp 155°). A mixture of 2.0 g (0.020 mole) of the amide and 2.9 g (0.020 mole) of phosphorus pentoxide were thoroughly mixed and the flask was connected for distillation; the mixture was heated at 200–220° for 4 hr. At the end of this time, 0.717 g (44%) of a colorless liquid had distilled, $n^{24}D$ 1.4302 (lit.[24] $n^{16}D$ 1.4331). The cyclobutanecarbonitrile had an absorption maximum at 2240 cm^{-1}. Vapor phase chromatography (diisodecyl phthalate on diatomaceous earth, 88°) indicated that the sample was homogeneous.

Cyclobutylamine[25a] (8).—To a mixture of 63 ml of concentrated sulfuric acid, 235 ml of chloroform, and 21.1 g (0.21 mole) of cyclobutanecarboxylic acid (Aldrich Chemical Co.) heated to 45–55° was slowly added 26.2 g (0.403 mole) of sodium azide. The addition required 2.5 hr. The reaction mixture was then heated at 50–55° for 1.5 hr more. Two hundred grams of ice was added and the solution was basified with 50% aqueous sodium hydroxide. The reaction mixture was steam distilled, the distillate was collected in dilute hydrochloric acid. The steam distillate was concentrated under vacuum to give a white solid. A slurry of potassium hydroxide was added to the white solid and the mixture distilled to give 14.0 g of a colorless liquid, boiling at 79–81° uncor (lit.[25b] bp 82–83°). Vpc (polyethylene glycol on Teflon, 87°) of this liquid indicated that the amine was contaminated with less than 10% water. Cyclobutylamine has absorption at 3400–3100 (broad), 1615 (m), and 1585 cm^{-1} (m).

Cyclobutylformamide (9).—A solution of 14 g of the cyclobutylamine, 42 g (0.72 mole) of ethyl formate, and a catalytic amount of *p*-toluenesulfonic acid was heated at reflux for 23 hr. The reaction mixture was distilled to give 16.8 g of a colorless liquid, bp 72.8–75.0° uncor (0.8 mm). The formamide has absorption at 3330 (s), 1670 (s), and 1540 cm^{-1} (s). *Anal.* Calcd for C_5H_9NO: C, 60.57; H, 9.15; N, 14.13. Found: C, 60.61; H, 9.10; N, 14.09.

Cyclobutylisonitrile (10).—To a solution of 23.0 g (0.12 mole) of *p*-toluenesulfonyl chloride in 48 g (0.37 mole) of quinoline,

(17) H. M. Walborsky and F. M. Hornyak, *J. Am. Chem. Soc.*, **78**, 872 (1956).

(18) L. G. Thorne, *Chem. Ber.*, **36**, 582 (1903).

(19) W. Logemann, D. Artini, and R. Tosolini, *ibid.*, **91**, 2566 (1958).

(20) J. Casanova, Jr., R. E. Schuster, and N. D. Werner, *J. Chem. Soc.*, 4280 (1963).

(21) E. S. Wallis and S. C. Nagel, *J. Am. Chem. Soc.*, **53**, 2787 (1931).

(22) D. W. Hughes and J. C. Roberts, *J. Chem. Soc.*, 903 (1960).

(23) H. Normant and R. Voreux, *Compt. Rend.*, **231**, 703 (1950).

(24) A. W. Reitz and R. Skrabal, *Monatsh.*, **70**, 398 (1937).

(25) (a) N. D. Werner and J. Casanova, Jr., *Org. Syn.*, in press; (b) D. C. Iffland, G. X. Criner, M. Koral, F. J. Lotspeich, Z. B. Papanastassion, and S. M. White, Jr., *J. Am. Chem. Soc.*, **75**, 4044 (1953).

heated to 50° and connected for vacuum distillation with the receiver cooled in liquid nitrogen, was added 8.0 g (0.8 mole) of cyclobutylformamide over a 10-min period. The pressure of the system was maintained at 5–10 mm. The reaction mixture was heated for 0.5 hr after the addition of the formamide. Two vacuum-line transfers of the material collected in the liquid nitrogen trap gave 1.6 g (24%) of cyclobutylisonitrile. The cyclobutylisonitrile has strong absorption at 2140 cm^{-1}. Vapor phase chromatography of the cyclobutylisonitrile (diisodecyl phthalate on diatomaceous earth, 86°, retention volume 2.23 × 10^3 cc) indicated that the sample was homogeneous. *Anal.* Calcd for C_5H_7N: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.09; H, 8.66; N, 17.42.

Thermal Rearrangement of Cyclobutylisonitrile to Cyclobutanecarbonitrile.—A sample of cyclobutylisonitrile, sealed in a glass tube which had been rinsed with pyridine and dried at 140° under vacuum, was heated at 200.0° for 6 hr. Vapor phase chromatography of the heated sample (diisodecyl phthalate on diatomaceous earth, 88°) indicated that there was no cyclopropaneacetonitrile or allylcarbinyl cyanide formed, but only cyclobutanecarbonitrile (same retention time as an authentic sample).

