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Final Technical Report

Research on the Effects of Substituents on the Stability of Cyclic Organic Compounds

Contract Nonr-723(00)

for the period

February 1, 1952 to January 31, 1954

by

Ronald F. Brown, Principal Investigator

and

Norman M. van Gulick, Research Assistant

The Department of Chemistry

University of Southern California

Los Angeles 7, California

April 30, 1954

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Preface

This "Final Report" is final only in the sense that it covers the period for which the contract with the Office of Naval Research specified. The problem is by no means resolved. The synthetic aspects of the problem are pretty well worked out although one or two questions remain in getting to the 4-bromo-2,2-diphenyl, and di-p-tolylbutylamine hydrobromides. We were unable to do as much kinetic work as was expected because of the time demand of the many difficulties encountered in the synthetic work. Nevertheless, enough progress was made on the kinetics to point out the necessity of obtaining very precise hydrogen ion concentrations of the buffers used and to indicate ultimate success in the entire undertaking. With this in mind, we plan to submit a request for continued support of this project in the near future.

This report is based on the Ph.D. dissertation submitted to the Graduate School of the University of Southern California by Norman M. van Gulick in partial fulfillment of the requirements for the Ph.D. degree. As such, all of the preliminary work on the problem done before the contract was negotiated is included to give a complete picture.

It is a pleasure to acknowledge the support of the Office of Naval Research for this work, without which progress would have been quite slow. The pleasant cooperation of all representatives of the ONR should also be mentioned as contributing to the progress attained. And the satisfaction of watching the development of the research assistant from an inexperienced worker into a collaborator who knew how to make things work, and who had more than a share in originating ideas is the greatest recompense of academic work. In no small measure is the success of this project due to Mr., now Dr., van Gulick.

Ronald F. Brown

LIST OF TABLES

TABLE		Page
I.	Summary of Kinetic Studies	31
II.	$C_6H_5OCH_2CH_2CR_2CN$	55
III.	$C_6H_5OCH_2CH_2CR_2CH_2NH_2$ and hydrobromides	56
IV.	$BrCH_2CH_2CR_2CH_2NH_2 \cdot HBr$	61
V.	3,3-Disubstitutedpyrrolidines	61

TABLE OF CONTENTS

CHAPTER		Page
I.	INTRODUCTION	1
II.	DISCUSSION	7
	A. Synthetic Aspects of the Investigation	7
	4-Bromobutylamine hydrobromide	7
	4-Bromo-1,1-dimethylbutylamine hydrobromide	9
	4-Bromo-2,2-dialkylbutylamine hydrobromide	17
	4-Bromo-3,3-dimethylbutylamine hydrobromide	23
	B. Kinetic Aspects of the Investigation	28
III.	EXPERIMENTAL	36
	4-Phenoxybutyronitrile	36
	4-Phenoxybutylamine	36
	4-Bromobutylamine hydrobromide	36
	Methyl 3-cyanopropionate	37
	4-Aminobutanol	37
	Hexamethylenetetramine adduct of tetramethylene dibromide	38
	Methyl 4-methyl-4-nitropentanoate	38
	4-Hydroxy-1,1-dimethylbutylamine	39
	4-Bromo-1,1-dimethylbutylamine	40
	2,2-Dimethylpyrrolidine hydrobromide	41
	1-Butyl-2,2-dimethylpyrrolidine hydrobromide	42
	2-Methylpentanol-2	42
	2-Methylpentylamine-2	43

CHAPTER Page

N-Benzenesulfonyl -2-methylpentylamine-2 43

3-Ethoxypropanol 44

3-Ethoxypropyl bromide 45

5-Ethoxy-2-methylpentanol-2 45

4-Ethoxy-1,1-dimethylbutylamine 46

2-Chloro-5-ethoxy-2-methylpentane 46

5-Ethoxy-2,2-dimethylvalerophenone 47

4-Amino-2,2-dimethylpentanoic acid hydrochloride . . . 48

2,2-Dimethyl-4-pentenamide 48

N-Benzyl-2,2-dimethyl-4-pentenamide 49

Pivalophenone 50

Pivalanilide 50

N-t-Butylbenzamide 50

Beckmann rearrangement of pivalophenone oxime 50

2,2-Dimethyl-5-phenoxyvalerophenone 51

2,2-Dimethyl-5-phenoxyvalerophenone oxime 51

N-Benzoly-1,1-dimethyl-4-phenoxybutylamine 52

Acid hydrolysis of N-t-butylbenzamide and t-butylamine . 54

Alpha-alkylation of nitriles 54

Dimethyl- and diethylacetonitriles 57

Di-p-tolylacetic acid and nitrile 58

Diisopropylacetonitrile 59

4-Bromo-2,2-dialkylbutylamine hydrobromides 59

As-Dimethylsuccinic anhydride 61

As-Dimethylsuccinimide 62

CHAPTER Page

3,3-Dimethylpyrrolidine and its benzenesulfonamide . . . 63
3,3-Dimethylglutaric anhydride 64
4,4-Dimethylpyrrolidone-2 65
Isopropylidinecyanoacetic ester 66
Ethyl 2-cyano-3,3-dimethyl-4-nitrobutanoate 66
Basic hydrolysis of ethyl 2-cyano-3,3-dimethyl-4-nitrobutanoate 67
Acid hydrolysis of ethyl-2-cyano-3,3-dimethyl-4-nitrobutanoate 68
The Curtius reaction of 3,3-dimethylglutaric anhydride . 69
The preparation and Hofmann degradation of 3,3-dimethyl-glutaramic acid 69
The preparation and Hofmann degradation of methyl 3,3-dimethylglutaramate 70
2,2-Dimethylbutanediol-1,4 71
1,4-Dibromo-2,2-dimethylbutane 72
1-Bromo-2,2-dimethyl-4-phthalimidobutane 72
4-Bromo-3,3-dimethylbutylamine hydrobromide 72
Hydroxypivalaldehyde 73
2,2-Dimethyl-4-nitro-3-butenol-1 73
3,3-Dimethyl-4-hydroxybutylamine 73
4-Bromo-3,3-dimethylbutylamine hydrobromide 73
Acetoxypivalaldehyde 74
The attempted condensation of acetoxypivalaldehyde with nitromethane 74
Opening of as-dimethylsuccinic anhydride with amines . . 74

CHAPTER Page

2,2-Dimethylpropanediol-1,3 76

2,2-Dimethylpropanediol-1,3 monotosylate 77

2,2-Dimethyl-4-methoxypropanol-1 77

2,2-Dimethyl-4-methoxybutyronitrile 78

2,2-Dimethyl-4-methoxybutylamine 78

Methyl alpha-bromoisobutyrate 79

Kinetic studies 79

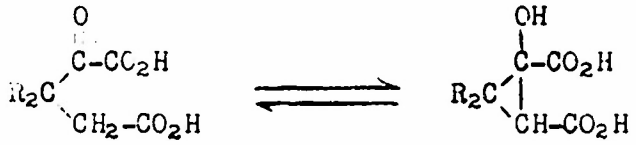
IV. SUMMARY 88

BIBLIOGRAPHY 94

I. INTRODUCTION

It is a well-known general rule that the introduction of alkyl groups, particularly geminal alkyl groups, into a suitably chosen bifunctional compound strikingly enhances the tendency of that compound to cyclize. Conversely, a geminally substituted cyclic compound resists scission to a far greater degree than does the parent unsubstituted cycle. Since it is beyond the scope of this introduction to present a full survey of the voluminous literature pertaining to this phenomenon as it obtains in cyclic anhydrides, lactones, imides, etc., only a few selected examples of a more interesting nature shall be given.

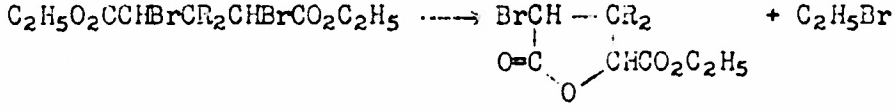
The equilibrium constant for the following ketocyclol tautomeric reaction is R-dependent[1]



I II

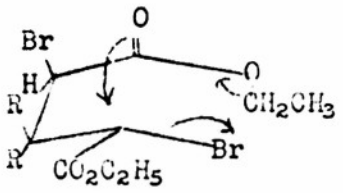
Thus, it is found that when R is hydrogen or methyl, the equilibrium is shifted so far to the left that only the keto acid (I) may be detected. On the other hand, if R_2 is pentamethylene, then only the cyclic modification (II) may be detected. However, if R is either ethyl or n-propyl, then both forms exist together in the equilibrium mixture.

It has been found that brominated glutaric esters such as III are thermally unstable with respect to the lactone (IV) and ethyl bromide.[2]



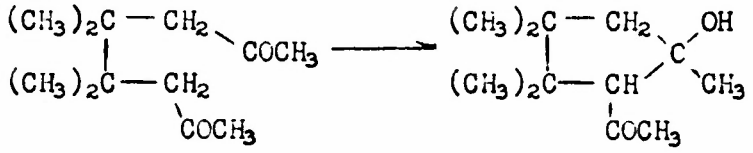
III IV

If R is hydrogen, the reaction fails to occur, but if R_2 is dimethyl, diethyl, or tetramethylene, traces of the lactone may be isolated, while if R_2 is pentamethylene, the reaction goes to completion upon slow distillation. This reaction is given as an example of the geminal alkyl effect, since it seems reasonable that the reaction may involve a bicyclic transition state such as V



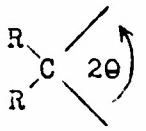
V

It is known that 1,6-diketones are quite stable as such, although they do cyclize with ease in the presence of acids or bases. However, the tetramethyl ketone (VI) exists only in the cyclic form (VII).[3]



VI VII

Ingold and Thorpe, publishing numerous papers in the years from 1915 through 1929, were the principal workers in this field and, in fact, were the only investigators to offer an explanation for this phenomenon. Thus, in 1915 the geminal alkyl effect was postulated to be principally steric in nature and the "Valency Deflection Hypothesis' was proposed.[4] According to this hypothesis, a carbon atom will be strictly tetrahedral only if its four substituents are identical. Otherwise, the valence angles will adjust themselves according to the atomic volumes of the substituents. If the geminal substituent is a cyclic polymethylene radical, then the external valence angles will adjust themselves in the remaining space.



VIII

Some of the calculated valence angles (2θ of figure VIII), as obtained by these workers, are given in Table 1. The starred cyclic groups were assumed to be planar, an error which was corrected in a later paper.[5]

Table 1

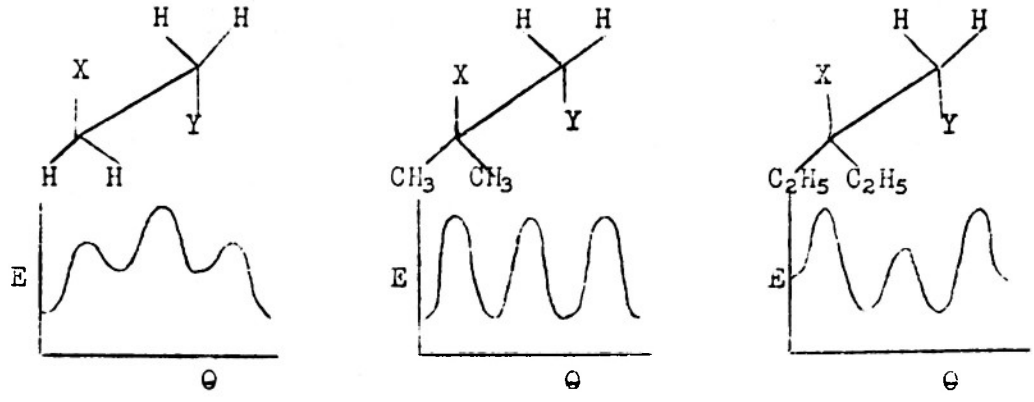
R_2	$2\theta^o$	R_2	$2\theta^o$	R_2	$2\theta^o$
H_2	115.3	$(CH_2)_2$	116.9	$(CH_2)_5^+$	107.2
$(CH_3)_2$	109.5	$(CH_2)_3$	113.0	$(CH_2)_6^+$	105.3
$(C_2H_5)_2$	107	$(CH_2)_4$	109.7	$(CH_2)_7$	103.7

This hypothesis was used with success to give qualitative correlations between the valence angle 2θ and the ionization constants of malonic[6] and glutaric[7] acids, and the hydrolysis rates[8] and dipole moments[9] of malonic esters. Even more spectacular was the demonstration of a linear relationship between the calculated valence angle, 2θ, and the logarithm of the velocity constant for alkaline hydrolysis of 5,5-dialkyl-hydantoins.[10]

The "Valency Deflection Hypothesis" survived a minor attack by W. Huckel[11] and still stands today in opposition to modern bond angle measurements. Indeed, the latest "substantiation" of this hypothesis appeared in 1942.[9]

It may not be amiss to consider a possible alternative to the "deflection hypothesis" at this point. Certainly it would be unwise to assume that the bond angles of a carbon atom are absolutely constant regardless of the nature of the substituents, but bond deflection, if it exists, must certainly be a second order effect of small magnitude in comparison to the profound effect of substitution on rotational isomerism. Of course, in the event that the geminal substituent is either the di- or trimethylene group, valency deflection must be considered as well as rotational isomerism, since the external bond angles are greater than tetrahedral for these cases.[12,13] Since cyclization requires the formation of a cyclic transition state from a molecule, presumably in the ground state lowest energy linear configuration, by a process of bond rotation, it is clearly seen that rotational energy barriers of a steric nature effectively contribute to the ΔH^+ of cyclization. Thus, figures X and XI show the expected effect of progressively increasing the size of the geminal substituents upon the shape of the energy-configuration curve of the parent compound (I). The abscissas represent the angle of bond rotation with respect to the reference configurations indicated. The corresponding configurational energies are plotted on the ordinates in terms of completely arbitrary and mutually independent scales. The radicals X and Y are functions which for the sake of argument are taken to be equal to methyl

in bulk, and which can interact to form a cycle. The formation of the transition state requires a rotation of 180° from the reference position and the absorption of energy in the amount of ΔH^{+}_{rot}.



IX X XI

While it is impossible to assess the relative magnitudes of ΔH^{+}_{rot} in this series, undoubtedly there is a trend of increasing or decreasing ΔH^{+}_{rot} with increasing substituent bulk. Entropy effects are more evident, however, since the angular distance between X and Y in the ground state configuration would decrease with increasing bulk of the geminal groups and thence the decrease in entropy on going into the transition state would likewise become smaller. For a series of compounds differing only in the bulk of the geminal group, it seems reasonable to write, as an approximation,

$$\Delta H^{+} = (\Delta H^{+}_{E} + \Delta H^{+}_{I} + \Delta H^{+}_{D} + \Delta H^{+}_{rot} + \cdots) \cong (\Delta H^{+}_{rot} + C).$$

ΔH^{+}_{E} refers to the energies of the bonds being formed and broken; ΔH^{+}_{I} refers to the inductive effect of the substituents relative to hydrogen which would be reasonably constant for alkyl groups in the middle of a long chain, and ΔH^{+}_{D} refers to bond angle deformation in the event that the ring being formed has fewer than five members. For each of the ΔH terms there is a corresponding ΔS term and so $\Delta S^{+} = \Sigma(\Delta S^{+}_{n}) \cong (\Delta S^{+}_{rot} + C)$ likewise. Further speculation without quantitative data is unwarranted, however, and the acquisition of such quantitative data is the express purpose of the investigation now underway in these laboratories. To this end, then, it was decided to examine the variation of ΔH^{+} and ΔS^{+} for a suitable cyclization reaction as influenced by geminal substituents. A suitable reaction should be

mechanistically simple, free from side reactions, and the ring closing operation must necessarily be the rate determining step. Among others, a family of reactions which meet these criteria are the cyclizations of halo carboxylic acids, halohydrins, halothiols, and halo amines to give, respectively, lactones,[14] epoxides, cyclic sulfides, and cyclic imines.[15] The halo amine system was selected not only because Freundlich[16] demonstrated that the cyclization is first order for the unsubstituted halo amines and that it is irreversible if the ring formed has more than three members and free from side reactions, if the ring formed has five or six members, but also because of the relatively greater synthetic availability of aliphatic amines over other classes of compounds. Thus, some of the general methods of preparing aliphatic amines involve reduction of nitriles, amides, oximes, and nitro compounds; reductive amination of carbonyl compounds; alkylation of ammonia and ammonia derivatives; reaction of Grignard reagents with methoxyamine; Hofmann rearrangement of amides; and Beckmann rearrangement of oximes. More specifically, the 4-bromobutylamine system was selected because of its large cyclization rate constant and because the product, a five-membered ring, is the largest planar ring possible. This planarity simplifies transition state geometry, and furthermore, a five-membered ring is large enough to allow ample opportunity for substitution. Unfortunately, the irreversibility of the system does not allow a study of ring stability. To study the effect of positional geminal substitution, it would be necessary to prepare 1,1-, 2,2-, and 3,3-dimethyl-4-bromobutylamines. The effect of the bulk of the geminal substituent would be shown by a comparison of 4-bromobutylamine, and 2,2-dimethyl-, 2,2-diethyl-, and 2,2-diisopropyl-4-bromobutylamines. While examination of 2,2-diphenyl-and-di-p-tolyl-4-bromobutylamines would allow a decision to be made as to the magnitude of inductive effects while steric effects were held constant.

Unfortunately, we were not able to bring the investigation to a conclusion because of the time spent in overcoming the many difficulties encountered during the preparation of the various 4-bromobutylamines. The syntheses of these difficulty accessible compounds demonstrate definite limitations in many of the conventional methods for the preparation of quaternary-carbon compounds and make a valuable contribution to the chemistry of sterically hindered molecules.

We did begin the kinetic study. The results are given of the rate studies at 30° with various buffers. However, work at other temperatures and a continuation of the studies with various buffers is necessary to an understanding of the very interesting results obtained to date.

II. DISCUSSION

A. Synthetic aspects of the investigation.

The parent compound of the series, 4-bromobutylamine hydrobromide (II), is the only member which has been prepared previously. Surprisingly, Freundlich, who studied the rate of cyclization of this compound,[16] never described the method of preparation nor the properties of the material which he used. However, both Blank[17] and von Braun[18] prepared the bromo amine salt (II) from 4-phenoxybutylamine (I) by cleavage with hydrobromic acid. In both cases the product was described only as a "hygroscopic solid."

$$C_6H_5OCH_2CH_2CH_2Br \xrightarrow{KCN} C_6H_5OCH_2CH_2CH_2CN \xrightarrow[ROH]{Na}$$

$$C_6H_5OCH_2CH_2CH_2CH_2NH_2 \xrightarrow{aq.\ HBr} BrCH_2CH_2CH_2CH_2NH_2 \cdot HBr$$

I II

Repetition of this sequence afforded a good yield of 4-bromobutylamine hydrobromide (II) which was adequately characterized.