A large sample of cyclobutylisonitrile, sealed in a glass tube (rinsed with pyridine and dried at 140°) under vacuum, was heated at 200° for 15 hr. The volatile material was transferred away from polymeric material in a high-vacuum line. The colorless liquid was subjected to vapor phase chromatography (polypropylene glycol on diatomaceous earth, 100°) and the cyclobutanecarbonitrile was collected. The infrared spectrum of the collected material was identical with that of an authentic sample.

Thermal Rearrangement of Cyclobutylisonitrile to Cyclobutanecarbonitrile as Followed by Nmr.—A sample of cyclobutylisonitrile was sealed under vacuum in an nmr tube (rinsed with pyridine) with TMS as an internal standard. The nmr spectrum of the unheated sample consisted of a quintet centered at 3.99 (from TMS) and a complex multiplet centered at 2.07 (from TMS), but no signals in the range 0.0–1.0 ppm. The area of the respective peaks was 1:6. The tube was then placed in a block maintained at 200°. After 1.75 hr at this temperature a new set of peaks centered at 3.0 ppm could be clearly discerned in the nmr spectrum. These new signals appeared as a quartet, but one of the signals of the expected quintet was probably obscured by the complex multiplet due to the remaining ring hydrogens. The half-life for the cyclobutylisonitrile–cyclobutanecarbonitrile rearrangement appeared to be 6 hr when the intensity of the nmr signals due to the α hydrogens of the respective compounds was compared visually. The sample was heated for a total of 9 hr at 200.0°. The nmr spectrum of the sample at the end of this time still did not show any signals in the region 0.9–1.0 ppm which would be due to cyclopropyl hydrogens.

The Reaction of Cyclopropaneacetonitrile with Ethylisonitrile and Allylcarbinyl Cyanide with Ethylisonitrile (Control).—Cyclopropaneacetonitrile and allylcarbinyl cyanide were isolated by preparative gas phase chromatography (Beckman Megachrome, polyethylene glycol column, 86°) from a mixture[26] containing these two compounds. Vapor phase chromatography (diisodecyl phthalate on diatomaceous earth, 88°) indicated that the purified cyclopropaneacetonitrile contained approximately 3% allycarbinyl cyanide. Approximately equal volumes of cyclopropaneacetonitrile and ethylisonitrile were sealed in a glass tube, rinsed with pyridine, dried at 140° under vacuum, and heated for 7.25 hr at 200°. Vapor phase chromatography of the reaction mixture indicated that no cyclobutanecarbonitrile or allylcarbinyl cyanide was formed. When this sample was mixed with authentic cyclobutanecarbonitrile and allylcarbinyl cyanide, three distinct peaks were obtained upon vapor phase chromatography (diisodecyl phthalate on diatomaceous earth, 88°, retention volume of allylcarbinyl cyanide, 2.47 × 10^3 ml, retention volume of cyclopropaneacetonitrile, 3.13 × 10^3 ml; retention volume of cyclobutanecarbonitrile, 3.64 × 10^3 ml).

The nmr spectrum of cyclopropaneacetonitrile (solution in $CDCl_3$ with $CHCl_3$ internal standard) has a doublet centered at 2.33 ppm (J = 6.4 cps) and a complex group of sharp lines between 0.2 and 1.3 ppm. The ratio of the areas of the respective peaks is 2:5.

(26) Sample generously supplied by A. Rosen, California Institute of Technology, Pasadena, Calif.

A sample of allylcarbinyl cyanide was sealed in a glass tube, rinsed with pyridine and dried at 140°, with an equal volume of ethylisonitrile and heated at 200.0° for 6 hr. Vapor phase chromatography of the reaction mixture indicated that no cyclopropaneacetonitrile or cyclobutanecarbonitrile was formed under these conditions.

Formanilide[27] (88%) had bp 88° (1 mm), mp 46° (Eastman).

Phenylisonitrile.[28a]—A solution of 13.5 g (0.11 mole) of formanilide and potassium *t*-butoxide prepared by adding 11.7 g (0.30 g-atom) of potassium to 140 ml of *t*-butoxide prepared by adding 11.7 g (0.30 g-atom) of potassium to 140 ml of *t*-butyl alcohol, was cooled in an ice–water bath and 10.2 g (0.067 mole) of phosphorous oxychloride was added dropwise over a period of 5 min. The solution was then heated to 50° for 5 min and cooled to room temperature, and 10 g of Dry Ice was added slowly. This solution was then poured into 750 ml of ice–water, and the aqueous phase was extracted with four 30-ml portions of pentane. The extracted material was washed with two 50-ml portions of ice–water and dried over sodium sulfate. Upon distillation of the extract under reduced pressure, 4.14 g (40%) of phenylisonitrile was collected, bp 55° (15 mm). The product immediately began turning blue.[29] Samples were distilled at room temperature in a high-vacuum line immediately before use.

***p*-Chloroformanilide.**—A solution of 29.4 g (0.23 mole) of *p*-chloroaniline and 34.0 g (0.46 mole) of ethyl formate was heated at reflux for 72 hr. The solution was evaporated and the solid was recrystallized from chloroform, yielding 21.4 g (60%) of the formamide, mp 101–102° (lit.[30] mp 102°), infrared maximum ($CHCl_3$) at 1689 cm^{-1} (C=O).

***p*-Chlorophenylisonitrile.**[28b]—To a solution, cooled in an ice–water bath, of 34.0 g (0.30 mole) of potassium *t*-butoxide (MSA Research Corp.), 113 g (1.53 mole) of *t*-butyl alcohol, and 15.6 g (0.10 mole) of *p*-chlorophenylformanilide was added 10.2 g (0.066 mole) of phosphorus oxychloride dropwise over a period of 5 min. The solution was then heated between 40 and 50° for 5 min and 10 g of Dry Ice was added slowly. The entire reaction mixture was then poured into 750 ml of ice–water. The solution was extracted with four 30-ml portions of pentane, washed with 50 ml of ice–water, and dried over anhydrous sodium sulfate. The pentane was removed under vacuum and the solid material was sublimed to yield 5.85 g (43%) of *p*-chlorophenylisonitrile, mp 73°, infrared maximum ($CHCl_3$) at 2150 cm^{-1} ($-\overset{+}{N}\equiv\overset{-}{C}$).

***p*-Methoxyformanilide.**—A solution of 24.6 g (0.20 mole) of *p*-anisidine, 29.6 g (0.40 mole) of ethyl formate, and a trace (~100 mg) of *p*-toluenesulfonic acid was heated at reflux for 16 hr. The solution was evaporated and the solid was recrystallized from chloroform, yielding 10.1 g (33%) of the formanilide, mp 80° (lit.[31] mp 80–81°), infrared maximum ($CHCl_3$) at 1692 cm^{-1} (C=O).

***p*-Methoxyphenylisonitrile.**[28b]—To a solution of 10.0 g (0.065 mole) of *p*-methoxyformanilide, cooled in an ice–water bath, 37.1 g (0.47 mole) of pyridine, and 13.0 ml (0.16 mole) of chloroform was added dropwise 6.12 g (0.40 mole) of phosphorus oxychloride. The solution was then allowed to stir at room temperature for 1.5 hr, at which time the solution was added to 55 ml of ice–water; the aqueous phase was extracted with 2–10-ml portions of chloroform. The extracted material was then dried and upon distillation under reduced pressure, 3.45 g (40%) *p*-methoxyphenylisonitrile was collected, bp 76° (1 mm), infrared maximum ($CHCl_3$) at 2137 cm^{-1}.

Kinetic Procedure. Proton Nmr Method.—Thick-walled 4.92-mm nmr tubes with a standard taper joint were employed for reaction vessels. Each sample tube was rinsed three times in reagent grade pyridine, dried at 90°, and pumped on a high-vacuum line to remove any traces of pyridine. To each sample tube was added 0.5 ml of anhydrous diglyme and 100 mg of the isonitrile. The samples were then degassed three times by a freeze–pump–melt cycle on a high-vacuum line and sealed under

(27) G. Tobias, *Ber.*, **15**, 2443 (1882).

(28) (a) I. Ugi, G. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, *Angew. Chem. Intern. Ed. Engl.*, **4**, 472 (1965); (b) I. Ugi and R. Meyr, *Chem. Ber.*, **93**, 239 (1960).

(29) The blue, nonvolatile reaction product of phenylisonitrile has been established to be the tetramer, the dianil of indigo [C. Grundmann, *ibid.*, **91**, 1380 (1858)].

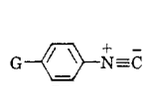
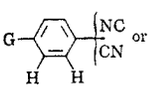
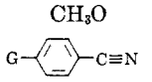
(30) F. D. Chattaway, K. J. P. Orton, and W. H. Hurtley, *Ber.*, **32**, 3635 (1899).

(31) E. Fröhlich and E. Wedekind, *ibid.*, **40**, 1009 (1907).

vacuum. Samples were placed in a 3-kg aluminum block in which holes had been drilled to hold sample tubes snugly. The ends of the holes were covered with glass wool to minimize temperature gradient effects. The reaction temperature was obtained by a fixed heater and maintained by an intermittent heater which was controlled by a mercury relay switch. The temperature could be maintained at 200.0 ± 0.5° for extended periods of time. Samples were removed at intervals of time, quenched by immersion in water, and the proton nmr could be determined immediately. The tubes were then returned to the heater for the next heating period. The total heat-cool cycle period represented less than 0.1% of 1 half-life, even with the fastest rearrangements. The integral spectrum of the isonitrile–nitrile mixture was determined several times and an average of the integral area was used. The nmr data are given in Table III. The area under the aromatic proton region was employed for the phenyl and *p*-chlorophenyl cases, and the area under the methyl peaks was employed for the *p*-methoxyphenyl case. The least-square rate constants were calculated as log [area(ArNC) + area(ArCN)]/area(ArNC) = kt, using a first-order rate constant computer program.[10] The results are presented in Table I.