Another possible sequence for the preparation of 4-bromobutylamine hydrobromide (II) was investigated.

$$CH_2=CHCO_2CH_3 \xrightarrow{KCN} NCCH_2CH_2CO_2CH_3$$

$$\text{III} \downarrow LiAlH_4$$

$$NH_2CH_2CH_2CH_2CH_2OH \xrightarrow{aq.\ HBr} \text{II}$$

IV

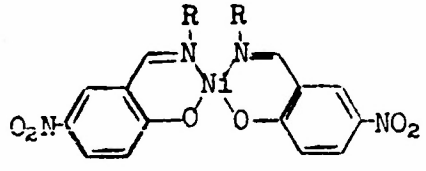
Unfortunately, a low yield of 20% in the reduction step (done early in the work) caused the method to be abandoned. This low yield apparently was due to isolation difficulties, since the amino alcohol (IV) proved to be so water-soluble that it could not be extracted adequately from aqueous systems. However, in view of our development of a technique for decomposing lithium aluminum hydride reduction mixtures with a limited quantity of saturated aqueous sodium chloride solution to give high yields of amino alcohols, it would seem that this sequence, starting from readily available methyl acrylate, is potentially superior to the method of Blank.

The Delepine method[19] for the preparation of amines by hydrolysis of the adducts formed from alkyl halides and hexamethylenetetramine (Hex) suggested a short and simple synthesis of 4-bromobutylamine hydrobromide (II):

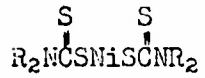
$$Br(CH_2)_4Br \xrightarrow{Hex} \underset{V}{Br(CH_2)_4(Hex)^+ Br^-} \xrightarrow{HBr} \quad II$$

Although the quaternary adduct (V) was obtained in quantitative yield by allowing a chloroform slurry of the reactants to stand for a week at room temperature, so much difficulty was experienced in the subsequent hydrolysis that this otherwise elegant synthesis failed. Even prolonged treatment with 48% hydrobromic acid at the boiling point failed to hydrolyse the adduct completely, and dark colored tars which smelled of formaldehyde were invariably produced.

Treatment of 4-bromobutylamine hydrobromide with benzenesulfonyl chloride and aqueous sodium hydroxide under the conditions of the Hinsberg test gave N-benzenesulfonylpyrrolidine. Cyclization presumably occurred before the substitution with benzenesulfonyl chloride since 4-bromobutylamine in the free state has a half-life of approximately one second.[16] Thus, the Hinsberg test failed as such when applied to bromo butyl amines, although it does yield useful derivatives. The nickel tests for distinguishing among primary, secondary, and tertiary amines[20] were also misleading when applied to bromo butyl amines. The nickel test for primary amines depends upon the fact that primary amines react instantly with an aqueous triethanolamine solution of nickel chloride and 5-nitrosalicylaldehyde to give insoluble complexes (VI). Secondary amines, but not primary or tertiary amines, react instantly with an aqueous ammoniacal solution of nickel chloride saturated with carbon disulfide to give insoluble nickel dithiocarbamates (VII).



VI



VII

These tests are considered general and reliable,[20] but since the test media were alkaline, they failed to give conclusive results with bromo amines.

(Furthermore, as will be seen, these tests sometimes failed with geminally alkylated amines.) Thus, 4-bromobutylamine hydrobromide gave an instantaneous test for a primary amine and a slow (one hour) test for a secondary amine.

4-Bromo-1,1-dimethylbutylamine hydrobromide (X) was successfully prepared by the sequence:

$$CH_2{=}CHCO_2CH_3 \xrightarrow[\text{base}]{(CH_3)_2CHNO_2} O_2NC(CH_3)_2CH_2CH_2CO_2CH_3$$

VIII

$$\text{VIII} \xrightarrow{LiAlH_4} HOCH_2CH_2CH_2C(CH_3)_2NH_2$$

IX

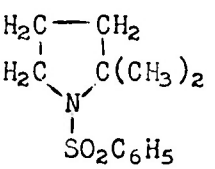
$$\text{IX} \xrightarrow{\text{aq. HBr}} BrCH_2CH_2CH_2C(CH_3)_2NH_2 \cdot HBr$$

X

The amino alcohol (IX) gave anomalous negative tests with both nickel reagents. The Hinsberg test gave both the expected product (XI) and also N-benzenesulfonyl-2,2-dimethylpyrrolidine (XII).

$C_6H_5SO_2NHC(CH_3)_2CH_2CH_2CH_2OH$

XI



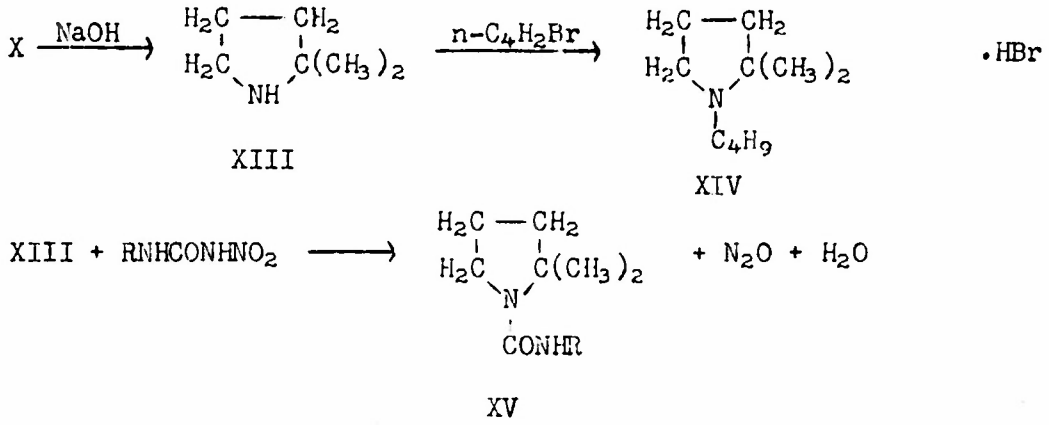
XII

The cyclic derivative (XII) most likely arose by cyclization of 4-benzenesulfonamido-4,4-dimethylbutyl benzenesulfonate (XI-benzenesulfonate). It is well known that alkyl toluenesulfonates are as reactive as alkyl bromides in displacement reactions.[21]

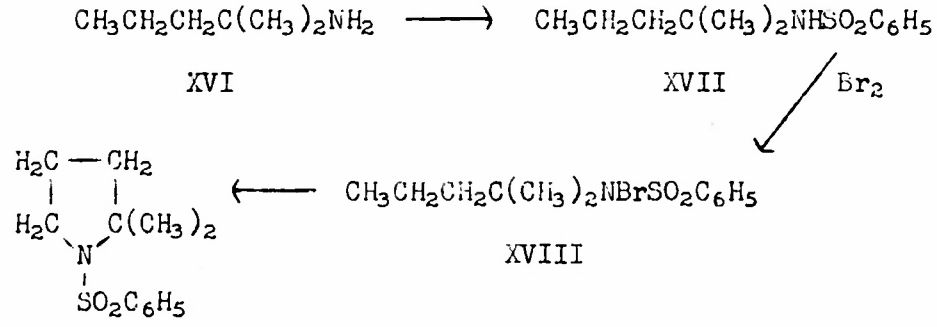
4-Bromo-1,1-dimethylbutylamine hydrobromide gave a negative primary amine test and a slow positive secondary amine test with the nickel reagents. The Hinsberg reaction gave N-benzenesulfonyl-2,2-dimethylpyrrolidine (XII) identical with that from 4-hydroxy-1,1-dimethylbutylamine (IX). Although this bromo amine salt was stable in the solid state and when dissolved in non-hydroxylic solvents, some cyclization with concomitant loss of hydrogen bromide occurred in aqueous solution. Thus, the pH of a 0.02 M solution

dropped from 4.6 to 3.0 over a period of two days. This corresponded to about 5% reaction. Since 4-bromobutylamine hydrobromide was stable in aqueous solution,[16] the "geminal alkyl effect" was established in this series of bromo amines.

The structure of 4-bromo-1,1-dimethylbutylamine hydrobromide (X) was established as correct by comparison of the melting points of several derivatives of the cyclized product, 2,2-dimethylpyrrolidine (XIII), with literature values. The N-n-butyl derivative (XIV) has been reported by Elderfield,[22] and the picrate and 2,4-dinitrophenylurea (XV where R is 2,4-dinitrophenyl) have been reported by Buckley and Elliott.[23]



Another scheme for the structure proof was based upon a free radical cyclization reaction of N-bromobutylamine derivatives discovered by Coleman.[24]



The tertiary carbinamine (XVI) gave a benzenesulfonamide (XVII) which was found to be insoluble in both aqueous sodium and potassium hydroxide solutions, even above the melting point of the benzenesulfonamide. The lower homolog, N-t-butylbenzenesulfonamide, was freely soluble in cold aqueous base.

Thus a definite limitation to the Hinsberg classification test was demonstrated. Bromination of the benzenesulfonamide XVII was attempted in the presence of bases such as sodium acetate, sodium hydroxide, and potassium t-butoxide. In none of the cases was the N-bromo derivative (XVIII) isolated. The reaction mixtures were directly exposed to sunlight to effect ring closure. The starting material was isolated in each case. That the N-bromo compound XVIII ever existed may be questioned.

The following method was successfully used for the preparation of 4-ethoxy-1,1-dimethylbutylamine (XX), a precursor of 4-bromo-1,1-dimethylbutylamine hydrobromide (X).

$$C_2H_5OCH_2CH_2CH_2Br + CH_3COCH_3 \xrightarrow{Mg} C_2H_5OCH_2CH_2CH_2(CH_3)_2OH$$

$$C_2H_5OCH_2CH_2CH_2(CH_3)_2OH \quad (XIX) \quad \downarrow \begin{matrix} NaCN \\ H_2SO_4 \end{matrix}$$

$$C_2H_5OCH_2CH_2CH_2(CH_3)_2NH_2 \xleftarrow{H_2O} C_2H_3OCH_2CH_2CH_2CH_2(CH_3)_2NHCHO$$

XX

Since the ether group of the amine (XX) must be subsequently replaced by bromine to form the required bromo amine salt (X), it would be desirable to use phenoxypropyl bromide in the first step because of the case of cleavage of phenyl alkyl ethers with hydrobromic acid. However, it was found in the literature [25] and confirmed in the laboratory that the Grignard reagent from phenoxypropyl bromide decomposes as formed, giving phenoxide ion and cyclopropane. In contrast, the Grignard reagent from ethoxypropyl bromide was found to be stable. Steps two and three represent an extension of the excellent Ritter and Kalish method for the conversion of tertiary carbinols to tertiary carbinamines by "S_N1 cyanolysis."[26] The yield of 55% was unusually low for this method and was probably due to hydrolysis of the ethoxy group in the highly acidic medium. The application of classification tests to the ethoxy amine (XX) were misleading, since the Hinsberg test indicated a secondary amine and the nickel tests for both primary and secondary amines were negative. This behavior is identical to that of the desethoxy analog, 1,1-dimethylbutyl amine (XVI), as previously described. The structure of the ethoxy amine (XX) was indeed correct, however, since cleavage with hydriodic acid and subsequent treatment with benzenesulfonyl

chloride and aqueous sodium hydroxide produced N-benzenesulfonyl-2,2-dimethylpyrrolidine, identical with authentic material (XII).

It was adjudged of interest to attempt the conversion of the ethoxy alcohol (XIX) to the ethoxy amine (XX) by the one other satisfactory method for preparing tertiary carbinamines from tertiary carbinols:[27]

$$C_2H_5OCH_2CH_2CH_2C(CH_3)_2OH \xrightarrow{HCl} C_2H_5OCH_2CH_2CH_2C(CH_3)_2Cl$$

XIX XXI

$$\xrightarrow[NH_2OCH_3]{Mg} C_2H_5OCH_2CH_2CH_2C(CH_3)_2NH_2$$

XX

2-Chloro-5-ethoxy-2-methylpentane (XXI) had been prepared previously by treatment of 5-ethoxy-2-methylpentene-2 with hydrochloric acid and was reported to be thermally stable.[28] However, since this compound, as prepared from hydrochloric acid and the alcohol (XIX) was found to undergo excessive thermal decomposition upon distillation and only a 35% yield was realized, the sequence was not pursued.

In principle, 1,1-dimethyl-4-ethoxybutyl amine (XX) could be obtained by the following scheme which involves Hofmann rearrangement of the appropriate amide (XXIII):

$$C_2H_5O(CH_2)_3Br + C_6H_5COCH(CH_3)_2 \xrightarrow{NaNH_2} C_2H_5O(CH_2)_3C(CH_3)_2COC_6H_6$$

XXII

$$\xrightarrow{NaNH_2} C_2H_5OCH_2CH_2CH_2C(CH_3)_2CONH_2$$

XXIII

$$\xrightarrow[NaOH]{Br_2} C_2H_5OCH_2CH_2CH_2(CH_3)_2NH_2$$

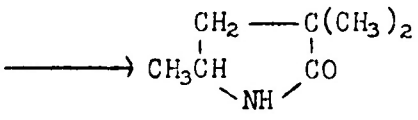
XX

The alkylation of isobutyrophenone proceeded smoothly, but subsequent cleavage of the ketone (XXII) gave a crude partially crystalline product. Since this could not be purified easily, it was directly subjected to rearrangement conditions. Only a trace of crude primary amine, as determined

by the nickel test, was formed and could not be the required amine (XX) which, as we have seen, does not give a primary amine test. The main product of the reaction was recovered starting material. It seemed that the treatment with sodium hypobromite merely served to purify the crude product from the cleavage of the ketone (XXII) with sodamide. This cleavage product proved to be 3,3,5-trimethylpyrrolidone-2 (XXV), the properties of which were identical with those reported by Haller and Bauer for authentic material from the cleavage of allyldimethylacetophenone with sodamide and from an independent synthesis.[29] These authors proposed, but did not prove, that their cleavage proceeded normally to give 2,2-dimethyl-4-pentenamide (XXIV), which then cyclized under the basic conditions.

$$CH_2{=}CHCH_2C(CH_3)_2COC_6H_5 \xrightarrow{NaNH_2} CH_2{=}CHCH_2C(CH_3)_2CONH_2 + C_6H_5Na$$

XXIV



XXV

In order to establish the possibility that 2,2-dimethyl-4-pentenamide (XXIV) was an intermediate in this unusual reaction, it was prepared from the corresponding nitrile (XXVI), which was available by alkylation of isobutyronitrile with allyl chloride in the presence of lithium diethylamide according to the procedure of Ziegler.[30]

$$CH_2 = CHCH_2Cl + HC(CH_3)_2CN \xrightarrow{base} CH_2{=}CHCH_2C(CH_3)_2CN$$

XXVI

$$\xrightarrow{NaOH} CH_2{=}CHCH_2C(CH_3)_2CONH_2$$

XXIV

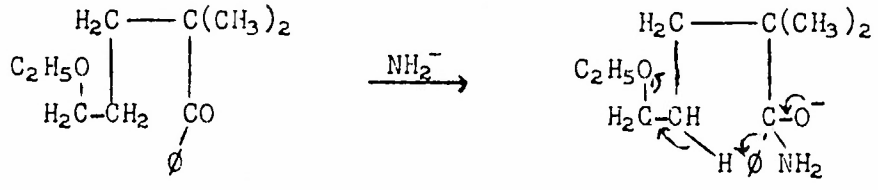
Indeed, it was found that the amide (XXIV) was converted smoothly to the pyrrolidone (XXV) upon boiling in a toluene suspension of sodamide.

The addition of bases to olefins (excluding Michael additions) is a relatively unknown phenomenon. There are a few examples of addition of bases to double bonds activated by aromatic rings, such as the addition of Grignard reagents to fulvenes[31] and the addition of potassium amide to styrene.[32] Apparently, the only recorded case of the addition of a base to an unactivated

olefin was reported by Bartlett, who succeeded in adding isopropyllithium to ethylene.[33] In the light of these examples, it is seen that the cyclization of the comparatively weakly basic anion of 2,2-dimethyl-4-penteneamide is completely unprecedented. Since the concentration of active hydrogen in a boiling toluene suspension of sodamide is rather low, it would seem that the overall reaction must preliminarily involve the energetically prohibitive generation of a carbanion from the anion of an acylamide, unless a transition state of the following nature obtains.

In order to remove the objection that ammonia amide ion, or even toluene, can furnish protons, the cyclization was carried out with sodium hydride in Skellysolve E and found to be quite facile. Furthermore, N-benzyl-2,2-dimethyl-4-pentenamide, the ion of which lacks the N-H bond, was inert under the same conditions and could be recovered unchanged. This gives further support to the proposed mechanism.

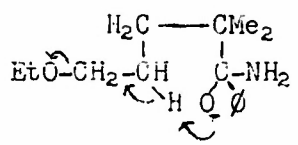
Returning again to the formation of 3,3,5-trimethylpyrrolidone-2 (XXV) from the sodamide treatment of 5-ethoxy-2,2-dimethylvalerophenone (XXII), it was reasonable to assume that the reaction took the following course.



XXII XXVII

$$XXVII \longrightarrow C_6H_6 + C_2H_5O^- + XXIV \longrightarrow XXV$$

The transition state XXVII, giving rise to E2 ether cleavage of the ethoxy ketone (XXII) and formation of 2,2-dimethyl-4-penteneamide (XXIV), was favored by Winstein[34] as being more likely than an alternate scheme whereby the negative oxygen initiated the ether cleavage.



Many examples are known of ether cleavages, which, from inspection of the products, must involve S_N2 mechanisms.[35] Less frequently found are authentic examples of the E2 cleavage of unactivated ethers, and these have only been observed under the influence of organometallic reagents.[33,36,37,38,39] Apparently, there are no recorded examples of E2 cleavage resulting from the action of sodamide, a weaker base than organometallic reagents. Accordingly, the cleavage of dibutyl ether with sodamide was attempted. However, after boiling a suspension of 0.25 mole of sodamide in 200 ml. of pure dibutyl ether for 16 hours, only a trace of the cleavage product, 1-butene, was formed, as determined by treatment of the exit gases with 2,4-dinitrobenzenesulfenyl chloride. Since these conditions are appreciably more drastic than those required for the facile cleavage of 5-ethoxy-1,1-dimethylvalerophenone with sodamide, it may be concluded that the latter reaction is completely unprecedented.