TABLE III

^{1}H NMR CHEMICAL SHIFTS FOR AROMATIC ISONITRILES AND NITRILES IN DIGLYME

G, in	δ,[a] ppm	
		OCH_3
H	7.40	...
Cl	7.47	...
CH_3O	7.26	4.82
		
H[c]	7.70[b]	...
Cl[d]	7.75[b]	...
CH_3O[e]	7.37[b]	3.87

[a] Relative to internal tetramethylsilane in separate reference samples. [b] A complex multiplet centered at the value shown. [c] Eastman (487). [d] Eastman (2157). [e] Eastman (6216).

N-Methylformamide, Fluka A. G., Buchs, Switzerland, was used without further purification.

Methylisonitrile[20] was obtained from N-methylformamide (65% yield), bp 59–60°, 99+% (vapor phase chromatograph), infrared (gas) maximum at 2170 cm^{-1} (–$\overset{+}{N}\equiv\overset{-}{C}$). See Table IV for the proton resonance spectrum.

N-Ethylformamide (Eastman, 7369) was used without further purification.

Ethylisonitrile[20] was obtained from N-ethylformamide (50% yield) bp 78–79°, 99+% (vapor phase chromatography), infrared (gas) 2151 cm^{-1} (–$\overset{+}{N}\equiv\overset{-}{C}$). For proton nmr see Table IV.

N-Isopropylformamide.—A solution of 29.5 g (0.50 mole) of isopropylamine, 74.0 g (1.00 mole) of ethyl formate, and a trace of *p*-toluenesulfonic acid was heated at reflux for 16 hr in a nitrogen atmosphere. The formamide was distilled under reduced pressure and 39.3 g (90%) was collected, bp 92° (5 mm) (lit.[32] bp 220°).

Isopropylisonitrile.—A solution of 35.2 g (0.40 mole) of isopropylformamide, 179 g (2.27 mole) of pyridine, and 88 ml of pentane was cooled at 0 to 5° and 69.6 g (0.23 mole) of phosphorus oxychloride was added dropwise over a period of 45 min. The solution was then heated to 60° for 30 min and cooled to 0 to 5°, and 200 ml of ice–water was added. The aqueous phase was then extracted with four 30-ml portions of pentane. The extracted material was then dried over calcium hydride and distilled, yielding 8.25 g (30%) of isopropylisonitrile, bp 86–87°, 99+% (vapor phase chromatography) [lit.[33] bp 82–83° (750 mm)]; infrared (gas) showed 2127 cm^{-1} (–$\overset{+}{N}\equiv\overset{-}{C}$). For the proton nmr spectrum, see Table IV.

sec-**Butylformamide.**—A solution of 36.6 g (0.50 mole) of *sec*-butylamine and 74.0 g (1.00 mole) of ethyl formate was heated at reflux for 2 hr under a nitrogen atmosphere. The formamide was distilled under reduced pressure and 36.0 g (70%) was collected, bp 56° (0.35 mm), n^{25}D 1.4359 [lit.[34] bp 104–106° (12 mm), n^{20}D 1.4365].

sec-**Butylisonitrile.**[20]—A solution of 20.0 g (0.199 mole) of *sec*-butylformamide, 89.5 g (1.13 moles) of pyridine, and 44 ml of pentane was cooled at 0 to 5° and 34.8 g (0.11 mole) of phosphorus oxychloride was added dropwise over a period of 20 min. The solution was heated to 60° for 15 min and cooled to 0 to 5°, and 200 ml of ice–water was added. The aqueous layer then extracted with two 30-ml portions of pentane. The extracted material was dried and distilled, yielding 7.34 g (50%) of *sec*-butylisonitrile, bp 110–111°, 98% (vapor phase chromatography), infrared (CCl_4) 2125 cm^{-1} (–$\overset{+}{N}\equiv\overset{-}{C}$). For the proton nmr spectrum, see Table IV.

t-**Butylformamide.**—A solution of 54.8 g (0.75 mole) of *t*-butylamine and 92.5 g (1.25 moles) of ethyl formate was heated at reflux for 2 hr under a nitrogen atmosphere. The formamide was distilled under reduced pressure and 48.7 g (64%) was collected, bp 50° (0.025 mm), n^{24}D 1.4263 [lit.[34] bp 135–136° (107 mm), n^{20}D 1.4275].

t-**Butylisonitrile.**—A solution of 20.0 g (0.199 mole) of *t*-butylformamide, 89.5 g (1.14 mole) of pyridine, and 44 ml of pentane was cooled at 0 to 5°, and 34.8 g (0.114 mole) of phosphorus oxychloride was added dropwise over a period of 30 min. The solution was then heated to 60° for 15 min and cooled to 0 to 5°, and 200 ml of ice–water was added. The aqueous phase was then extracted with two 30-ml portions of pentane. The extracted material was then dried and distilled, yielding 12.1 g (61%) of *t*-butylisonitrile, bp 100° [lit.[35] bp 92–93° (750 mm), infrared (CCl_4) 2127 cm^{-1} (–$\overset{+}{N}\equiv\overset{-}{C}$)]. For the proton nmr spectrum, see Table IV.

Kinetic Procedure. Gas Chromatographic Method.—Samples of isonitriles (100 mg) were transferred into glass tubes 100 × 3.3-mm o.d. (1.8-mm i.d.) in a high-vacuum line. The tubes had previously been rinsed three times with reagent grade pyridine, dried at 90°, and pumped under high vacuum to remove traces of pyridine. The samples were sealed under vacuum and used immediately for thermal isomerization.

Samples were heated at 200.0 ± 0.5° as described earlier, removed at intervals of time, and quenched in a water bath. They were stored at 0° until ready for analysis. All analyses for given run were carried out in rapid sequence. The samples were analyzed on a 2-m polypropylene glycol column. Each sample was injected twice after an initial injection to condition the column.[36]

The area under both peaks in the chromatogram was measured using a planimeter,[37] and the retention volumes are shown in Table V. The average of two determinations was recorded. The peak area factors were weighed according to the chromographic results of known authentic mixtures of the nitrile and isonitrile. To check for possible rearrangement on the column, pure samples of the isonitriles were injected on the column under the same analytical conditions, and no evidence of the corresponding nitriles was detected. The least-square rate constants were calculated as log [area(RNC) + area(RCN)]/area(RNC) = kt, using a first-order rate constant program.[10] The results are presented in Table II. In two cases [R = CH_3, and R = $(CH_3)_3C$] the rates obtained by the vapor chromatographic

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(33) H. Feuer, H. Rubinstein, and A. T. Nielsen, *J. Org. Chem.*, **28**, 1107 (1958).

(34) U. S. Department of Agriculture, Agricultural Research Service, Entomological Research Branch, ARS-33-17 (1956) [*Chem. Abstr.*, **50**, 8125*d* (1956)].

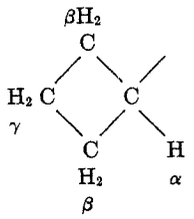
(35) L. Malatesta, *Gazz. Chim. Ital.*, **77**, 238 (1947).

(36) For reasons which are unclear, the first sample of an isonitrile injected into a column that had not been used for several hours failed to give any peak whatever. All subsequent injections gave peaks which were reproducible from the second run onward. Any isonitrile of the group studied here could be employed to thus "condition" the column for use with any other isonitrile.

(37) In a careful study of the precision of various integration methods, J. Gill (Varian-Aerograph) concluded that the planimetric method leads to a standard deviation ($\bar{\sigma}$) of 4.06% (private communication).

TABLE IV

^{1}H NMR SPECTRA OF SOME ALKYLISONITRILES

R, in RNC (neat liquids)	δ, ppm, relative to TMS internal standard				J, cps				
	α-H	β-H	γ-H	δ-H	$J_{N\alpha}$	$J_{N\beta}$	$J_{N\gamma}$	$J_{\alpha\beta}$	$J_{\alpha\delta}$
CH_3	2.73[a] (2.85)[b]	...	...	...	2.4 (2.7)[b]	...	...	...	...
CH_3CH_2 β α	3.39[c]	1.28[d]	...	...	2.0	2.4	...	7.3	...
$(CH_3)_2CH$ β α	3.69[e] (3.87)[b]	1.29[f] (1.45)[b]	...	...	(1.8)[b]	(2.6)[b]	...	(7.0)[b]	...
$CH_3CH_2C(CH_3)H$ γ β δ α	3.24[g]	1.62[g]	1.10[g]	1.34[h,i]	*j*	*j*	2.2	*j*	6.7
$(CH_3)_3C$ β	...	1.17[a] (1.44)[b]	...	...	...	2.4 (1.4)[b]	...	...	...
	3.99[k] (3.95)	(2.07)[l]	...	...	*j*	*j*	*j*	*j*	*j*

[a] Symmetrical, triplet. [b] P. Von R. Schleyer, *J. Chem. Phys.*, **35**, 1533 (1961) [CCl_4, TMS internal, 40 Mc/sec]; somewhat different values for the proton shifts have been reported recently [A. Loewenstein and Y. Margalit, *ibid.*, **69**, 4152 (1965)]. [c] Trebled quartet, ratio 1:1:1:2:2:2:2:2:2:1:1:1, total relative area = 2. [d] Trebled triplet, ratio 1:1:1:3:3:3:1:1:1, total relative area = 3. [e] Trebled heptet, ratio 1:1:1:3:3:3:5:5:5:7:7:7:5:5:5:3:3:3:1:1:1, total relative area = 1. [f] Trebled doublet, ratio 1:1:1:1:1:1, total relative area = 6. [g] Complex multiplet, centered at the value of δ specified. [h] Trebled doublet, ratio 1:1:1:1:1:1. [i] For the total spectrum, relative areas are 1:2:3:3 for α:β:γ:δ, respectively. [j] Not available from a first-order analysis of the spectrum. [k] Complex multiplet, total relative area = 1. [l] Complex multiplet, total relative area = 6.