In concluding the study of synthetic routes leading to the 4-bromo-1,1-dimethylbutylamine hydrobromide skeleton, the Beckmann rearrangement of 5-phenoxy-1,1-dimethylvalerophenoxime was investigated. It had been reported that pivalophenone oxime, a model compound, gave benzonitrile exclusively upon treatment with phosphorus pentachloride. However, treatment with a solution of hydrogen chloride in acetic acid was reported to give pivalanilide.[40] In spite of these discouraging facts, pivalophenone oxime was prepared and subjected to rearrangement under various conditions. Indeed, the rearrangement with phosphorus pentachloride, even under the mildest possible conditions, led to the exclusive formation of benzonitrile. That the rearrangment with hydrogen chloride in acetic acid gave pivalanilide was also confirmed. It seemed likely that the benzenesulfonyl chloride method of rearranging oximes[41] might produce the desired result, since the rearrangement occurs in an alkaline environment. Indeed, such was the case. The rearrangement was carried out in the manner of a Hinsberg reaction. The benzenesulfonyl ester was unstable and rearranged <u>in situ</u>, giving N-t-butylbenzamide in 72% yield. The rearrangement under these conditions followed two competing paths since the odor of benzonitrile was evident at the end of the reaction.

Because of the success of the model rearrangement, 2,2-dimethyl-5-phenoxyvalerophenone (XXVIII) was prepared by alkylation of isobutyrophenone

with phenoxypropyl bromide in boiling toluene in the presence of sodamide. Although 1.5 equivalents of isobutyrophenone per equivalent of sodamide was used to avoid excessive basicity which would lead to cleavage and cyclization, the reaction was not clean cut, as evidenced by a product boiling range of 130°. The liquid ketone was not further purified as such, but was converted into the oxime. The low overall yield (38%) may be attributed to the high temperature used for alkylation. Undoubtedly extensive cyclization took place. Beckmann rearrangement of the oxime under Hinsberg conditions produced an 84% yield of N-benzoyl-1,1-dimethyl-4-phenoxybutylamine (XXIX).

$$C_6H_5O(CH_2)_3C(CH_3)_2COC_6H_5 \longrightarrow \text{oxime}$$

XXVII

$$\xrightarrow[\text{base}]{C_6H_5SO_2Cl} C_6H_5OCH_2CH_2CH_2C(CH_3)_2NHCOC_6H_5$$

XXIX

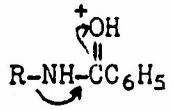
The amide proved extremely resistant to basic hydrolysis. After treatment for 6 hours with 20 equivalents of sodium butoxide in refluxing butanol, 47% of the amide was recovered unchanged. The free amine was obtained in 25% yield. Potassium hydroxide in refluxing ethylene glycol likewise failed to afford complete conversion, giving only 18% of the amine. Furthermore, the latter conditions were drastic enough to cleave the ether linkage, since phenol was detected in the product.

Acid hydrolysis, using hydrobromic acid, was attempted in the hope that simultaneous cleavage of the amide and ether functions would lead directly to the required bromo amine salt. However, the only products observed were phenol, benzoic acid, ammonium bromide, and a neutral oil containing bromide and this approach to the synthesis was abandoned.

Obviously, scission of the C-N bond had occurred, and in order to elucidate the nature of this reaction, both t-butylamine and N-t-butylbenzamide were subjected to acid hydrolysis under the same conditions. It was found that although the former compound was completely inert to scission, the latter compound cleaved readily to give t-butyl bromide, benzoic acid and ammonium bromide. The C-N bond is obviously weakened in t-butyl benzamide and a transition state such as the following one (where R is t-butyl), which is/

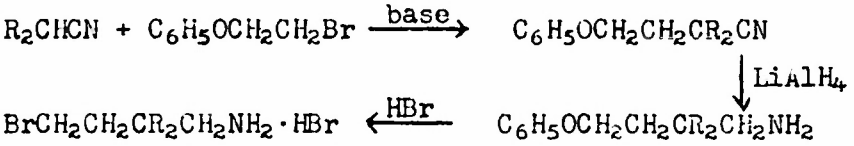
similar

to that proposed for the alcoholysis of t-butyl esters,[42] seems feasible.



Other examples of this type of phenomenon are known. Thus, M. S. Kharasch found that triphenylcarbinamine is 70% cleaved by 0.05 N aqueous hydrochloric acid at 100° in one hour although t-butylamine, dimethylphenylcarbinamine, and methyldiphenyl-carbinamine are inert under the same conditions.[43] Hickenbottom observed that although t-butylamine and N-n-alkylanilines are unaffected by treatment with hot mineral acids, N-t-butyl aniline is easily hydrolysed.[44] It is now clear why Ritter and Kalish[26] used only basic conditions for the hydrolysis of the N-t-alkylformamides in their elegant synthesis of t-carbinamines. They make no special point of this fact, however, and do not mention the difficulties encountered during acid hydrolysis.

The excellent method of Ziegler for using lithium diethylamide in the alkylation of nitriles[30] successfully served as the basis for the preparation of members of the 2,2-dialkyl-4-bromobutylamine series, where R may be methyl, ethyl, isopropyl, phenyl, or p-tolyl.



Diphenylacetonitrile was a commercial product, but the other disubstituted acetonitriles were prepared from the corresponding amides by dehydration with thionyl chloride. The disubstituted acetamides were in turn prepared from the corresponding disubstituted acetic acids via the acid chlorides. These transformations were carried out by use of a novel technique which was developed for the large scale conversion of an acid to the corresponding nitrile in yields of approximately 90% with a minimum of manipulation. Although this technique is described in detail in the experimental chapter, a brief outline is appropriate here. A mixture of the acid and a 10% excess of thionyl chloride was allowed to stand overnight for conversion to the acid chloride. The crude product containing thionyl chloride was taken up directly in dry ether and slowly dripped into a solution of liquid ammonia and commercial tetrahydrofuran which was kept cold in a dry-ice bath.

Petroleum ether was added and the slurry was filtered while still cold. The precipitated mixture of crude amide and ammonium chloride was dehydrated directly by covering with a solvent such as chloroform or ethylene chloride and adding a 20% excess of thionyl chloride. After boiling for several hours, the nitrile was isolated in the usual manner. This method was specifically designed for acids, such as isobutyric acid, whose amides are so soluble in water that they cannot be prepared by the usual technique from the acid chloride and aqueous ammonia without great losses. Isobutyric and diethylacetic acids were commercial products, but di-p-tolylacetic was prepared by the unusual route:

$$Cl_3CCHO + C_6H_5CH_3 \xrightarrow{H_2SO_4} (p\text{-}CH_3C_6H_4)_2CHCCl_3$$

$$(p\text{-}CH_3C_6H_4)_2CHCCl_3 \xrightarrow[ROH]{NaOR} (p\text{-}CH_3C_6H_4)_2C{=}C(OR)_2$$

$$(p\text{-}CH_3C_6H_4)_2C{=}C(OR)_2 \xrightarrow{HCl} (p\text{-}CH_3C_6H_4)_2CHCO_2H$$

XXX

This roundabout method was used since the proposed reaction of the D.D.T. analog (XXX) with sodamide to give the nitrile directly did not work. Dehydrohalogenation occurred instead. Diisopropylacetonitrile was prepared by a substantial improvement of Marshall's method.[45]

$$CH_2(CO_2C_2H_5)CN \xrightarrow[\text{2 steps}]{\text{base}\ /\ i\text{-}C_3H_7I} (i\text{-}C_3H_7)_2C(CO_2C_2H_5)CN \xrightarrow{KOH} (i\text{-}C_3H_7)CHCN$$

Use of easily prepared sodium isopropoxide as the alkylation base gave diisopropylcyanoacetic ester in easily reproducible yields of 93% and the yield would have been higher if some dehydriodination had not occurred. Marshall, using the weaker base, sodium ethoxide, was only able to obtain a yield of 58% in this step. Thus, it is now possible to introduce secondary alkyl groups into cyanoacetic ester quite as easily as primary alkyl groups if a base stronger than sodium ethoxide is used. Upon slowly distilling diisopropylcyanoacetic ester from molten potassium hydroxide, smooth hydrolysis and decarboxylation ensued, affording diisopropylacetonitrile directly in 83% yield. Marshall conducted the hydrolysis and decarboxylation separately

in unstated overall yield.[45]

Returning to the main sequence of reactions leading to the 2,2-dialkyl-4-bromobutylamine hydrobromides, the yields for alkylation of the disubstituted acetonitriles with phenoxyethyl bromide where R may be methyl, ethyl, isopropyl, phenyl, or p-tolyl, were 88%, 75%, 25%, 87%, and more than 88%, respectively. The decreasing yields on going from methyl to ethyl to isopropyl clearly indicate the effects of increasing steric hindrance. In fact, steric hindrance is so great in the last case, as will be discussed later, that the isolation of any product at all was quite surprising. There is no literature precedent for the preparation of trialkylacetonitriles with such bulky substituents by Ziegler's method, or any other method, for that matter. The yield of 4-phenoxy-2,2-di-p-tolylbutyronitrile is stated to be greater than 88% since the nitrile could not be isolated at this point and the crude product was reduced directly to give an 88% overall yield of the corresponding amine in the second step. Sodamide may also be used in the alkylation step but is not so easily prepared and handled as is lithium diethylamide and, in addition, it gave distinctly lower yields. For example, the alkylation of isobutyronitrile with phenoxyethyl bromide, using sodamide, was only 59%, as compared to 88% obtained with lithium diethylamide.

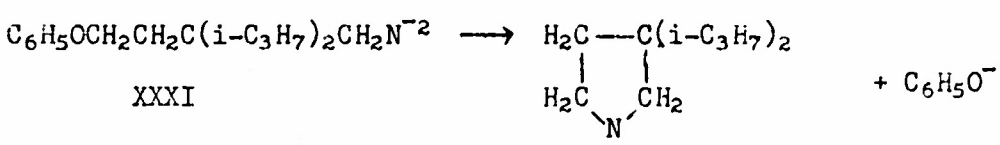
In the second step of the sequence, reduction was carried out with lithium aluminum hydride in ether where R was methyl, ethyl, phenyl, and p-tolyl, and afforded yields of 81%, 80%, 90% and greater than 88%, respectively. The use of sodium with 2-butanol as a reducing agent was also tried in the cases where R was methyl and phenyl. When R was methyl, the yield was only 62%, however, and when R was phenyl, the reaction took another course, giving phenyl 3,3-diphenylpropyl ether in 91% yield along with sodium cyanide.

$$C_6H_5OCH_2CH_2C(C_6H_5)_2CN \xrightarrow[\text{alc.}]{Na} C_6H_5OCH_2CH_2CH(C_6H_5)_2 + NaCN$$

This type of cleavage is common with nitriles having aryl groups in the alpha position.[46]

The reduction of 2,2-diisopropyl-4-phenoxybutyronitrile with lithium aluminum hydride in ether proceeded very slowly and incompletely, in comparison to the vigorous reductions of the other nitriles. Furthermore, the amine

isolated was not the expected product, 2,2-diisopropyl-4-phenoxybutylamine, although the anion (XXXI) of this amine must have been the proximate product, since 3,3-diisopropylpyrrolidine was isolated in 9% yield, the starting material being recovered in the amount of 85%



$C_6H_5OCH_2CH_2C(i\text{-}C_3H_7)_2CH_2N^{-2}$ ⟶ $H_2C(-CH_2)C(i\text{-}C_3H_7)_2$ (N) + $C_6H_5O^-$

XXXI

Also, a trace of cyanide ion was detected. At the higher temperature of boiling tetrahydrofuran, lithium aluminum hydride afforded 26% of 3,3-diisopropylpyrrolidine, while 49% of the starting material was recovered. No cyanide was detected in this case. The inordinate instability of the anion XXXI strikingly demonstrates the profound effect which geminal isopropyl groups must exert upon ring closures. Sodium and alcohol were also utilized in the hope of effecting the reduction, since any anion of type XXXI might be expected to equilibrate with the alcoholic solvent before ring closure could occur. However, 76% of the starting material was recovered, 11% of a neutral solid, $C_{10}H_{23}NO_2$, was isolated, cyanide ion was detected, and only a trace of basic material could be obtained. The steric requirements of lithium aluminum hydride are known to be considerably less than those of surface active catalysts and less than those of the Ponndorf reagent in the reduction of sterically hindered carbonyl groups.[47,48] Accordingly, it was felt that catalytic hydrogenation would effect the reduction slowly, but without cyclization, if sufficiently drastic conditions were used. Of course, if the conditions should be too drastic, hydrogenation of and hydrogenolysis of the phenoxy group would occur. Results were disappointing as treatment of the nitrile with Raney nickel and hydrogen at 100 atmospheres and a temperature of 100° gave only a trace of basic material of formula $C_{10}H_{19}N$, the starting material being recovered almost quantitatively.

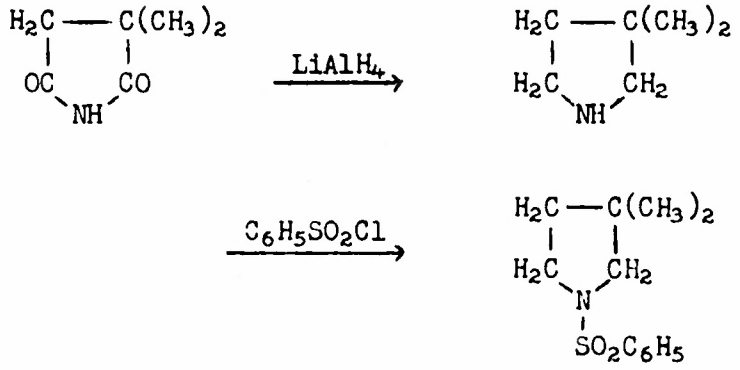
It was proposed that a 4-alkoxy-2,2-diisopropylbutylamine might possibly be synthesized if the less easily displaced methoxy group were substituted for the phenoxy group in the general sequence as previously outlined. Indeed, such was found to be the case. 2,2-Diisopropyl-4-methoxybutyronitrile was reduced to 2,2-diisopropyl-4-methoxybutylamine in

92% yield by treatment with lithium aluminum hydride in ether for a period of sixteen hours.

The dimethyl and diethyl phenoxyamines and the di-isopropylmethoxyamine were converted readily to the corresponding bromoamine hydrobromides by the usual treatment with hydrobromic acid. But the diphenyl and ditolyl phenoxyamines reacted only sluggishly and gave high yields of the cyclization products. This was indeed a surprising phenomenon, and no explanation has yet been devised. Small amounts of impure bromoamine hydrobromides were eventually isolated, in very low yield. Repetition of these syntheses using the methoxy group rather than the phenoxy should enable the cleavage step with hydrobromic acid to be more successful, and this could be the reason why no difficulty was experienced with the di-isopropylmethoxyamine.

All of the 2,2-dialkyl-4-bromobutylamine hydrobromides in the series gave negative nickel tests for primary amines and positive tests for secondary amines. The Hinsberg reaction gave the N-benzenesulfonyl-3,3-dialkyl-pyrrolidines by cyclization. That these bromoamine salts cyclize readily in aqueous solution, as does 1,1-dimethyl-4-bromobutylamine hydrobromide, was demonstrated by the observation that the pH of a 0.01 M solution of 2,2-dimethyl-4-bromobutylamine hydrobromide decreased from a value of 4.13 to 2.93 in the span of fifteen hours. The bromoamine salts may be crystallized from chlorinated hydrocarbons in which they are quite stable. An exception is 4-bromo-2,2-diisopropylbutylamine hydrobromide. Solutions of this salt in carbon tetrachloride begin to evolve hydrogen bromide visibly at 50°.

It was necessary to prove the structures of the compounds of the 2,2-dialkyl-4-bromobutylamine hydrobromide series to preclude the possibility of rearrangement in the ether cleavage step. The recorded melting point of 3,3-diphenylpyrrolidine hydrochloride, a known compound,[49] checked that of the same compound as prepared *via* the cyclization of 2,2-diphenyl-4-bromo-butylamine hydrobromide. Furthermore, N-benzenesulfonyl-3,3-dimethyl-pyrrolidine (XXXII), the product of the Hinsberg reaction with 2,2-dimethyl-4-bromobutylamine hydrobromide, was synthesized unequivocally by an independent method (discussed below). Finally, 3,3-di-isopropylpyrrolidine from the cyclization of the corresponding bromoamine salt was found to be identical with material from the reduction of 2,2-diisopropyl-4-phenoxybutyronitrite



XXXII

Although lithium aluminum hydride has been used for the reduction of N-phenylsuccinimide[50] and lactams[49,51] to the corresponding cyclic imines, the reduction of N-unsubstituted succinimides with this reagent has not been reported. It might be expected that the highly acidic hydrogen of succinimides would interfere in the reduction. Such was not the case, however, and reduction of as-dimethylsuccinimide afforded 3,3-dimethylpyrrolidine in 80% yield. Since lactams have been reduced with sodium and alcohol,[52] this method was also tried on as-dimethylsuccinimide. However, with ten gram atoms of sodium per mole, only a trace of low boiling basic material could be isolated, which, since it failed to give positive nickel tests for either primary or secondary amines, could not have been 2,2-dimethylpyrrolidine which gives a strongly positive secondary amine test. The attempted stepwise reduction of as-dimethylsuccinimide with four gram atoms of sodium per mole gave only a neutral high-melting bimolecular reduction product, $C_{12}H_{18}O_2N_2$. It was also desired to prepare 4,4-dimethylpyrrolidone-2 for the purpose of reduction to 3,3-dimethylpyrrolidine, since this lactam is available in 35% yield from 3,3-dimethylglutaric anhydride by a Hofmann rearrangement of the corresponding glutaramic acid.[53] However, an attempted duplication of this work gave only a negligible yield of the pyrrolidone, which was found to be so highly soluble in all solvents that purification was impossible.

The basic skeleton of 4-bromo-2,2-dimethylbutylamine hydrobromide could, in principle, be obtained alternatively by Michael addition of the elements of hydrogen cyanide or nitromethane to ethyl 3-methyl-2-butenoate. Unfortunately, these additions failed to take place, possibly because of the

unfavorable steric and inductive effects of the methyl groups. If the double bond was doubly activated, however, addition of nitromethane occurred readily.

$$CH_3NO_2 + (CH_3)_2C{=}C(CN)CO_2C_2H_5 \xrightarrow{\text{base}} O_2NCH_2C(CH_3)_2CH(CN)CO_2C_2H_5$$

XXXIII

Acidic and basic hydrolyses of the nitro ester XXXIII were attempted, but it was not possible to isolate any of the desired 3,3-dimethyl-4-nitrobutanoic acid. The alkaline hydrolysis yielded tar, which can be explained by the fact that alkaline treatment of primary nitroalkanes is known to yield trimeric condensation products,[54] among other things. Acid hydrolysis and decarboxylation produced large quantities of ammonium carbonate and a small quantity of as-dimethylsuccinic acid. Acid treatment of primary nitroalkanes is known to induce oxidation of the nitro-bearing carbon atom giving hydroxylamine or ammonia and an acid having the same number of carbon atoms.[53] As-dimethylsuccinic acid would be the expected product of such a reaction.

Another conceivable route for establishing the basic skeleton of 4-bromo-2,2-dimethylbutylamine hydrobromide would involve the Hofmann rearrangement of 3,3-dimethylglutaramic acid (XXXIV).

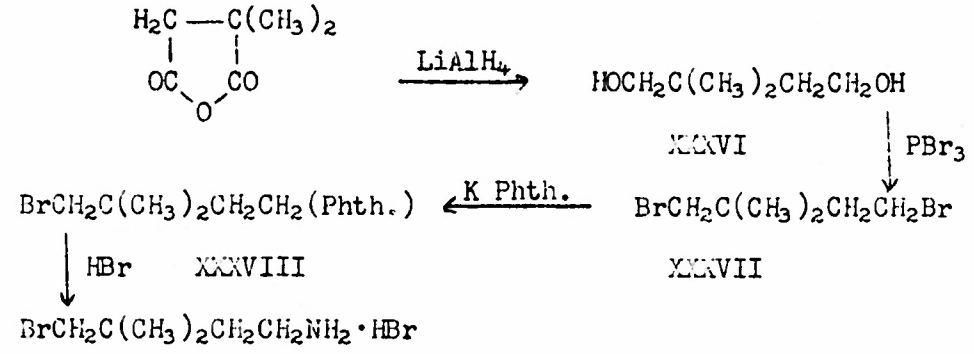
$$NH_2COCH_2C(CH_3)_2CH_2CO_2H \xrightarrow[CH_3ONa]{Br_2} H_3COCONHCH_2C(CH_3)_2CH_2CO_2Na$$

XXXIV XXXV

The urethane XXXV was produced in low yield along with large quantities of 3,3-dimethylglutarimide which was formed by cyclization of the starting material in the basic medium. The Hofmann rearrangement of methyl 3,3-dimethylglutaramate (XXXIV methyl ester) again produced 3,3-dimethylglutarimide along with a neutral solid of empirical formula $C_7H_9O_2NBr_2$ or $C_8H_{11}O_4NBr_2$. No urethane was isolated. Along the same line of thought, since the Curtius degradation could be used with anhydrides, as well as with acid chlorides, the reaction of sodium azide with 3,3-dimethylglutaric anhydride was tried but it gave only a negligible quantity of a crude product which was not further worked up.

4-Bromo-3,3-dimethylbutylamine hydrobromide (XXXIX) was prepared by a rather novel method which expressly depended upon the fact that neopentyl

halides are hindered with respect to displacement of halogen by intermolecular attack. The glycol, 2,2-dimethylbutanediol-1,2 was converted to the dibromide, and the more reactive bromine replaced by an amino group via the Gabriel synthesis.



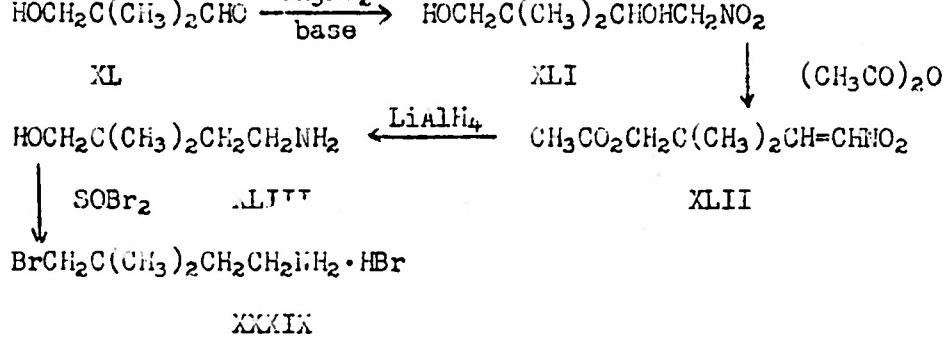
(where Phth. refers to phthalimide)

The only unsatisfactory step was the second one. Repeated attempts to convert 2,2-dimethylbutanediol-1,4 (XXXVI) to 1,4-dibromo-2,2-dimethylbutane (XXXVII) with phosphorus tribromide and pyridine under various conditions gave consistent yields of around 10%. Reaction of the dibromide with potassium phthalimide gave 1-bromo-2,2-dimethyl-4-phthalimidobutane (XXXVIII) in a yield of 80%. The Gabriel synthesis was carried out in dimethylformamide, an excellent solvent which allows the reaction to proceed at a low temperature in high yield.[57]

4-Bromo-3,3-dimethylbutylamine hydrobromide (XXXIX) gave a positive nickel test for a primary amine and a slowly developing secondary amine test. Cyclization was instantaneous in aqueous sodium hydroxide and treatment with benzene sulfonyl chloride gave N-benzenesulfonyl-3,3-dimethylpyrrolidine identical to that derived from 4-bromo-2,2-dimethylbutylamine hydrobromide. Thus the structures of 4-bromo-3,3-dimethylbutylamine hydrobromide and its precursors were unequivocally established. That cyclization should occur rapidly in base is due to the fact that, although the neopentyl-type bromide is hindered with respect to intermolecular displacement, the molecular structure is such that intramolecular displacement may occur readily. This point is nicely shown by examination of molecular models.

The following alternative sequence for the preparation of 4-bromo-3,3-dimethylbutylamine hydrobromide (XXXIX) may have been successful on a small

scale according to indirect evidence.



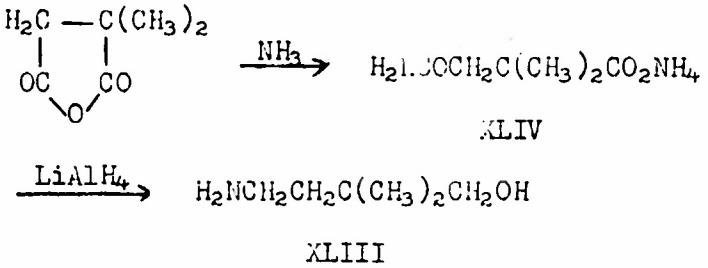
The addition of nitromethane to hydroxypivalaldehyde (XL) using diethylamine or sodium methoxide as a catalyst under a variety of conditions gave completely unreproducible yields of the nitro glycol XLI in the range 0-66%. It was impossible to purify this material which distilled over a range of 100°. Furthermore, since it was difficult to remove all traces of catalyst from the nitroglycol because of its solubility properties, the distillation was quite hazardous. An attempt to avoid this difficulty by substituting acetoxypivalaldehyde (XL acetate) was not practical, since the corresponding product, from which the catalyst can be removed easily by washing with water, was obtained in very low yield.

4-Hydroxy-3,3-dimethylbutylamine (XLIII) differed from the isomer 4-hydroxy-1,1-dimethylbutylamine (IX) in that the Hinsberg reaction gave only a base-soluble oil, $HOCH_2C(CH_3)_2CH_2CH_2NHSO_2C_6H_5$, which, upon treatment with benzenesulfonyl chloride and triethylamine, formed N-benzenesulfonyl-3,3-dimethylpyrrolidine, identical with authentic material. When 4-hydroxy-3,3-dimethylbutylamine (XLIII) was treated with thionyl bromide, a small quantity of gummy material was obtained which gave a trace of N-benzene-sulfonyl-3,3-dimethylpyrrolidine under Hinsberg conditions. This is not conclusive proof that the bromo amine salt XXXIX was formed, since the sulfonamide, only a trace of which was isolated, may have arisen from 4-hydroxy-3,3-dimethylbutylamine.

Some comments on the peculiar properties of acetoxypivalaldehyde (XL acetate) are in order at this point. The material decomposed extensively by several paths upon distillation at atmospheric pressure. The identified products were formaldehyde, isobutyl acetate and a colorless high boiling

residue which may be the known dimer.[58] Even upon vacuum distillation decomposition occurred, but to a lesser extent. The distilled material effervesced for days, evolving an odorless gas, which was presumably carbon monoxide. Distillation of acetoxypivalaldehyde in the presence of a trace of toluenesulfonic acid gave rise to still another mode of decomposition, since an unsaturated gas, perhaps isobutene, could be detected. This unusual behavior is in direct contrast to that of hydroxypivalaldehyde, which can be distilled with essentially no decomposition unless a trace of base is present, in which case formaldehyde and isobutyraldehyde are formed by a reverse aldol condendation.

The following transformations represent an alternate synthesis of 4-hydroxy-3,3-dimethylbutylamine (XLIII).



Reduction of the ammonium salt XLIV proceeded with difficulty because of poor solubility in boiling tetrahydrofuran and gave only a 16% yield of amino alcohol. Treatment of the amino alcohol with boiling hydrobromic acid gave 27% of a crystalline salt and a large quantity of intractible gum. The crystalline solid was shown to be 4-bromo-2,2-dimethylbutylamine hydrobromide by comparison of the melting point and X-ray powder diagram with those of authentic material and by formation of N-benzenesulfonyl-3,3-pyrrolidine with benzenesulfonyl chloride and aqueous sodium hydroxide. That 4-bromo-2,2-dimethylbutylamine hydrobromide was produced in such quantity was unexpected and indeed surprising, since it must have arisen from an abnormal opening of as-dimethylsuccinic anhydride. This abnormal opening is not consonant with either steric or inductive effects. The isomeric as-dimethylsuccinamic acids were isolated in the free state but losses were great due to facile cyclization giving as-dimethylsuccinimide.

Phenylhydrazine, a much larger molecule than ammonia, opened as-dimethylsuccinic anhydride to give a homogeneous product, but treatment with lithium

aluminum hydride failed to convert this product to 4-hydroxy-3,3-dimethylbutylamine (XLIII) in spite of the fact that lithium aluminum hydride is known to effect hydrogenolysis of N-N bonds.[59,60]

Transformations XL to XLVII represent another alternative scheme for establishing the skeleton of 4-hydroxy-3,3-dimethylbutylamine (XLIII) and are based upon an observation by Hartung that esters of cyanohydrins undergo facile hydrogenolysis at room temperature and under diminished pressure of hydrogen to give nitriles.[61]

$$\underset{\text{XL}}{HOCH_2C(CH_3)_2CHO} \xrightarrow{HCN} \underset{\text{XLV}}{HOCH_2C(CH_3)_2CH(OH)CN} \xrightarrow{(CH_3CO)C} \underset{\text{XLVI}}{CH_3CO_2CH_2C(CH_3)_2CH(O_2CCH_3)CN} \xrightarrow[Pd]{H_2} \underset{\text{XLVII}}{CH_3CO_2CH_2C(CH_3)_2CH_2CN}$$

However, the acetate (XLVI) of the known cyanohydrin XLV[98] failed to take up hydrogen at one atmosphere. More drastic conditions were not attempted. Still another alternative scheme, represented by transformations XLVIII to L, was attempted in the hope of establishing the 4-bromo-3,3-dimethylbutylamine skeleton.

$$\underset{\text{XLVIII}}{HOCH_2C(CH_3)_2CH_2OH} \xrightarrow[base]{TsCl} \underset{\text{XLIX}}{HOCH_2C(CH_3)_2CH_2OTs} \xrightarrow{KCN} \underset{\text{L}}{HOCH_2C(CH_3)_2CH_2CN}$$

Although 1,3-dibromo-2,2-dimethylpropane (XLVIII dibromide) does undergo displacement reactions, forcing is usually required.[62,63] It was found that the monotosylate (XLIX) had not reacted with potassium cyanide after fourteen hours in boiling ethanol. Forcing was not tried since dimethyltrimethylene oxide would undoubtedly have been formed from the monotosylate (XLIX) under the basic conditions. In an attempt to avoid this possibility, 3-methoxy-2,2-dimethylpropanyl-1 p-toluenesulfonate (XLIX methyl ether) was prepared and successfully subjected to forcing conditions with potassium cyanide. Reduction of the nitrile so produced (LI) afforded 4-methoxy-3,3-dimethylbutylamine (LII)

$$CH_3OCH_2C(CH_3)_2CH_2CN \xrightarrow[ROH]{Na} CH_3OCH_2C(CH_3)_2CH_2CH_2NH_2$$

LI LII

Treatment of the methoxy amine (LII) with boiling hydrobromic acid failed to cleave the ether. Further treatment with hydrogen bromide in acetic acid did cleave the ether, but gave only rearranged products of an undetermined nature.

The last alternative synthesis of the 4-hydroxy-3,3-dimethylbutylamine skeleton which was attempted was based upon the fact that ethyl isobutyrate may be alkylated with ethyl alpha-bromoisobutyrate in the presence of triphenylmethylsodium to give diethyl tetramethyl succinate.[64] Since acetonitrile is considerably less hindered than ethyl isobutyrate, one might expect that it could easily be alkylated with methyl alpha-bromoisobutyrate.

$$LiCH_2CN + BrC(CH_3)_2CO_2CH_3 \longrightarrow NCCH_2C(CH_3)_2CO_2CH_2$$

Disappointingly, the sole isolable products were a trace of neutral solid of empirical formula $C_4H_6NO_3$ and considerable quantities of tar.

B. Kinetic aspects of the investigation.

The mechanism of the cyclization reaction of the 4-bromobutylamine hydrobromides may be set up on the basis of a fast equilibrium with the free amine followed by the slow step in which the amino group engages C_4 on the side opposite to the bromine, which when expelled leaves the positive pyrrolidinium ion. This may be formulated as:

$$AH^+ \underset{k_2}{\overset{k_1}{\rightleftharpoons}} A + H^+ \qquad (1)$$

$$A \xrightarrow{k_3} PH^+ + Br^- \qquad (2)$$

$$PH^+ \underset{k_5}{\overset{k_4}{\rightleftharpoons}} P + H^+ \qquad (3)$$

The rate of formation of Br^- is

$$\frac{dBr^-}{dt} = k_3A \qquad (4)$$

To obtain A as a function of Br^-, the steady state convention is employed, or

$$\frac{dA}{dt} = 0 = k_1 AH^+ - k_2 A \cdot H^+ - k_3 A \tag{5}$$

The stoichiometry of the reaction

$$AH_0^+ = AH^+ + A + PH^+ + P \tag{6}$$

$$Br^- - Br_0^- = PH^+ + P \tag{7}$$

gives by substituting (7) in (6), and solving for AH^+ gives (8)

$$AH^+ = AH_0^+ - A - Br^- + Br_0^- \tag{8}$$

which, substituted in turn into (5), gives (9).

$$A = \frac{k_1 (AH_0^+ + Br_0^- - Br^-)}{k_1 + k_2 H^+ + k_3} \tag{9}$$

Substituting (9) into (4) and rearranging gives (10).

$$\frac{dBr^-}{AH_0^+ + Br_0^- - Br^-} \quad \frac{k_1 k_3}{k_1 + k_2 H^+ + k_3} dt \tag{10}$$

Assuming that the hydrogen ion concentration could be held constant, and integrating between the limits Br_0^- to Br^- for 0 to t, gives (11).

$$k_{exp.} = \frac{k_1 k_3}{k_1 + k_2 H^+ + k_3} = \frac{2.303}{t} \log \frac{AH_0^+}{AH_0^+ + Br_0^- - Br^-} \tag{11}$$

If there is no other source of bromide ion, then $AH_0^+ = Br_0^-$ and Br_∞^- at the completion of the reaction (infinite time) is twice Br_0^-, or

$$\frac{AH_0^+}{AH_0^+ + Br_0^- - Br^-} = \frac{Br_0^-}{2Br_0^- - Br^-} = \frac{Br_\infty^- - Br_0^-}{Br_\infty^- - Br^-} \tag{12}$$

Also, since

$$\left(N_{KSCN}\right)\left(V_{KSCN}\right) = \left(N_{Br^-}\right)\left(V_{Br^-}\right) \tag{13}$$

then

$$Br_t^- = (N_{Br^-})_t = \frac{N_{KSCN}}{V_{Br^-}} (V_{KSCN})_t \tag{14}$$

or the concentration of bromide ion at any time is determined by a constant

(the ratio of the normality of the potassium thiocyanate solution used as the titrant to the volume of the pipet used for withdrawing samples from the reaction mixture) times the volume of titrant solution used. Dropping the KSCN in the subscript, and substituting (14) in (12), and (12) in (11), gives

$$k_{exp.} = \frac{2.303}{t} \log \frac{V_0 - V_\infty}{V_t - V_\infty} \qquad (15)$$

which is the equation used to calculate $k_{exp.}$.

Before any runs were made, it was recognized that extensive buffering would be necessary since with an initial concentration of amine salt of about 0.01 M, enough hydrobromic acid would be liberated during the reaction to lower the pH to 2. Rough estimates indicated that an acetate buffer, 1 M in each component, salt and acid, would be required to hold the concentration of hydrogen ion constant enough to avoid a change greater than 1% in the rates for the start and finish of the reaction. Using the dimethylbromoamine (see Table I), the effect of changing ionic strength, buffer capacity, and buffer ratio was investigated.

Comparison of Runs 1 and 7 ($k_{exp.}$ = 2.04; 2.04 x 10^{-4}) illustrates the excellent reproducibility of the system. With the addition of inert salt, potassium nitrate, as in Run 3 ($k_{exp.}$ = 2.03 x 10^{-4}) with sodium acetate at 1 M, no effect was noted. However, by maintaining a constant buffer ratio of 1, and using potassium nitrate to maintain the salt strength at 1M, comparison of Runs 7, 6, and 9 shows that $k_{exp.}$ decreases steadily ($k_{exp.}$ = 1.04; 1.80; 1.71 x 10^{-4}) as the buffer concentration decreases. At first glance, this appears to be a mild Brönsted general acid or base catalytic effect. But removal of the inert salt, compare Runs 9 and 11 ($k_{exp.}$ = 1.71; 2.10 x 10^{-4}), allows the rate constant to increase. The maintenance of constant salt strength, a buffer ratio of 1/2 for CH_3COONa/CH_3COOH, but decreasing buffer concentration again causes a decrease in $k_{exp.}$ as shown by Runs 2 and 10 ($k_{exp.}$ = 0.963; 0.878 x 10^{-4}). Also these latter runs should be 1/2 the rates of Runs 6 and 9 if the hydrogen ion concentration is determined only by the buffer ratio. Such discrepancies precluded the use of buffer ratios as a means of calculating the pH of the solutions. In extending the work it will be necessary to determine the pH of the reaction mixtures very carefully.