TABLE V

VAPOR PHASE CHROMATOGRAPHIC BEHAVIOR OF SOME ALIPHATIC ISONITRILES AND NITRILES

R, in RNC or RCN[a]	Column temp, °C	Flow rate, cc/min	Retention vol, cc RNC	Retention vol, cc RCN
CH_3	75	70	292	422
C_2H_5	75	45	362	550
$(CH_3)_2CH$	100	90	297	421
$C_2H_5C(CH_3)H$	100	80	496	687
$(CH_3)_3C$	100	97	333	446

[a] Authentic samples of aliphatic nitriles used for standards were obtained commercially [CH_3CN, Eastman (488); C_2H_5CN, Eastman (528); $(CH_3)_2CHCN$, Eastman (P7253), and distilled before use] or prepared by dehydration of the appropriate amide (*vide infra*).

method were checked against those obtained by the proton nmr method (using *small* samples of neat liquid isonitriles to ensure gas phase reaction) and they agreed closely.

Discussion

Retention of optical activity in the isomerization of (+)-*sec*-butylisonitrile, the absence of carbon skeleton rearrangement in the isomerization of cyclobutylisonitrile, and the lack of a significant substituent effect on the rate of rearrangement of arylisonitriles are all observations which are consonant with a single picture for the transition state in the isonitrile–nitrile rearrangement. These features should be characteristic of a rearrangement in which the bond-breaking and bond-making processes are essentially synchronous. The question of continuity of bonding during this rearrangement may be considered in two parts. The first pertains to the degree of physical association maintained by the fragments during the course of the reaction. The second involves change in electronic character of the migrating group as it passes from the initial state to the transition state.

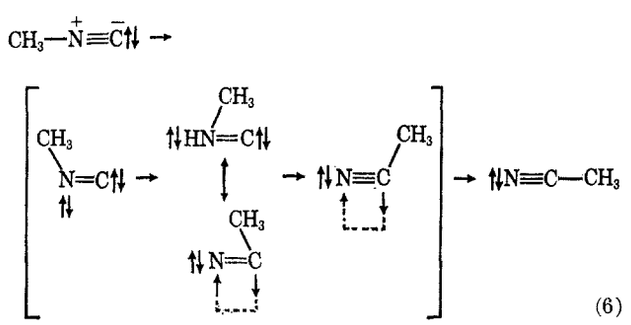
In connection with the first question, there are several lines of evidence which establish that the fragments remain within immediate range of each other during the entire isomerization process. Rearrangement of *p*-tolylisonitrile,[4a] *p*-methoxyphenylisonitrile, and *p*-chlorophenylisonitrile led to the corresponding nitriles, uncontaminated with the isomeric nitriles which would have resulted if positional rearrangement at the carbon fragment had accompanied functional group rearrangement. The conversion of (+)-*sec*-butylisonitrile to (+)-2-methylbutyronitrile, a reaction in which the absolute configuration of the asymmetric carbon atom is preserved, requires that an asymmetric environment be maintained throughout the reaction. The entropy of activation for the rearrangement measured by Kohlmaier and Rabinovitch[4a] is −4.8 eu for *p*-tolylisonitrile in the gas phase and is consistent with the intervention of a cyclic transition state. This conclusion is hardly surprising in view of the results of previous investigations dealing with this rearrangement and by analogy to the results encountered for all of the saturated rearrangements which have been investigated so far.[7] In particular, the Hofmann,[38a] Curtius,[38b] and Wolff[38c] rearrangements of optically active biphenyls without loss of optical activity show that interruption of bond integrity in these reactions, if it occurs at all, must be for a time shorter than is required for a molecular rotation.

The second question deals with changes in the electronic character of the migrating carbon atom. Several experiments suggest that little or no charge separation develops between the migrating carbon atom and the N≡C residue during the isomerization. The value of 4.5×10^{-4} sec^{-1} for the first-order rate constant in

(38) (a) E. S. Wallis and W. W. Moyer, *J. Am. Chem. Soc.*, **55**, 2598 (1933); (b) F. Bell, *J. Chem. Soc.*, 835 (1934); (c) J. F. Lane and E. S. Wallis, *J. Org. Chem.*, **6**, 443 (1941).

the *p*-tolylisonitrile rearrangement at 200° in Nujol is little different from the values of 2.4×10^{-4} sec^{-1}, 2.8×10^{-4} sec^{-1}, and 3.1×10^{-4} sec^{-1} obtained in this study for *p*-chlorophenyl-, phenyl-, and *p*-methoxyphenylisonitrile at 200° in diglyme, a solvent of much higher polarity. If charge separation developed in the transition state, the reactions conducted in the more polar solvent would be expected to be faster. Moreover, the gas phase rearrangement of *p*-tolyl isonitrile at 200° and 30 mm proceeds even more rapidly, with a rate constant of 7.5×10^{-4} sec^{-1}, and no solvent effects can be present in this case. This measurement appears to be already in the pressure-insensitive region.[4a]

The lack of carbon skeleton rearrangement during the isomerization of cyclobutylisonitrile, and the failure of variation in *para* substituents to significantly influence the rate of rearrangement in the aromatic series suggest little or no charge separation in the transition state. Orbital-rehybridization and electron-redistribution processes can function to always compensate for any electron imbalance that would otherwise develop during the migration. A valence-bond representation of this formalism is shown below. Equation 6 illustrates the rearrangement as a simple



(6)

extension of a C–N–C bending vibration. Resonance structures for the transition state are intended to show that with an appropriate amount of addition π bonding, it is not necessary to write charge-separated structures. The two-electron, three-centered bond present in electron-deficient bonds such as are proposed for the pinacol rearrangement does not adequately describe the electronic environment of the migrating group in this case. Hence, the migrating carbon is never electron deficient. Viewed in this way, the magnitude of the polar substituents effect in the aromatic isonitrile rearrangement is reasonable. Since no atoms other than those three immediately involved in the rearrangement are undergoing a covalency change, timing in the departure or entry of other groups is not a consideration in this reaction. Electron compensation for developing charge separation will be virtually instantaneous with respect to the time required for atomic motion. The result in the present case stands in marked contrast to the polar substituent effects observed in saturated rearrangements. It is generally agreed that free, neutral, electron-deficient species are not intermediates in saturated rearrangements.[7a,39] Most values for ρ for saturated rearrangements vary between -1 and -4, indicating a marked acceleration by electron-donating substituents. However, a wide range of values of ρ is encountered even for a single type of reaction under different conditions,[39b] suggesting that the transition state for the final rearrangement step may lie virtually anywhere along the reaction coordinate between extensive participation and little or no participation of the migrating group in facilitating the departure of the leaving group. It would appear that the value of ρ appropriate to the isonitrile–nitrile rearrangement could represent an upper limit for ρ in saturated rearrangements, representing the case in which no participation occurs. A value of approximately -0.3 for ρ in the present case is nearly identical with the value of -0.25 reported for the Beckmann rearrangement of benzophenone oxime in polyphosphoric acid. This has been cited as a case in which a neutral, electron-deficient intermediate could be present.[39b]

Another indication that the transition state for this rearrangement is not substantially stabilized by electron donation from the migrating group is available from the relative migratory rates of the alkylisonitriles. The order observed in the present case, Bu-*t* < Bu-*i* ~ Pr-*i* < Me < Et (see Table II), is neither the Baker–Nathan order of hyperconjugative stabilization, nor the order observed in Wagner–Meerwein rearrangements,[12b] in which the bonding to the migrating group in the transition state is most certainly electron deficient, nor the order anticipated from an estimate of bond dissociation energies of the $>$C–N$^+$ bond in the starting isonitriles.[12a] If there is little or no electron deficiency at the migrating carbon atom during the isonitrile rearrangement, then hyperconjugative stabilization of the transition state will not be important. The observed sequence for alkyl migration is that which would be expected if the reaction rates were entropy controlled. It is reasonable that since the rotation about the bond connecting the migrating carbon to the NC fragment should be converted to vibrations in the transition state, the entropy of activation should be more negative for the substituent with the larger moment of inertia. The reversion of entropy control to enthalpy control would be said to occur at the ethyl substituent. Determination of activation parameters for the entire alkyl series would provide a test for this speculation. Data which will resolve this question are the subject of current investigation by other laboratories.[40] Another rationalization of the order of migratory rates in the alkyl series is founded on the assumption that the steric requirements of the cyano group for nonbonded interaction are rather larger than might be anticipated on an *a priori* basis. If this were true, then clearly crowding in the transition state for the *t*-butylisonitrile would exceed that for methylisonitrile, whereas similar effects would not be important in the ground state for either of these compounds. (See Chart III.) While this reasoning can account successfully for the gross rate trend in the alkyl series, it does not recognize the unusual inversion of methyl and ethyl.

(39) (a) W. Lwowski has recently provided clear evidence for the absence of nitrenes in the thermal Curtius rearrangement [W. Lwowski and G. T. Tisue, *J. Am. Chem. Soc.*, **87**, 4022 (1965)]; (b) See however, P. T. Lansbury and N. R. Mancuso [*Tetrahedron Letters*, 2445 (1965)] for an example of the Beckmann rearrangement [D. E. Pearson and R. M. Stone, *J. Am. Chem. Soc.*, **83**, 1715 (1961)] which the former authors regard as proceeding with very little participation from the migrating group.

(40) B. S. Rabinovitch, private communication.