Table I

Summary of Kinetic Studies

Run	Substance	Buffer					$k_{exp.} \times 10^4$ ($sec.^{-1}$)	k_{rel}
		NaAc	HAc	NaF_0	HF_0	KNO_3		
5*	BrbutylNH$_2$	2.0	0.5				0.067	
12	"	0.5	0.25				0.0266 ± .0005	1.00
13*	1,1-dimethyl	0.5	0.25				0.055	
17	"	0.5	0.25				0.0584 ± .0025	2.19
1	2,2-dimethyl	1.0	1.0				2.04 ± .06	
7	"	1.0	1.0				2.04 ± .02	
3	"	1.0	1.0			1.0	2.03 ± .02	
6	"	0.5	0.5			0.5	1.80 ± .01	
9	"	0.25	0.25			0.75	1.71 ± .03	
11	"	0.25	0.25				2.10 ± .05	158
2	"	0.5	1.0			0.5	0.963 ± .014	
10	"	0.25	0.5			0.75	0.878 ± .010	
16	"			0.5	1.0		0.0796 ± .0008	
8	"						0.0047 ± .0005≠	
19	2,2-diethyl			0.5	1.0		0.299 ± .017	594
4*	2,2-diisopropyl	0.5	1.0			0.5	56	9190
18*	2,2-diphenyl	0.5	0.25				140	5250
14*	3,3-dimethyl	0.5	0.25				0.0042	0.158

* Indicates runs which are to be regarded as preliminary results, and are good only as an indication of magnitude.

≠ This value is for $k'_{exp.}$

In the meantime, it appears that both the primary and secondary salt effects are in operation, either on the reaction step of cyclization or on

See, for example, H. S. Taylor and H. A. Taylor, "Elementary Physical Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 2nd ed., 1937, pp. 544-550.

the buffer equilibria involved. Since the reaction step, (2), is the reaction of a neutral molecule to form both a positive and a negative ion, one would predict that an increase in ionic strength would favor the rate, a primary effect, but with small magnitude. At the same time, there would be little effect on the preceding equilibrium except by way of influence of the salt on the hydrogen ion concentration. This secondary effect could be large, since the ionic strength increase causes an increase in the ionization constant of acetic acid giving a higher hydrogen ion concentration for a given buffer ratio. In turn, the ionic strength causes a change in the activity coefficients of the buffer salt and inert salt such that different effects will appear at various concentrations. Since the activity coefficients of uni-univalent salts generally reach a minimum at about 1 M, and may or may not increase very much at about 2 M, the constancy in $k_{exp.}$ between runs 7 and 3, in which the ionic strength goes from 1 to 2, is not surprising. Likewise the decrease in ionic strength from 1 M to 0.25 M in going from Run 9 to Run 11, is in a region of rapidly changing activity coefficient, and the overall effect is to decrease the ionization constant of acetic acid, increasing the pH somewhat, and resulting in an increase in $k_{exp.}$ from 1.71 to 2.10×10^{-4}.

The reaction is quite sensitive to the hydrogen ion concentration, and it is a tool which, it is hoped, will be applied to the elucidation of salt effects in great detail in various buffer systems. From (11), by taking the reciprocal and rearranging:

$$\frac{1}{k_{exp.}} = \frac{k_2}{k_1 k_3} H^+ + \frac{k_1 + k_3}{k_1 k_3} \qquad (16)$$

Plotting the reciprocal of the observed rate constant against the hydrogen ion concentration would give a straight line. The intercept is interesting since if $k_1 \gg k_3$, then the value approaches $1/k_3$, which substituted into the

value of slope would give K_1, a term not directly measurable by titration or other methods because of the ease of cyclization of the free base.

Inspection of Run 11 shows a definite trend to lower values of the rate constant as the reaction proceeds, with $\mu = 0.25$. It did not seem wise to go below this value, and in all subsequent runs the buffer salt concentration was made up to 0.50 M.

It was of interest to look into the kinetics of the unbuffered cases. Rigorously,

$$H^+ = A + PH^+ + P + P \tag{17}$$

but if the assumption is made that $k_5 > k_4$, then P must be small as compared to H^+. By substituting (7) into (17), and ignoring the other P, the value of H^+ so obtained may be substituted into (9), which on expansion gives (18).

$$A^2 + A\left(\frac{k_1 + k_3}{k_2} + Br^- - Br_o^-\right) - \frac{k_1}{k_2}\left(AH_o^+ + Br_o^- - Br^-\right) = 0 \tag{18}$$

Since A is a steady state concentration, then $A^2 << A$, and dropping out the A^2 and substituting $AH_o^+ = Br_o^-$, (18) gives (19). Substitution of (19) into (4), and

$$A = \frac{k_1(2Br_o^- - Br^-)}{k_1 + k_3 - k_2Br_o^- + k_2Br^-} \tag{19}$$

rearranging and integrating gives (20), which is still in awkward form.

$$2.303(k_1 + k_3 + k_2Br_o^-)\log\frac{Br_o^-}{2Br_o^- - Br^-} + k_2(Br_o^- - Br^-) = k_1k_3t \tag{20}$$

By assuming that $k_2Br_o^- >> (k_1 + k_3)$, (20) may be rearranged and converted by the use of (12) to (14) into (21), which was used in the calculations for

$$k'_{exp.} = \frac{k_1k_3}{k_2Br_o^-} = \frac{2.303}{t}\log\frac{V_o - V_\infty}{V_t - V_\infty} + \frac{1}{t}\left(\frac{V_t - V_\infty}{V_o - V_\infty} - 1\right) \tag{21}$$

Run No. 8. Using 0.0047×10^{-4} as the value of $k'_{exp.}$, and 95.89×10^{-4} M for Br_o^-, the value of K_1k_3 turns out to be about 4.51×10^{-9}.

Using the data of Run No. 9, and (16), using H^+ as 1.74×10^{-5} M (which is questionable because of the salt effect of 0.75 M KNO_3 present), $\frac{k_1 + k_3}{k_1k_3}$ turns out to be 1.99×10^3. If this value is taken as $1/k_3$, then K_1 is 9.0×10^{-6}, which is decidedly higher than the expected value on the order

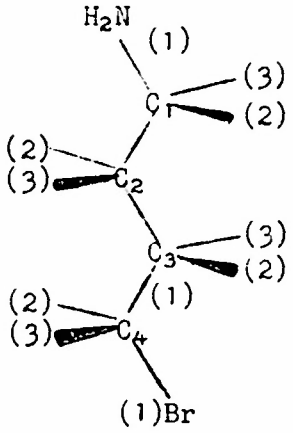
of 10^{-8} to 10^{-10}. Resolution of this question must await the accurate determination of H^+ concentrations in the buffer solutions used.

The effect of change of position of substitution is seen to be large; for two methyls at the first carbon, the rate is only doubled as compared to the parent molecule. But at the second carbon, the maximum effect appears, being 158 x faster. And at carbon No. 3, there is a depression in rate, being only about 1/6 as fast as the parent. However, the bromine in this molecule is in a neopentyl position, and the observed rate is a decided acceleration in rate for such a hindered displacement reaction.

The effect of size is shown in that, on the No. 2 position, ethyl is 3.76 x better than methyl, isopropyl is 56.7 x better, and phenyl is 33.2 x better. This seems to rule out any electronic effects of the substituents as exerting anything other than a minor influence on the rates, since phenyl and isopropyl would have opposite electronic effects but similar steric or bulk factors.

As a speculation, an extension of the explanation of the effect of geminal substituents given previously (pp. 3-4) might be given.

If one considers the bromobutylamine in the extended configuration as illustrated, with C_2 considered as fixed in space, then the number of other configurations may be calculated for different rotational configurations. For the time being, neglect the rotation about the C_1-N bond. Then there will be three favored positions for rotation about the C_1-C_2 bond wherein the amino group will appear at positions (1), (2) or (3) about C_1. Similarly, by rotating the C_2-C_3 bond, the $-CH_2Br$ group will appear at positions (1), (2) and (3) about C_3. And rotation about C_3-C_4, will cause the bromine to appear at (1), (2) or (3) about C_4. All of these positions represent non-eclipse configurations for atoms or groups attached to neighboring carbons. Designate the configuration shown as 12-1 [the amino in position (1)], 23-1 [the $-CH_2Br$ in position (1)], and 34-1 [the bromine in position (1)]; or still more simply 111 (reading from top to bottom). Since the carbon chain is oriented north and south, position (2) is chosen as that reached by the key group from (1) when the rotation is to the east



about the chosen C-C bond. Following this convention, it is possible to write 27 different configurations, of which 13 are paired with 13 mirror images, and one unique structure, the extended conformation as shown. Thus 221 and 331 represent structures closest to and equally likely to be forerunners of the transition state leading to cyclization.

If hydrogens are on C_2 (the parent bromoamine), the molecule has a wide choice of low energy configurations for existence. If methyls replace these hydrogens (as in the 2,2-dimethylbromoamine), then the non-bonded interactions act to push the amino into C_1 (2) or (3), and the bromomethyl group into C_3 (2) or (3). This disfavors the extended structure and 7 other pairs. Roughly then, the configurational choice is reduced from 27 to 12, or the chance of getting into the 221 or 331 states is increased from 2/27 to 2/12!

As the groups on C_2 increase still more in size, it becomes increasingly difficult for the bromine to get into positions C_4 (2) or (3) regardless of the position of the $-CH_2Br$ in C_3 (2) or (3). Of the remaining 6 pairs of states, this removes another 4 pairs, leaving only the 221-331, and 231-321 pairs as possibilities. The chance of getting into the 221-331 state is now 1/2!

This discussion has ignored the height of the energy barrier between rotational configurations and the relative energies of the configurations. When the entropies of activation become available, it will be of interest to refine this approach by introducing such refinements to test the agreement between prediction and result.

It is unfortunate that time did not permit a more conclusive study. Obviously, many questions remain unanswered, and it will be necessary to obtain data at several different temperatures and under a variety of conditions before much can be said definitely about this reaction.

III. EXPERIMENTAL

4-Phenoxybutyronitrile. - Trimethylene bromide was prepared from the glycol,[65] and converted into phenoxypropyl bromide.[66] A solution of 35.8 g. (0.55 mole) of potassium cyanide in 94 ml. of water was added to a solution of 99.6 g. (0.462 mole) of phenoxypropyl bromide in 285 ml. of 95% ethanol. After heating the mixture under reflux for 14 hours in the hood, 250 ml. of solvent was removed at the water pump. Next, 70 ml. of water and 30 ml. of benzene were added. The layers were separated and the aqueous layer was extracted with two 35 ml. portions of benzene. The benzene solution was successively washed with dilute sodium hydroxide and water, dried, and distilled to give 71 g. (96% yield) of oil, b.p. 155-75° (20 mm). Upon redistillation, the material boiled at 158-70° (20 mm) and soon recrystallized to give 4-phenoxybutyronitrile as a low-melting solid.

4-Phenoxybutylamine (I). - A solution of 64.1 g. (0.389 mole) of 4-phenoxybutyronitrile in 174 ml. (1.89 mole) of 2-butanol and 100 ml. of toluene was added to a stirred slurry of 40.4 g. of molten sodium (1.75 atom) in 150 ml. of toluene over a period of 10 minutes. The mixture was heated for an additional half-hour. The solution was washed with water and extracted with dilute hydrochloric acid. Base was added and the amine collected and distilled, giving 54.1 g. (83%), b.p. 148-51° (22 mm). Marvel reports b.p. 146-8° (17 mm).[67]

4-Bromobutylamine Hydrobromide (II). - A solution of 49.5 g. (0.3 mole) of 4-phenoxybutylamine in 330 ml. of concentrated hydrobromic acid was distilled over a period of about four hours from an oil bath at 145°, giving 250 ml. of distilled hydrobromic acid. The solution was evaporated to dryness at the aspirator and the remaining traces of solvent were removed by codistillation with ethylene chloride on the steam bath. The residue was taken up in acetone and decolorized. After concentration, the addition of ethyl acetate gave 50.9 g. (73%) of product m.p. 156-8°. The material was recrystallized from a mixture of 10 ml./g. of ethyl acetate and 1 ml./g. of acetonitrile with 90% recovery, m.p. 157-8°. The pure material was hygroscopic, but much less so than was the crude material.

Anal. Calcd. for $C_4H_{11}Br_2N$: C, 20.60; H, 4.76. Found: C, 20.82; H, 4.76.

An attempt to prepare the picrate of the bromo amine by prolonged boiling of a t-butanol solution of the hydrobromide and picric acid was partially successful, as the yellow color deepened, but the trace of picrate could not be separated from the hydrobromide, which was less soluble in all solvents. The addition of one equivalent of silver picrate to II gave very impure picrate, which, after many recrystallizations from ethylene chloride, had m.p. 110-12°. Melting points of 105° and 127° have been reported for the picrate.[17,18]

Hinsberg treatment of II gave N-benzenesulfonylpyrrolidine, m.p. 51.5-2.0° from carbon tetrachloride, identical with material from authentic duPont pyrrolidine.

Methyl 3-Cyanopropionate (III). - A solution of 172.2 g. (2 moles) of methyl acrylate, 120 g. (2 moles) of glacial acetic acid, and 2 l. of 95% ethanol was warmed to 35°, and a solution of 260 g. (4 moles) of potassium cyanide in 750 ml. of water was added over a quarter-hour period with stirring. Stirring was continued for four hours, and then the solution was allowed to stand for eight hours. Benzene and a saturated solution of sodium chloride were added and the layers were separated. The aqueous layer was extracted twice with benzene and the combined organic layers were washed twice with saturated solution of sodium chloride solution. The benzene solution was distilled at atmospheric pressure to remove the bulk of the benzene and then subjected to vacuum distillation to give 152 g. (67%) of oil, b.p. 72-90° (1 mm).

4-Aminobutanol (IV). - A solution of 57 g. (0.5 mole) of cyanoester (III) in 600 ml. of absolute ether was added dropwise with stirring to a mixture of 26.5 g. (0.7 mole) of lithium aluminum hydride and 750 ml. of absolute ether. During the addition, a gummy white precipitate was formed. After the addition was completed, the mixture was stirred for two hours on a warm water bath, after which time the gummy mass had disintegrated into a white powder. Sufficient water was added dropwise to destroy excess lithium aluminum hydride, and 325 ml. of concentrated hydrochloric acid was added. All material was brought into solution by warming. The acid

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* See p. 39 for a superior method of decomposition of lithium aluminum hydride reductions, the product of which are hydroxyamines.

solution was extracted with ether to remove non-amine impurities and then added dropwise to 400 g. of sodium hydroxide as a 33% solution. Not all alumina formed went back into solution, however, and it was found necessary to heat the mixture to boiling. The solution, after allowing to cool, was filtered and extracted five times with chloroform. Distillation gave 9 g. (20% yield) of oil, b.p. 201-205°. Henry reported b.p. 206°.[68] 4-Aminobutanol was converted to 4-bromobutylamine hydrobromide by the procedure that was used with 4-phenoxybutylamine (I).

Hexamethylenetetramine Adduct of Tetramethylene Dibromide (V). - A mixture of 44 g. (0.2 mole) of tetramethylene dibromide, 84 g. (0.6 mole) of hexamine, and 500 ml. of chloroform was heated on the steam bath for 5 minutes to bring most of the hexamine into solution. The mixture was allowed to stand for one week, during which time the hexamine slowly dissolved as the reaction proceeded. The adduct was filtered off, washed with chloroform and dried. It weighed 71.4 g. (100%). The melting point of the adduct varied from 140° to 160° (with decomposition 10° below the m.p.) depending upon the batch and was not a good characteristic constant for the compound.

One gram of adduct was warmed with 2 ml. of concentrated hydrobromic acid for an hour on the steam bath. The hydrobromic acid was removed *in vacuo* and the solid was extracted with chloroform. The solution was evaporated to dryness and the residue crystallized from ethyl acetate. Recrystallization from ethylene chloride afforded a small quantity of colorless hygroscopic needles, m.p. 151-4°.

When the above procedure was applied to 172 g. of adduct, intractable dark-colored tars resulted. Similar treatment of 71.4 g. gave a dark tar, which was further treated with hydrogen bromide in acetic acid. The latter more drastic treatment was ineffective likewise. A slight odor of formaldehyde was still noted above warm acidic solutions of the tar, even after all of the foregoing treatment.

Methyl 4-Methyl-4-Nitropentanoate (VIII). - The directions given by Bruson were followed.[69] Forty-three grams (0.5 moles) of freshly distilled methyl acrylate was added dropwise, with stirring, over a one-hour period, to a solution of 44.5 g. (0.5 mole) of commercial 2-nitropropane, 25 ml. of t-butanol and 6 g. of Triton B (35% in methanol). The temperature was

maintained between 35° and 40° during the addition. The mixture was then stirred for five hours at 25-30°, made acid to litmus with dilute hydrochloric acid, and extracted with ethylene dichloride. The organic layer was washed with water and distilled at the water pump to remove solvent. The residual oil was vacuum distilled; giving 75 g. (86% yield) of blue liquid, b.p. 95-105° (5 mm).

4-Hydroxy-1,1-dimethylbutylamine (IX). - A solution of 44 g. (0.25 mole) of methyl 4-methyl-4-nitropentoate in 125 ml. of ether was added dropwise to a stirred refluxing slurry of 23.7 g. (0.625 mole) of lithium aluminum hydride in 700 ml. of ether. The rate of addition was giverned by the capacity of the condenser. Heating was continued for 30 minutes. After the addition, the reaction mixture was decomposed by slowly adding 192 ml. (2.5 moles) of 2-propanol with cooling. Next, 156 ml. of saturated sodium chloride was added and stirring was continued for 15 minutes to break up the lumps of inorganic material. The mixture was filtered and the filter cake was washed with a mixture of two parts of 2-propanol and 3 parts of ether. The solvents were removed from the amino alcohol solution in vacuo. leaving a blue oil, which was distilled at 13 mm. to give 21.5 g. (74%) of blue product, b.p. 100-120°. Partial crystallization occurred upon standing.

The blue color undoubtedly arose from an impurity in the original nitro ester, which was blue when freshly prepared. Purification of the amino alcohol was attempted through the formation of a suitable salt. The picrate, p-chlorobenzoate, trichloroacetate, citrate, maleate and p-toluenesulfonate were all found to be liquids as initially prepared, although the last salt crystallized at the end of a week. The oxalate was found to be a solid.

A solution of 8.9 g. (0.07 mole) of oxalic acid dihydrate in 100% ethanol was added to a solution of 16.2 g. (0.14 mole) of the crude amino alcohol in 100% ethanol. The salt (13.8 g., 63%) was collected and recrystallized several times from ethanol containing a small amount of methanol. During this process, the m.p. decreased from 206.7°d. to 199° d.

Anal. Calcd. for $C_{14}H_{32}N_2O_6$: C, 51.83; H, 9.94. Found: C, 52.05; H, 9.70.