CHART III

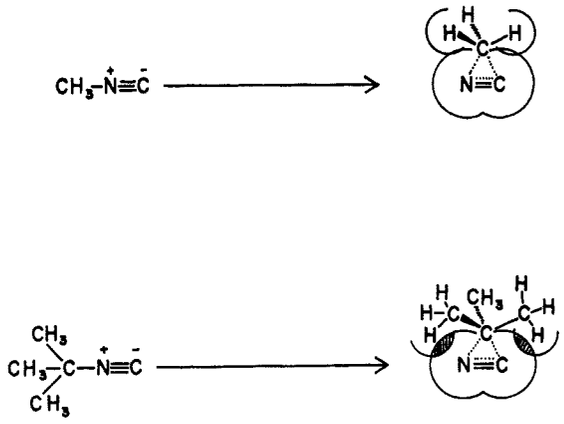
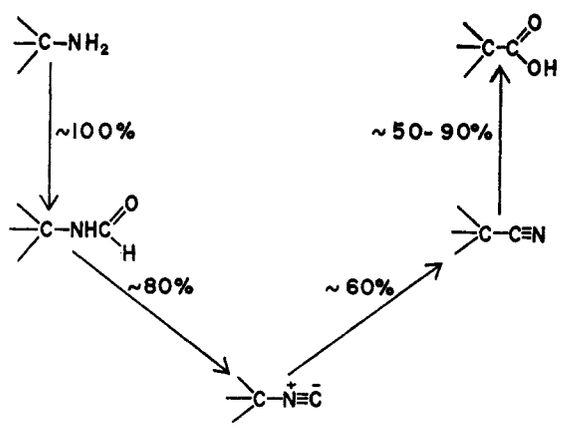


CHART IV



The conversion of optically active amines stereospecifically into optically active carboxylic acids is a desirable but heretofor difficult transformation. The present work suggests that a synthetic route which utilizes the isonitrile–nitrile rearrangement for such a sequence, shown in Chart IV, is a practical method to accomplish this objective. Subject to the obvious limitation of partial racemization in compounds which possess an α-hydrogen atom, and to the additional disadvantage of manipulation of a vile-smelling substance, this sequence of reactions nevertheless represents a potentially useful method of accomplishing an otherwise difficult transformation. Thus, it constitutes a process which compliments the many reactions known for the conversion of optically active carboxylic acids into optically active amines.[7]

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The Solvolysis of Derivatives of 3-Azabicyclo[3.3.1]nonane[1]

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The solvolyses of the amino alcohol *p*-nitrobenzoate esters **8–13** have been studied in aqueous dioxane. The relative rates of reaction of each of the pairs of epimers are similar, suggesting that in none of the cases does the nonbonded electron pair on nitrogen provide substantial aid to ionization of the C–O bond. The products from the secondary alcohol derivatives **8** and **11** correspond to simple ester hydrolysis while the products from the tertiary phenylcarbinol derivatives **10** and **13** correspond to ionization followed by fragmentation. The tertiary methylcarbinol derivatives **9** and **12** are intermediate in behavior, giving products expected of ester hydrolysis and ionization. One epimer (**12**) also undergoes a competing elimination reaction to form the bicyclic olefin **49**. The results of these and earlier studies are interpreted as evidence for the existence of these bicyclic molecules primarily in chair–chair conformation **14a** with a lesser contribution from chair–boat conformation **14d**.

Extensive studies of the solvolytic ionization of various γ-amino alkyl halides (or esters) by Grob and co-workers[2] have demonstrated that the amino function may assist ionization of the alkyl halide when certain geometrical requirements are met. The most common manifestation of this assisted ionization is the synchronous fragmentation reaction which may occur when the nonbonded electron pair on nitrogen and the C–X bond bear one of the geometrical relationships illustrated in structures **1** and **2**. A less common (and apparently energetically less favorable) type of assistance is the backside displacement process (as in **3**) which can lead to nucleophilic displacement of the halogen atom with over-all retention of configuration.[2,3] When one of the above processes is not geometrically favorable, then ionization of the alkyl halide is not significantly aided by the amino function. The initially formed carbonium ion intermediate **7** may undergo subsequent fragmentation (to form **4**), ring closure (to form **5**), loss of a proton (elimination), or reaction with a nucleophile (substitution). (See Scheme I.)

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(2) (a) C. A Grob, *Experientia*, **13**, 126 (1957); (b) C. A. Grob in "Theoretical Organic Chemistry, Papers Presented to the Kekulé Symposium," Butterworth and Co. (Publishers) Ltd., London, 1959, pp 114–126; (c) C. A. Grob, *Bull. Soc. Chim. France*, 1360 (1960); (d) C. A. Grob, *Gazz. Chim. Ital.*, **92**, 902 (1962); (e) R. D'Arcy, C. A. Grob, T. Kaffenberger, and V. Krasnobajew, *Helv. Chim. Acta*, **49**, 185 (1966); (f) C. A. Grob, R. M. Hoegerle, and M. Ohta, *ibid.*, **45**, 1823 (1962).

(3) (a) S. Archer, M. R. Bell, T. R. Lewis, J. W. Schulenberg, and M. J. Unser, *J. Am. Chem. Soc.*, **79**, 6337 (1957); **80**, 4677 (1958); (b) also see S. Archer, T. R. Lewis, M. R. Bell, and J. W. Schulenberg, *ibid.* **83**, 2386 (1961).