The oxalate, although not very hygroscopic, did absorb moisture from the air. The oxalate may alternatively be prepared in acetone or in ether, which are good solvents for hydrated oxalic acid, but the product so obtained was usually oily. Since the oxalate is slightly soluble in ethanol, especially in the crude state, 2-propanol was a more satisfactory solvent for the preparation. The low yield of oxalate was due to the fact that the amount of oxalic acid which was used was calculated on the assumption that the amino alcohol was 100% pure. Since this was not the actual case, the oxalic acid was in excess and excess oxalic acid dissolves the precipitated diamine oxalate with the formation of the very soluble amine hydrogen oxalate.

The pure amino alcohol was liberated from the oxalate by treating a solution of 9.0 g. of the salt (0.028 mole) in 150 ml. of absolute methanol with a solution of 1.6 g. (0.056 atom) of magnesium in 100 ml. of absolute methanol. The supernatent liquid gave a negative test for magnesium with oxalic acid. The precipitate was digested, centrifuged, and washed twice with methanol. The methanol was removed from the clear solution by distillation and the residual oil was distilled to give 5.8 g. (90%) of colorless hygroscopic product, b.p. 108° (15 mm). The product completely solidified upon standing, f.p. 42.5°.

Treatment of the oxalate with either one or two equivalents of benzenesulfonyl chloride and aqueous potassium hydroxide gave two products in the same ratio, but in varying total yield. The major product, N-benzenesulfonyl-2,2-dimethylpyrrolidine (XII) was insoluble in base. It was crystallized from methanol, m.p. 62-3°.

Anal. Calcd. for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16. Found: C, 60.43; H, 7.28.

The minor product, N-benzenesulfonyl-4-amino-4-methyl-pentanol-1 (XI), was soluble in base. It was crystallized from Skellysolve B and recrystallized from aqueous methanol, m.p. 93-4°.

Anal. Calcd. for $C_{12}H_{18}NO_3S$: C, 56.00; H, 7.44. Found: C, 56.22; H, 7.19.

4-Bromo-1,1-dimethylbutylamine Hydrobromide (X). - A mixture of 3.24 g. (0.01 mole) of the oxalate and 20 ml. of concentrated hydrobromic acid was distilled from an oil bath at 150° until 15 ml. of distillate

had been collected. The remainder of the hydrobromic acid was removed *in vacuo*. The solid was dissolved in chloroform and the last traces of hydrobromic acid were codistilled. After concentration, ethyl acetate was added, precipitating 4.52 g. (87%) of amine salt, m.p. 179-80° (oxalic acid remained in solution). The salt was recrystallized several times from ethylene chloride with little loss and no change in m.p. The material can also be crystallized from acetonitrile (5 ml./g.).

Anal. Calcd. for $C_6H_{16}Br_2N$: C, 27.61; H, 5.79. Found: C, 27.51; H, 5.63.

The use of the oxalate salt gave a practically colorless product directly. The crude blue amino alcohol gave a lower yield (30%) of black product upon hydrobromic acid treatment.

The Hinsberg product was N-benzenesulfonyl-2,2-dimethylpyrrolidine (XIII) (m.p. and mixed m.p. with material from the amino alcohol).

The pH of a 0.02 molar solution varied with time as follows:

time (min.)	pH
(0)	4.60
35	4.00
85	3.80
1030	3.30
1930	3.14
2440	3.04

2,2-Dimethylpyrrolidine (XIII) was prepared from 4-bromo-1,1-dimethylbutylamine hydrobromide by treatment with aqueous sodium hydroxide. The amine layer was separated and dried first with potassium hydroxide and then with calcium hydride. Distillation afforded 61% of product, b.p. 106°. Buckley and Elliott reported b.p. 105-6°.[23] The yield was remarkable as no extraction solvents were used to aid in the isolation of the hygroscopic base.

The 2,4-dinitrophenylurea derivative (XV) (m.p. 129-30°) and the picrate (m.p. 186-7°) were prepared according to the directions of Buckley and Elliott, who report melting points of 131° and 190-1° respectively.[23]

2,2-Dimethylpyrrolidine Hydrobromide. - In an attempt to prepare 1-butyl-2,2-dimethylpyrrolidine hydrobromide (XIV), 1 g. of 4-bromo-1,1-dimethylbutylamine hydrobromide was treated with aqueous sodium hydroxide

and the upper layer of 2,2-dimethylpyrrolidine was taken up in ether and the resulting ethereal solution was dried with magnesium sulfate. Butyl bromide (5 ml.) was added and after standing for 2 weeks, the hygroscopic crystals of product were collected and recrystallized from ethylene chloride, m.p. 173-4°. Since this was not the m.p. of the N-butyl compound, a sample of 2,2-dimethylpyrrolidine hydrobromide was prepared from the free base (liberated by alkaline treatment of the bromo amine salt) by neutralization with hydrobromic acid. The hygroscopic salt was found to have m.p. 173-4°. The mixed m.p. was undepressed.

1-Butyl-2,2-dimethylpyrrolidine.Hydrobromide (XIV). - One gram of 4-bromo-1,1-dimethylbutylamine hydrobromide was treated with aqueous sodium hydroxide and the pyrrolidine layer was separated and dissolved in methanol. Butyl bromide (3 ml.) and 2 drops of phenolphthalein were added. The solution was allowed to stand one week, during which time small amounts of 25% sodium hydroxide were periodically added to maintain slight alkalinity, and to prevent the separation of the poorly soluble 2,2-dimethylpyrrolidine hydrobromide. The solution was treated with hydrochloric acid and evaporated to dryness. The solid was taken up in base and the amine layer was separated. The amine was heated with acetic anhydride in benzene to destroy unreacted pyrrolidine. The benzene solution was extracted with dilute hydrobromic acid. Evaporation of the acid solution in vacuo left a brown solid which was recrystallized several times from an ethylene chloride and carbon tetrachloride mixture, once from ethyl acetate, twice from dioxane, and once more from ethyl acetate with a few drops of acetone to give 0.3 g. of white crystals. With recrystallization, the salt became less hygroscopic and the m.p. was raised from 144-5.5° to 146-7°. Elderfield[22] reports m.p. 148-9.5° for this compound.

Anal. Calcd. for $C_{10}H_{22}BrN$: N, 5.93.
Found: N, 6.06.

2-Methylpentanol-2. - A solution of 136 ml. (1.5 moles) of propyl bromide in 500 ml. of ether was added over a period of one hour to 36.5 g. (1.5 atom) of magnesium in 300 ml. of ether. The mixture was heated under reflux for 0.5 hour after the addition, and then cooled. A solution of 110 ml. of acetone in 150 ml. of ether was added dropwise over a period of 0.5 hour. The mixture was heated under reflux for 0.5 hour. Decomposition

was effected by the addition of 215 ml. of saturated ammonium chloride solution. The ether solution was distilled to give 116 g. (76%) b.p. 115-130°. Redistillation gave 111 g. (73%), b.p. 116-125°. Henry[70] lists b.p. 122-3°.

2-Methylpentylamine-2 (XVI). - To a mixture of 126 ml. (1 mole) of 2-methylpentanol-2, 125 ml. of acetic acid, and 51.8 g. (1 mole) of 95% sodium cyanide, was added a solution of 136 ml. of conc. sulfuric acid and 125 ml. of acetic acid over a period of 30 minutes with stirring, under a hood. A cold water bath was used to maintain the temperature between 50 and 60°. The mixture was stirred for 0.25 hour after the addition and allowed to stand overnight. A condenser was attached and a solution of 500 g. of sodium hydroxide in 1750 ml. of water was added through the top. After heating under reflux for 7 hours, the amine was steam distilled into 100 ml. of conc. hydrochloric acid. The acidic solution was extracted with benzene, decolorized, and made basic with 33% sodium hydroxide. The amine was separated and the basic solution was extracted with ether. The amine and extract were combined, dried with potassium hydroxide, and distilled to give 75 g., b.p. 99-104°. Montagne[71] reported b.p. 101-3°. The amine was found to be highly volatile and therefore the ether forerun and the residue were acidified with hydrochloric acid and evaporated to dryness. The residue was crystallized from chloroform-ethyl acetate and recrystallized from 2-propanol-ethyl acetate to give 8.5 g. of the amine hydrochloride m.p. 207-8°. Bewad[72] listed m.p. 190-98°. The total yield was 80%. The amine salt was found to give the same benzenesulfonamide as the liquid amine.

N-Benzenesulfonyl-2-methylpentylamine-2 (XVII). - A mixture of 10.1 g. (0.10 mole) of amine, 15.4 ml. (0.12 mole) of benzenesulfonyl chloride, 12 g. (0.30 mole) of sodium hydroxide and 90 ml. of water were shaken for several minutes. The crystalline product was filtered off and crystallized from Skellysolve B to give 22.7 g. (95%) of product, m.p. 89-90°. The analytical sample was recrystallized several times from Skellysolve B and finally from methanol, lowering the melting point to 88-9°.

Anal. Calcd. for $C_{12}H_{19}NO_2S$: N, 5.80.
Found: N, 5.88.

The sulfonamide was degraded by hydrolysis in order to verify its structure. A mixture of 13 g. of the sulfonamide and 70 ml. of conc. hydrobromic acid was distilled at a bath temperature of 150°. The oil was decanted from the distillate, washed with water and dried. Two distillations afforded a low boiling unsaturated fraction, b.p. 40-70° which instantaneously added bromine, and a liquid of b.p. 131° d. which instantaneously reacted with silver nitrate. Favorskii[73] reported for 2-bromo-2-methylpentane, b.p. 77-78° (145 mm). The corresponding boiling point at 760 mm. was estimated to be 132°. Timmermans[74] listed 2-methylpentane-2, b.p. 67.3°.

A methanolic solution of the sulfonamide with sodium acetate as a base instantaneously decolorized bromine. The solution was placed in the sun for 2 days. A negative starch-iodide test was obtained and addition of water precipitated unchanged starting material as the sole product. Behavior with sodium hydroxide was similar. The sulfonamide was dissolved in a solution of potassium t-butoxide in absolute t-butanol. The solution instantly decolorized bromine, and after 2 days in the sun, the starch-iodide test was found to be negative. In working up the mixture, the product was accidently evaporated to dryness and charred. The sole isolable product from the tar was benzenesulfonamide (m.p. and mixed m.p. with authentic sample).

An attempt was made to prepare phenoxypropylmagnesium bromide by adding a solution of 99.6 g. (0.5 mole) of phenoxypropyl bromide in 200 ml. of ether to 13.4 g. (0.55 atom) of magnesium in 100 ml. of ether. The formation of a white precipitate during the reaction necessitated adding 200 ml. of benzene to maintain homogeneity. At the end of the reaction, Gilman's test[82] for RMgX was negative, and no thermal effect was noted when 73.5 ml. (0.55 mole) of acetone in 100 ml. of ether was added. After decomposition with saturated ammonium chloride, the ether was decanted and extracted with 20% sodium hydroxide to remove phenol. Evaporation of the ether left a white solid which was crystallized from Skellysolve B to give 2 g. of crystals, m.p. 82-3°. This was undoubtedly the Wurtz product, 1,6-diphenoxyhexane, for which m.p. 83° was reported.[75]

3-Ethoxypropanol was prepared in 45% yield from ethyl bromide and the monosodium salt of trimethyleneglycol, using an excess of the glycol

as the solvent according to the procedure of Smith and Sprung[76] who claimed a 65% yield. Because of the unworkable viscosity of the alkoxide solution two further runs were made, using dimethylcellosolve as a diluent in one case and toluene in the other. The yields were 44% and 36%, respectively.

3-Ethoxypropyl bromide was prepared in a 34% yield from the alcohol using phosphorus tribromide, according to the method of Anderson.[77] When their procedure was modified, however, by using pyridine to neutralize free hydrogen bromide, which might cleave the ether, a yield of 71% was realized.

A solution of 247 g. (2.47 moles) of 3-ethoxypropanol and 47.5 ml. (0.59 mole) of pyridine was added slowly (2 hours) with stirring to 90 ml. (0.95 mole) of phosphorus tribromide in an ice bath. The mixture was then heated to 75° for one hour. After cooling, the liquid phase was decanted from the pyridine salts, which were washed with benzene. The combined solution was washed successively with water and saturated sodium bicarbonate solution, dried, and distilled through a Vigreux column. The fraction, b.p. 135-55°, was collected and found to be slightly acidic. It was again washed with saturated sodium bicarbonate, dried, and distilled. The product, b.p. 145-55°, weighed 281 g. (71%).

5-Ethoxy-2-methylpentanol-2 (XIX) was prepared by adding a solution of 161 g. (0.965 mole) of 3-ethoxypropyl bromide in 300 ml. of ether to 26.6 g. (1.1 atom) of magnesium in 300 ml. of ether with stirring, the reaction being started with 1 ml. of methyl iodide. After the addition, which required 1.25 hours, the mixture was boiled for one hour. After cooling in ice, 85 ml. (1.2 mole) of acetone in 85 ml. of ether was added over a period of 0.5 hours. Toward the end of the addition, the mixture became almost solid with precipitated salts, necessitating the addition of 100 ml. of ether to increase the fluidity. The mixture was heated under reflux for 0.5 hours, and then decomposed with 165 ml. of saturated ammonium chloride. The ether solution was decanted and distilled, giving 105.2 g. (75%) of product, b.p. 175-188°.

In order to gain familiarity with the method of Ritter and Kalish[26] for converting a tertiary alcohol to the corresponding amine through

"S_N1 cyanolysis," t-butylamine hydrochloride was prepared in 61% yield according to their directions, which claim an 81% yield.

4-Ethoxy-1,1-dimethylbutylamine (XX). - In a 250 ml. Erlenmeyer flask was placed a mixture of 36.5 g. (0.25 mole) of 5-ethoxy-2-methylpentanol-2, 13 g. (0.25 mole) of 95% sodium cyanide, and 31 ml. of acetic acid. A solution of 34 ml. of conc. sulfuric acid in 31 ml. of acetic acid was added portionwise over an 0.5 hour period with shaking. The temperature did not exceed 55° during this operation. The flask was stoppered and allowed to stand overnight. After the addition of 150 g. of sodium hydroxide in 310 ml. of water, the mixture was heated under reflux for five hours and then steam distilled. Conc. hydrochloric acid (21 ml., 0.25 mole) was added to the first 400 ml. portion of distillate, which contained all of the amine. After ether extraction to remove insoluble oil, 40 g. of sodium hydroxide in 50 ml. of water was added to liberate the amine which was extracted with ether. The extract was dried and distilled, giving 20.1 g. of amine (55% yield), b.p. 170-80°, which was characterized as the picrate, m.p. 118-20° from chloroform.

Anal. Calcd. for $C_{14}H_{22}N_4O_8$: C, 44.92; H, 5.92; N, 14.97. Found: C, 44.86; H, 5.99; N, 15.71.

Concentrated hydrochloric acid was added to 0.37 g. of the picrate in a minimum quantity of water. The picric acid was filtered off and the solution was basified and steam distilled, catching the distillate in 2 ml. of concentrated hydriodic acid. The distillate was evaporated to dryness *in vacuo* and 2 ml. of acetic acid and 2.5 ml. of concentrated hydriodic acid were added. After heating under reflux for 1 hour, the solvent was removed *in vacuo*, water was added and an oily impurity was removed by extraction with carbon tetrachloride. Basification and treatment with 0.3 ml. of benzenesulfonyl chloride gave N-benzenesulfonyl-2,2-dimethylpyrrolidine, m.p. 62-3° from Skellysolve B. The mixed m.p. with authentic material (m.p. 63.5-64°) was 63-63.5°.

2-Chloro-5-ethoxy-2-methylpentane (XXI). - A mixture of 105 g. (0.72 mole) of 5-ethoxy-2-methylpentanol-2 and 360 ml. of concentrated hydrochloric acid (4.32 moles) was shaken for 10 minutes in a separatory funnel. The layers were separated, and the lower acid layer was extracted with Skellysolve B. The combined organic layers were washed with water and

saturated sodium bicarbonate solution, dried with calcium chloride, and distilled. Copious evolution of hydrogen chloride occurred during the distillation, and it was necessary to treat the distillate with potassium carbonate. After drying over phosphorus pentoxide, the material was distilled (more decomposition) to give 44 g. (37%) of product, b.p. 164-176°.

5-Ethoxy-2,2-dimethylvalerophenone (XXII). - Sodamide was prepared from 16.8 g. (0.73 atom) of sodium and 560 ml. of liquid ammonia. Toluene (560 ml.) was added and the ammonia was removed by warming. Next, 106 ml. (0.7 mole) of isobutyrophenone was added all at once and the mixture was heated under reflux for one hour. 3-ethoxypropyl bromide (117 g., 0.7 mole) was added over a period of 1.5 hours. After a reflux period of 10 hours, the mixture was decomposed with water and the toluene solution was distilled to give 129.5 g. (79%) of crude product, b.p. 70-112° (1 mm.). Since a slight excess of sodamide was used, the product was undoubtedly contaminated with allyldimethylacetophenone, b.p. 70° (1 mm).[29]

The ketone (0.55 mole) was added to a suspension of 1.1 mole of sodamide in 800 ml. of toluene. After a reflux period of 4 hours, ammonia evolution had ceased, and the mixture was decomposed with aqueous acetic acid. The toluene solution was distilled to give 57 g. of product, b.p. 110-160° (15 mm) which soon deposited crystals upon chilling. These crystals went into solution at room temperature and therefore were not collected.

A solution of 14.4 g. (0.624 atom) of sodium in 300 ml. of absolute methanol was added to 54 g. of the above cleavage product in 250 ml. of absolute methanol. Next, 16.0 ml. (0.312 mole) of bromine in 100 ml. of absolute methanol was added with swirling. After heating for 15 minutes on the steam bath, 40 g. of sodium hydroxide in 100 ml. of water was added. After 8 hours of refluxing, the mixture was distilled to remove the methanol and volatile product. The distillate was acidified and extracted to remove 31 g. of high boiling liquid which could not be distilled, even at reduced pressure, because of serious foaming. The solution was rendered basic and extracted with chloroform. The extract was fractionally distilled to give 4 g. of crude amine, b.p. 160-90°, and 10 g. of a fraction, b.p. 240°, which solidified on standing. The nickel reagents showed the amine

to be primary. The solid, m.p. 90-1°, after several crystallizations from Skellysolve B and a sublimation, was analyzed.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.02; M.W., 127. Found: C, 66.18; H, 10.38; N, 10.92; M.W. 160 (Rast).
The solid showed no melting point depression when mixed with 3,3,5-trimethylpyrrolidone-2 from the original cleavage with sodamide.

A mixture of 200 ml. of dry dibutyl ether and 0.25 mole of sodamide was heated under reflux for 16 hours, the exit gases being collected in a dry ice trap filled with toluene. The toluene solution was washed successively with cold dilute hydrochloric acid and cold water and then dried. An acetic acid solution of 1 g. of 2,4-dinitrobenzenesulfenyl chloride was added, and after standing for four days, the solution was poured into water and the toluene evaporated in a current of air. The gummy solid was chromatographed twice to give ca. 0.1 g. of yellow crystals, m.p. 77-80°. A sample of authentic butene-1 adduct, kindly supplied by Dr. N. Kharasch, gave m.p. 75-78°. The mixed melting point was 75-6°.

4-Amino-2,2-dimethylpentanoic acid hydrochloride. - Two grams of 3,3,5-trimethylpyrrolidone-2 and 20 ml. of concentrated hydrochloric acid were refluxed for 24 hours. The solution was decolorized and evaporated to dryness in vacuo. The product was washed with acetone and recrystallized several times from ethanol-acetone to give 1.5 g., m.p. 156-7°. Haller and Bauer[29] report m.p. 164°. The pyrrolidone is easily regenerated by neutralization of the hydrochloride.

Anal. Calcd. for $C_7H_{16}ClNO_2$: C, 46.28; H, 8.88. Found: C, 46.12; H, 8.54.

2,2-Dimethyl-4-pentenamide (XXIV). - The corresponding nitrile was prepared in 61% yield by alkylation of lithium isobutyronitrile with allyl chloride according to Ziegler.[78] The nitrile was hydrolysed by heating 5 g. under reflux for 6 hours with a solution of 15 g. of potassium hydroxide in 100 ml. of ethylene glycol and 5 ml. of water. After the addition of 100 ml. of saturated salt solution and 20 ml. of concentrated hydrochloric acid, the solution was extracted with methylene chloride. Distillation gave 5.3 g. (90%) of the acid, b.p. 104-8° (20 mm). The amide readily sublimes at 70° (20 mm) to give large sheets which are invisibly thin and show strong

interference colors.

Anal. Calcd. for $C_7H_{18}NO$: C, 66.10; H, 10.30; N, 11.02. Found: C, 66.40; H, 10.35; N, 10.94.

Sodium (0.72 g., 0.031 atom) was added portionwise to 50 ml. of ammonia containing a crystal of ferric nitrate. After conversion to sodamide, 20 ml. of toluene was added and the ammonia was allowed to evaporate. A solution of 2 g. of the amide in 15 ml. of toluene was added (vigorous ammonia evolution). After heating under reflux for 4 hours, the solution was cooled, treated with 5 ml. of acetic acid and extracted with saturated salt solution. The toluene solution was evaporated to small volume and decolorized. The addition of Skellysolve A and chilling gave 1.5 g. (75%) of 3,3,5-trimethylpyrrolidone-2, m.p. 90-1°. The mixed m.p. with authentic material was undepressed.

Alternatively, 1.00 g. (0.00787 mole) of the amide in 5 ml. of hot Skellysolve E was added to 0.38 g. (2 equivalents) of sodium hydride in 5 ml. of Skellysolve E at 80°. After the vigorous hydrogen evolution subsided, the mixture was heated under reflux for 1 hour, during which time a gummy sodium salt went into solution, leaving about one-half of the original sodium hydride on the bottom. The mixture was cooled and decomposed by the portionwise addition of 1 ml. of acetic acid. The mixture was filtered and heated to boiling to codistil traces of acetic acid. Cooling deposited 0.72 g. (72%) of 3,3,5-trimethylpyrrolidone-2.

N-Benzyl-2,2-dimethyl-4-pentenamide. - A solution of 2,2-dimethyl-4-pentenoyl chloride (from 2.56 g. of the acid and 4 ml. of thionyl chloride) in 5 ml. of ether was added portionwise to a solution of 10 ml. of benzylamine and 20 ml. of water maintained in an ice bath. The product, 3.5 g. (81%) was recrystallized from Skellysolve B and again from 70% methanol giving 3.2 g. of material, m.p. 55-6°. Sublimation at the water pump (100°) raised the m.p. to 56-7°.

Anal. Calcd. for $C_7H_{16}ClNO_2$: C, 46.28; H, 7.77. Found: C, 46.12; H, 8.54.

Treatment with sodium hydride in either Skellysolve E or toluene according to the procedure for 2,2-dimethyl-4-pentenamide gave the sodium salt as a gum. The benzylamide was recovered unchanged to the extent of 77%. No other product was isolated.

Pivalophenone was prepared by the procedure of Willemart,[79] in 44% yield by the addition of t-butylmagnesium bromide to benzonitrile and converted to the oxime, m.p. 163-4°, according to the same directions.

Pivalanilide, m.p. 133-5°, was prepared from aniline, pivaloyl chloride, and pyridine. Schroeter[40] reported m.p. 132°.

N-t-butylbenzamide, m.p. 134-6°, was prepared by the Schotten-Baumann procedure from t-butylamine and benzoyl chloride. Schroeter[40] reported m.p. 135.5°.

Beckmann rearrangement of pivalophenone oxime. - The procedure of Drake[80] using phosphorus pentachloride was modified. A solution of 6.5 g. (0.0312 mole) of phosphorus pentachloride in 50 ml. of benzene was added dropwise with stirring over a 20-minute period to a solution of 5.32 g. (0.030 moles) of the oxime in 100 ml. of ether maintained at 0°. After the addition, the mixture was allowed to stand overnight and then poured over ice. The mixture was neutralized and the organic layer distilled at 18 mm. The sole product, a liquid b.p. 75° (18 mm) was inferred to be benzonitrile by odor and b.p.

Hydrogen chloride was bubbled into a solution of 3.0 g. of pivalophenone oxime in 20 ml. of acetic acid for 0.5 hour. The solution was heated under reflux for 2 hours, cooled and poured onto ice. The solid was collected and recrystallized from aqueous methanol to give 2.1 g. of pivalanilide (70%), m.p. 134-5°. The compound did not depress the melting point of authentic pivalanilide, but did depress the melting point of N-t-butylbenzamide.

Benzenesulfonyl chloride (8.1 ml., 0.063 mole) in 8 ml. of acetone was added with stirring over a 5 minute period to a mixture of 10.64 g. (0.06 mole) of the oxime, 60 ml. of acetone, 50 ml. of water, and 5.5 g. (0.14 mole) of sodium hydroxide which was cooled in a water bath at room temperature. After the addition, stirring was continued for 1.5 hour and then the mixture was heated for 2 hours at 40°. When 100 ml. of water was added to the oily mixture, crystallization occurred. Acetone was removed at the aspirator, and the crystals were collected and washed with water. After crystallization from aqueous methanol, the product, m.p. 124-31°, weighed 7.62 g. (72%). A recrystallization from aqueous methanol gave 6.74 g. (67%), m.p. 133-5°. The product depressed the m.p. of pivalanilide, but did not depress the m.p. of N-t-butylbenzamide.

The compound charred when treated with conc. sulfuric acid at room temperature, but was partially hydrolyzed by heating a mixture of 2 g. in 8 ml. of 85% phosphoric acid with 3 drops of concentrated hydrochloric acid for 24 hours at 100°. When cooled, the upper liquid layer crystallized. The crystals of benzoic acid were collected, washed with water and dried. The crude benzoic acid, m.p. 116-18° and bicarbonate soluble, weighed 0.7 g. Dilution of the phosphoric acid deposited unchanged amide, insoluble in bicarbonate.

A solution of 20 g. of amide and 1.7 of sodium (6.5 equivalents) in 25 ml. of n-butanol was heated under reflux for 3 hours. Water (2 ml.) was added and the heating was continued for 1 hour. Excess water was added and the butanol was removed by steam distillation. Unreacted amide (0.91 g.) was filtered off and the solution was rendered acidic. Benzoic acid, m.p. 121-2° was collected in the amount of 0.54 g.

2-2-Dimethyl-5-phenoxyvalerophenone (XXIII). - To an ammonia slurry of sodamide from 11.5 g. (0.5 atom) of sodium was added 500 ml. of toluene, followed by the dropwise addition of 111 g. (0.75 mole) of isobutyrophenone. The ammonia was evaporated and the suspension heated under reflux for 1 hour. After cooling, 107.5 g. (0.5 mole) of 3-phenoxypropyl bromide in 40 ml. of toluene was added over a 1-hour period with stirring. After the addition, the mixture was kept at room temperature for 1 hour, heated on the steam bath for 18 hours, and then heated under reflux for 18 hours. At this point, the mixture was only slightly basic. After the addition of 200 ml. of water, the organic layer was separated and washed several times with dilute hydrochloric acid, followed by water. After removal of solvents and isobutyrophenone at the aspirator, the solution was distilled at 2 mm. The product, a yellow oil, was collected continuously over the range 70-200° (major fraction 142-162°). The distillate contained ca. 0.5 g. of crystals, which were acidic and proved to be benzoic acid (m.p. and mixed m.p.). The crude phenone was not further purified, but was converted directly to the oxime.

2,2-Dimethyl-5-phenoxyvalerophenone Oxime. - The entire quantity of the crude phenone was dissolved in 500 ml. of 95% ethanol. A solution of 21 g. (0.30 mole) of hydroxylamine hydrochloride and 41 g. (0.30 mole) of sodium acetate trihydrate in 50 ml. of water was added and the solution

was allowed to cool. The bright yellow crystals were collected and washed with Skellysolve A, which removed a yellow tar, leaving white crystals. The tar was again oximated to give 6 g. more of oxime. The oxime was recrystallized once from carbon tetrachloride and again from 100% ethanol. The product weighed 56.7 g. (38% from isobutyrophenone). The melting point dropped from 131-2° to 129-30° with the purification.

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.79. Found: C, 76.68; H, 7.78.

An unsuccessful attempt was made to regenerate the pure phenone by trans-oximation. Thus, 10.00 g. of oxime was dissolved in 250 ml. of acetone (100 equivalents) and 25 ml. of water and 5 ml. of acetic acid were added. After a 24-hour reflux period, water was added and 9.27 g. of the unchanged oxime was collected.

The phenone was successfully regenerated as follows. A solution of 9.22 g. of the oxime and 30 ml. of 2N hydrochloric acid (2 equivalents) in 200 ml. of 2-propanol was heated under reflux for 6 hours. Water was added, the unchanged oxime (2.70 g.) was removed, and the solution was partitioned between water and Skellysolve A. After removal of the Skellysolve A, the remaining oil was distilled to give 5.77 g., b.p. 154-166° (2 mm). Thus, the hydrolysis was 71% complete and the yield was 93% based upon unrecovered oxime. The yellowish phenone partially solidified upon standing (low melting crystals) but was at least 90% pure since 1 g. gave 0.9 g. of oxime of m.p. 129-30°. The mixed m.p. with the original oxime was undepressed.

N-Benzoyl-1,1-dimethyl-4-phenoxybutylamine (XXIX). - Ten grams of 2,2-dimethyl-5-phenoxyvalerophenone oxime (0.0335 mole) was added to a solution of 50 ml. of acetone and 25 ml. of water containing 5.0 g. (0.125 mole) of sodium hydroxide. A solution of 5 ml. (0.0393 mole) of benzenesulfonyl chloride in 5 ml. of acetone was added over a 5-minute period with stirring. The mixture was then heated to 45° and stirred at that temperature for 2 hours. The mixture was neutralized with acetic acid, and 100 ml. of water was added. The crystals were collected and recrystallized twice from aqueous methanol to give 8.42 g. (84%) of product, m.p. 91-2°.

Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.79. Found: C, 76.82; H, 7.98.

A solution of 1.5 g. of the amide and 20 equivalents of sodium n-butoxide in 50 ml. of absolute n-butanol was heated under reflux for

6 hours. Water (2 ml.) was added and heating continued for 1 hour. Water was added and the butanol distilled off. The remaining mixture was extracted with ether. The alkaline solution was acidified, precipitating benzoic acid and silica. The solid precipitate was extracted with sodium bicarbonate solution. Acidification gave benzoic acid, identified by m.p. and mixed melting point. The ether solution was extracted with dilute hydrochloric acid and the ether evaporated to give a solid which was recrystallized from chloroform Skellysolve A to give 0.7 g. of unchanged amide (identified by m.p. and mixed m.p.). The acidic extract was evaporated to dryness and the residue recrystallized once from chloroform-ethyl acetate and again from ethylene chloride to give 0.3 g. of 1,1-dimethyl-4-phenoxybutylamine hydrochloride, m.p. 173-4°. The extent of hydrolysis was 47%, and the yield of amine salt was 47% based upon unrecovered amine.

Anal. Calcd. for $C_{12}H_{20}ClNO$: C, 62.73; H, 8.77; N, 6.10. Found: C, 62.70; H, 8.96; N, 6.00.

Another basic hydrolysis was run as follows. A mixture of 1.0 g. of amide, 5 g. of potassium hydroxide (23 equivalents), 5 ml. of water, and 45 ml. of ethylene glycol was heated under reflux for 22 hours. The mixture was then acidified with 15 ml. of concentrated hydrochloric acid. The benzoic acid and silica were removed by filtration and the filtrate was extracted with ether to remove phenol and the remainder of the benzoic acid. (The phenol was identified as the tribromo derivative). The aqueous solution was evaporated to dryness in vacuo and the residue was extracted with acetone to remove traces of glycol. Recrystallization from chloroform-acetone afforded 0.14 g. (18%) of the amine salt (m.p. and mixed m.p.). No amide was recovered from any of the fractions.

An acid hydrolysis was conducted by heating a solution of 2.97 g. (0.01 mole) of the amide in 10 ml. of concentrated hydrobromic acid under reflux for 6 hours. More concentrated hydrobromic acid (10 ml.) was added and the solution was then slowly distilled from an oil bath (145-55°) for 3 hours. Water was added to the residue and after decolorizing to remove a small amount of tar, the solution was evaporated to dryness. The solid (0.8 g.) was inferred to be ammonium bromide by m.p. >300°, insolubility in chloroform and evolution of ammoniacal gas upon dissolving in base. The distillate was diluted with water and extracted with ether. The ethereal

extract was extracted with sodium bicarbonate to remove benzoic acid and with sodium hydroxide to remove phenol. The ether was then evaporated, giving a small quantity of an oil with a strong pleasant smell. Sodium fusion indicated bromine, but no nitrogen. The oil could not be induced to crystallize, and was not further characterized.

Acid hydrolysis of N-t-butylbenzamide and t-butylamine. - A mixture of 1.77 g. of N-t-butylbenzamide and 10 ml. of concentrated hydrobromic acid was distilled from an oil bath at 150° until 9 ml. of distillate had been collected. Almost immediately upon reaching the b.p. the originally clear solution became cloudy and separated into two phases. An oil passed over in the distillate for about 20 minutes and then stopped. Benzoic acid slowly sublimed throughout the distillation. The oil was decanted from the distillate, washed with water, and dried with calcium chloride. The b.p. was determined to be 73°. The oil was more dense than water and gave an instantaneous test with silver nitrate. These observations indicate t-butyl bromide, b.p. 73°. The residue (0.90 g., 92%) in the flask was ammonium bromide (insoluble in chloroform, behavior with base). It was found that t-butylamine was resistant to hydrolysis under identical conditions. Thus, no cloudiness was noted in the distillate and the amine salt, which was quantitatively recovered, was slightly but completely soluble in chloroform.

Alpha alkylation of nitriles. - Phenyllithium in ether was prepared in half molar quantity according to the directions of Gilman.[81] After cooling, 0.5 mole of calcium hydride dried diethylamine was added over a period of 5 minutes, followed by the addition of 0.5 mole of disubstituted acetonitrile in 100 ml. of ether (or benzene for the aryl nitriles) over a period of 5 minutes. The metallation was exothermic for the aryl nitriles, but not for the aliphatic nitriles. Gilman's color test[82] was negative for the aryl nitriles, but positive for the aliphatic nitriles. The solution was heated to the boiling point and 0.5 mole of phenoxyethyl bromide[66] was added dropwise at such a rate that the capacity of the condenser was not exceeded. The aliphatic nitriles react violently and the addition requires 0.5 hr., but with the aryl nitriles the bromide may be added over a period of 5-10 minutes. The solution was refluxed for an additional 2 hours and then cooled. After extraction with water and dilute

hydrochloric acid, the ether and benzene were removed on the steam bath and the aliphatic nitriles were distilled. When R was phenyl, methanol was added to the residue and the crystals were collected. This procedure was not successful when R was p-tolyl because the crystals melted at room temperature. Therefore, the crude tolyl compound was used directly in the subsequent step. Table I lists the substituted nitriles prepared by this method. Methoxyethyl bromide was prepared in addition in 26% yield by the procedure used for ethoxypropyl bromide (phosphorus tribromide and pyridine). Other workers have also had trouble with this method of preparation.[106] Diisopropylacetonitrile was alkylated with methoxyethyl bromide to give 31% of product, b.p. 129-32° (24 mm).

Table II - $C_6H_5OCH_2CH_2CR_2CN$

R	yield	bp(1mm)	m.p.	Calc. C	Calc. H	Found C	Found H
methyl	88	91-5°	37-9°	76.15	7.99	76.00	7.67
ethyl	75	110-13°	---	---	--	---	--
isopropyl	25	124-8°	---	78.32	9.45	78.40	9.25
phenyl	87	--	86-7°	84.31	6.11	84.13	5.80
p-tolyl	-	--	room temp.	---	--	---	--

Isobutyronitrile was also alkylated with sodamide prepared by adding 11.5 g. (0.5 atom) of sodium piecewise to a solution of 0.2 g. of ferric nitrate in 500 ml. of liquid ammonia. After complete conversion to the amide, 34.6 g. (0.5 mole) of isobutyronitrile was added. After 5 minutes, a solution of 100.6 g. (0.5 mole) of phenoxyethyl bromide in 200 ml. of ether was added over a 15-minute period. The ammonia was allowed to evaporate and stirring was continued for one hour. The solution was filtered and the salts were washed with ether. The ethereal solution was washed with dilute hydrochloric acid, then water, and dried. After removal of the ether on the steam bath, the nitrile was left as an oil, which crystallized on cooling. This was distilled at 2 mm to give 56 g. (59%), b.p. 96-126°. After three recrystallizations from Skellysolve A, 38.5 g. (41% yield of plates, m.p. 37-9°, were obtained.

The nitriles were reduced by adding one mole of nitrile in 400 ml. ether (benzene when R was phenyl) over a period of 30 minutes to a stirred refluxing slurry of 1.25 mole of lithium aluminum hydride in 1800 ml. of ether. After the vigorous reaction during the addition, heating was continued for 30 minutes and the reaction mixture was cautiously decomposed with 5 moles of 2-propanol, followed by 310 ml. of saturated salt solution. The mixture was filtered and the filter cake was washed with ether. The aliphatic amines were obtained by distillation and the aryl substituted amines were isolated in the form of their difficultly soluble hydrobromides by the addition of 125 ml. of concentrated hydrobromic acid to the ether solution. The purified aliphatic amines were converted to their hydrobromides and crystallized from ethylene chloride. The aromatic hydrobromides were crystallized from methanol. These compounds are listed in Table III.

Table III - $C_6H_5CCH_2CH_2CR_2CH_2NH_2$ and Hydrobromides

R		Methyl	Ethyl	Phenyl	p-Tolyl
yield		81	80	90	88
b.p. (20mm)		158-62°	183-7°	--	--
Hydrobromide m.p.		121-2°	140-1°	215-6°	246-7°
Calcd.:	C	52.56	55.63	66.33	67.60
	H	7.35	8.00	6.07	6.62
Found:	C	52.76	55.90	66.43	67.71
	H	7.33	8.22	6.22	6.82

3,3-diisopropylpyrrolidine was isolated in 9% yield when R was isopropyl and the starting material was recovered in 85% yield. The hydrobromide, m.p. 124-5° from carbon tetrachloride-ether, gave a poor analysis, undoubtedly because of a hygroscopic tendency.

Anal. Calcd. for $C_{10}H_{22}BrN$: C, 50.84; H, 9.39; N, 5.93. Found: C, 50.29; H, 9.49; N, 5.62.

N-benzenesulfonyl-3,3-diisopropylpyrrolidine, m.p. 88-9° from Skellysolve B, gave a better analysis.

Anal. Calcd. for $C_{18}H_{25}NO_2S$: C, 65.04; H, 8.53. Found: C, 65.37; H, 8.62.

The isopropyl compound was also reduced in refluxing tetrahydrofuran, using the same procedure as for ether. The pyrrolidine was isolated in 26% yield and the starting material was recovered in 49% yield. An attempt to reduce the isopropyl compound with Raney nickel and hydrogen at 100° and 100 atmospheres for a period of 4 hours was unsuccessful. The starting material was recovered quantitatively.

The nitrile reductions were also tried with sodium and alcohol, using the same procedure as that used for the reduction of phenoxybutyronitrile, where R was methyl, isopropyl, and phenyl. In the case of methyl, the yield was 62%, but, when R was isopropyl, a Prussian blue test for cyanide ion was obtained, and after extraction of a 0.5% yield of the pyrrolidine, the reaction mixture was distilled, giving a distillate of recovered nitrile (76%) and a crystalline neutral residue, m.p. 114-5° from carbon tetrachloride-Skellysolve B. An analysis indicates the empirical formula $C_{10.3}H_{22.2}NO_{2.3}$.

Anal. Found: C, 62.80; H, 11.37; N, 7.11.

Reduction of the phenyl compound gave a very heavy cyanide test and the sole isolable product was 1-phenoxy-3,3-diphenylpropane, m.p. 85-6° from ethyl acetate, in 91% yield.

Anal. Calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.10; H, 6.73.

The reduction of 2,2-diisopropyl-4-methoxybutyronitrile with lithium aluminum hydride was carried out in boiling ether for 16 hours to give 92% of 2,2-diisopropyl-4-methoxybutylamine, b.p. 132-6° (24 mm).

Dimethyl- and diethylacetonitriles. - One mole of the acid and 1.1 mole of thionyl chloride were allowed to stand overnight with a boiling chip to facilitate gas evolution. After heating on the steam bath for 15 minutes to complete the reaction, 150 ml. of ether was added and the acid chloride solution was dropped over a period of one half hour into a stirred solution of 4 moles of liquid ammonia in 400 ml. of tetrahydrofuran cooled in dry ice-acetone. After adding 600 ml. of Skellysolve B, the red slurry was filtered while still cold, and the solid was washed with additional Skellysolve B to remove most of the color. After adding 600 ml. of Skellysolve B, the filtrate was evaporated until the vapor temperature reached 100°. Cooling gave more solid. The total solid so collected was

allowed to dry and was suspended in 400 ml. of chloroform and 1.2 mole of thionyl chloride was added. The mixture was heated on the steam bath until hydrogen chloride evolution completely ceased (4-8 hours). Excess thionyl chloride was destroyed by the cautious addition of enough water to dissolve all solids. The chloroform layer was separated and washed with 5% sodium hydroxide and water. Good fractionation gave isobutyronitrile, b.p. 102-4°, in 89% yield and diethylacetonitrile, b.p. 141-3°, in 88% yield. The recorded values are b.p. 103.8° and 142-6° respectively.[83,84]

Di-p-tolylacetic acid and nitrile. - 1,1-(Di-p-tolyl)-2,2,2-trichloroethane was prepared by the sulfuric acid condensation of toluene and chloral according to the procedure of Fischer[85] in 54% yield, m.p. 86-7° from 2-propanol.

The hydrolysis was conducted by adding 0.5 mole of the above compound portionwise to a still hot solution of 2.5 atoms of sodium in 1 l. of redistilled carbitol. The mixture was heated under reflux for 8 hours. After cooling and filtration to remove salt, the bulk of the carbitol was removed by distillation in vacuo, leaving a thick syrup to which was added 250 ml. of concentrated hydrochloric acid. Water was added and the granular solid was collected, washed with water and crystallized from 100 ml. 80% acetic acid, giving 68 g. (51%) of dense stubby needles, m.p. 143-4°. Fritsch and Feldmann reported m.p. 144°.[86] The acid chloride was prepared by heating 0.246 mole of the acid with 0.28 moles of thionyl chloride and 50 ml. of ethylene chloride overnight on the steam bath (the reaction fails to go in refluxing chloroform). The solvent was removed in vacuo and 60 ml. of ether was added. The solution was added over a period of 0.5 hours to a solution of 85 ml. of concentrated ammonia and 120 ml. of 2-propanol in an ice-methanol bath, keeping the temperature below 15°. The crude amide, (98%), m.p. 184-5°, was removed by filtration. Dox and Thomas reported m.p. 190°.[87]

The amide was dehydrated by heating 0.246 mole with 0.295 mole of thionyl chloride and 50 ml. of ethylene chloride on the steam bath for 6 hours (the reaction fails to go in chloroform). The solvent was removed in vacuo, and the residue was taken up in Skellysolve B and extracted with 10% sodium hydroxide. The nitrile was distilled to remove color. Obtained 51 g. (94%) b.p. 168° (3 mm). Crystallization from 50 ml. of cold methanol

gave 49 g. m.p. 46.5-7°. The overall yield from the acid was 88%. Hoch reports b.p. 212° (18 mm).[99] The nitrile has never before been obtained in solid form.

Diisopropylacetonitrile. - Diisopropylcyanoacetic ester was prepared by adding 0.75 mole of cyanoacetic ester to a warm solution of 0.75 g.-atom of sodium in 500 ml. of absolute 2-propanol. The solution was heated under reflux for 2 hours after the addition of 0.75 mole of isopropyl iodide. A boiling solution of 0.75 g.-atom of sodium in 500 ml. of absolute 2-propanol was added rapidly (before it cools and solidifies), followed by another 0.75 mole portion of isopropyl iodide. After three hours of further boiling 850 ml. of solvent was removed by distillation and the residue was poured into water. The layers were separated and the product was washed with 10% sodium hydroxide to remove monoalkylated product. Upon distillation, 136 g. (93%) b.p. 120-5° (17 mm) was obtained. Marshall reported b.p. 238-41°.[45] The ester was slowly distilled from twice its weight of potassium hydroxide pellets in a copper flask. The distillate was redistilled and the residue was distilled again from potassium hydroxide. The combined distillates were fractionated to give an 83% yield of diisopropylacetonitrile, b.p. 169-70°. Marshall[45] reported b.p. 170-1°.

4-Bromo-2,2-dialkylbutylamine hydrobromides were prepared by hydrolysis of the corresponding amino ethers with concentrated hydrobromic acid. The methyl and ethyl compounds were hydrolysed according to the procedure for phenoxybutylamine, and were recrystallized from chloroform. Further recrystallization from acetonitrile removed a trace of color. The isopropyl compound was hydrolysed according to the same procedure, but after removal of the bulk of hydrobromic acid at the water pump, the remainder was removed in a desiccator over potassium hydroxide. The residue was taken up in a small volume of methylene chloride. The addition of Skellysolve B to the point of cloudiness and chilling deposited 47% of fairly pure bromo amine salt, m.p. 180-1° d. Addition of a large excess of Skellysolve B to the filtrate precipitated 3,3-diisopropylpyrrolidine hydrobromide (36%). The bromo amine salt was recrystallized twice with 85% recovery from a mixture of 18 ml./g. of warm (50°) carbon tetrachloride and 15 ml./g. of Skellysolve A.

2,2-Diphenyl-4-phenoxybutylamine hydrobromide was hydrolysed by boiling with 2 ml./g. of propionic acid which was found to be the best

solvent for this reaction and 2.7 ml./g. of concentrated hydrobromic acid for 48 hours. 2,2-Di-p-tolyl-4-phenoxybutylamine hydrobromide was boiled with 3 ml./g. of propionic acid and 2.7 ml./g. of concentrated hydrobromic acid for 15 hours, whereupon another 2.6 ml./g. of concentrated hydrobromic acid was added and the heating was continued for a total of 48 hours. The solutions were distilled at the water pump to remove the bulk of the hydrobromic and propionic acids. Trituration of the gummy residues with ethyl acetate extracted dark tars leaving behind the 3,3-diarylpyrrolidine hydrobromides in colorless crystalline form. The gem-phenylpyrrolidine salt was obtained in 72% yield and the gem-p-tolylpyrrolidine salt was obtained in 59% yield. The ethyl acetate extracts were evaporated to dryness in vacuo at a temperature of 50°. The residues were further dried in a desiccator over potassium hydroxide and triturated with dry ether to extract tars. This procedure left the crude bromo amine salts as tan powders. These were taken up in methylene chloride and filtered to remove the insoluble pyrrolidine salts. Treatment with charcoal removed all color and the solutions were evaporated almost to dryness at 40° in a current of air. The addition of ethyl acetate precipitated the bromo amine salts which were recrystallized from methylene chloride-ethyl acetate to give material which was still impure. The final yields in both cases were 3%.

All of the 4-bromo-2,2-disubstitutedbutylamine hydrobromides decompose at the melting point. After hydrogen bromide evolution is complete, the samples may be chilled, whereupon they solidify and remelt at the temperature of the corresponding pyrrolidine salt. All behave as secondary amines toward benzenesulfonyl chloride and the nickel reagents. Table IV lists the 4-bromo-2,2-disubstituted butylamine salts and Table V lists the corresponding pyrrolidines obtained by cyclization. The alkyl pyrrolidine salts were crystallized from ethyl acetate and the sulfonamides from Skellysolve B. The aryl pyrrolidine salts were crystallized from methanol and the sulfonamides from aqueous acetone.

Table IV

$BrCH_2CH_2CR_2CH_2NH_2 \cdot HBr$

R		Methyl	Ethyl	Isopropyl	Phenyl	p-Tolyl
yield		93%	63%	40%	3%	3%
m.p.		188-9°d.	170-1°d.	186-7°d.	194-5°d.	241-1°d.
Calcd:	C	27.61	33.24	37.87	49.89	52.32
	H	5.79	6.62	7.31	4.97	5.61
Found:	C	27.73	33.44	37.94	52.22	68.38
	H	5.84	6.62	7.35	5.85	6.86

Table V

3,3-Disubstitutedpyrrolidines

R		Methyl	Ethyl	Isopropyl	Phenyl	p-Tolyl
B.P.		114-5°	169-70°	206-8°	--	--
M.P.		---	---	---	oil	41-2°
Hydrobromide		103-5°	61-2°	124-5°	251-2°	230-1°
Calcd.	C			50.84	63.16	65.06
	H			9.39	5.96	6.67
Found:	C			50.29	63.24	65.23
	H			9.49	5.95	6.45
Benzenesulfonamide		49-50°	37-8°	88-9°	127-8°	100-1°
Calcd:	C	60.22	62.88	65.04	72.70	73.62
	H	7.16	7.92	8.53	5.82	6.44
Found:	C	60.26	62.70	65.37	72.98	73.76
	H	7.28	7.86	8.62	5.91	6.42

As-dimethylsuccinic anhydride was prepared from As-dimethylsuccinic acid which in turn was prepared by the method of Smith and Horwitz[88] which was modified to obtain higher yields. The acid was not isolated as such, but converted directly into the anhydride.

A mixture of 58 g. (1 mole) of acetone, 113 g. (1 mole) of ethyl cyanoacetate, 79 g. (1 mole) of pyridine, and 63 g. (1 mole) of acetic acid

was heated under reflux for one hour. Next, 100 ml. of absolute ethanol was added, and the heat source was removed. Immediately, 65 g. (1 mole) of potassium cyanide was added all at once, whereupon a vigorous reaction ensued. External heating was resumed for one hour. After cooling, 400 ml. of 3N hydrochloric acid was added and the mixture warmed to bring solids into solution. The layers were separated and the aqueous layer was extracted twice with ether. After removal of ether from the combined organic solution on the steam bath, 600 ml. of concentrated hydrochloric acid was added and the mixture was heated under reflux for 24 hours, after which time, another 150 ml. of concentrated hydrochloric acid was added, the heating being continued for another 24 hours. The solution was chilled, the crystals collected and the mother liquor evaporated to dryness in vacuo. All solid material was treated three times with hot acetone (600 ml. total) to separate the acid from ammonium chloride. The major portion of acetone was removed from the solution by distillation at atmospheric pressure, and 150 ml. (1.6 moles) of acetic anhydride was added. The remainder of the acetone was then removed, as well as some acetic acid, by distilling until the vapor temperature reached 120°. The heating was continued for a total of 1.5 hours, and then the solution was distilled at the water pump to give 86 g. of the anhydride (67% overall yield) b.p. 110-118°(18 mm). Auwers[89] gives b.p. 117° (22 mm).

As-dimethylsuccinimide. - A solution of 86 g. (0.67 mole) of the anhydride in 100 ml. of ether was run into a mixture of 300 ml. of ether and 46 g. (2.7 mole) of liquid ammonia maintained in a dry-ice bath. The ammonia was allowed to evaporate, and the ether was removed on the steam bath. Xylene (500 ml.) was added, and the mixture was heated to the reflux temperature. Continuous slow distillation removed water formed by the cyclization of the succinamic acid (formed by dissociation of the ammonium salt). After 0.5 hours, all solids had gone into solution, and within another 5 minutes, the clear solution suddenly became opaque and deposited a negligible quantity of a solid. The hot solution was filtered and chilled. The crystals were washed with Skellysolve A, and the mother liquor was evaporated and chilled again to give a small second crop, which was washed as before. The yield at this point was 80.4 g. (94%) of oily crystals.

Three crystallizations from ethyl acetate lowered the yield to 62.2 g. (73%), m.p. 107-9°. The m.p. is reported to be 106°.[90]

3,3-dimethylpyrrolidine. - Lithium aluminum hydride (61 g., 1.6 moles) was added to 1.5 l. of tetrahydrofuran. The mixture was refluxed with stirring for one hour to bring most of the hydride into solution. The solution was cooled in an ice bath, and a solution 57.2 g. (0.45 mole) of as-dimethylsuccinimide in 175 ml. of tetrahydrofuran was added over a period of 20 minutes. The ice bath was removed, and the mixture was slowly distilled over a period of one hour, 1 l. of tetrahydrofuran being taken off. The mixture was decomposed in the usual way, and 34.5 g. (79%) of 3,3-dimethylpyrrolidine, b.p. 114-15°C was isolated. The benzenesulfonamide was prepared by the Hinsberg method and recrystallized from aqueous methanol. It melted at 49-50° and the melting point was undepressed by admixture with the same compound (m.p. 49-50°) prepared from 2,2-dimethyl-4-bromobutylamine hydrobromide. Furthermore, either of the sulfonamides effectively seeded a solution of the other. The sodium reduction was conducted by rapidly adding a solution of 70 g. (0.55 mole) of the imide in 505 ml. (5.5 mole) of 2-butanol and 350 ml. of diethylcellosolve to a stirred slurry of 126 g. (5.5 atoms) of molten sodium in 250 ml. of diethylcellosolve. The mixture was heated under reflux for one hour. The excess sodium was destroyed with butanol, and then 500 ml. of water and 500 ml. of concentrated hydrochloric acid were added successively. Steam distillation removed the solvents, and a small amount of dark insoluble oil was removed by ether extraction. A solution of 100 g. of sodium hydroxide in 200 ml. of water was added, but ether extraction failed to separate more than a trace of the amine, so the basic solution was steam distilled in order to concentrate the amine. Sufficient sodium hydroxide was added to the distillate to make a 40% solution. A layer of amine failed to separate, therefore, the solution was extracted with o-toluidine (since ether was again unsuccessful). Distillation of the extract gave 5 g. of a product which, after two further distillations, had b.p. 78-81°. This liquid had a strong piperidine-like odor, but gave negative tests for primary and secondary amines with both benzenesulfonyl chloride and the nickel reagents. When treated with methyl iodide, a negligible quantity of crystalline material deposited. This was too soluble, even in Skellysolve B, for recrystallization.

The stepwise reduction of as-dimethylsuccinimide was conducted by rapidly adding a solution of 49.1 g. (0.39 mole) of the imide in 156 ml. (1.7 mole) of dry 2-butanol to a stirred slurry of 39.2 g. (1.7 atom) of sodium in 80 ml. of toluene. The solution was heated for 0.5 hours after the addition, and excess sodium was destroyed with ethanol. The solution was chilled in ice, and 150 ml. of water was added, followed by 142 ml. of concentrated hydrochloric acid. The layers were separated, and the aqueous layer was extracted with ether. The solvents were removed from the combined organic layers in vacuo. The residue was distilled at 20 mm. until crystals started subliming (240°). The distillate (b.p. 120-240°), upon chilling, deposited crystals identical with those of the residue. Fractional crystallization of the distillate and the residue from carbon tetrachloride and methanol, respectively, gave 1 g. of recovered starting material and ca. 10 g. of crystals, m.p. 232-3° with the empirical formula $(C_6H_2NO)_2$.

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.61; MW, 222. Found: C, 64.45; H, 8.30; N, 12.14; MW, 240 (Rast).

3,3-Dimethylglutaric anhydride was prepared by a method improved with respect to both ease of manipulation and yield over the method previously described in the literature by Vogel.[91]

A mixture of 800 ml. of commercial absolute ethanol, 147 ml. (2 moles) of acetone, and 450 ml. (4.24 moles) of ethyl cyanoacetate was cooled to -40°C., and 150 g. of liquid ammonia was added. The solution was allowed to warm up to 5° and placed in a refrigerator, at that temperature, for 12 hours. The crystalline mass was broken up and the flask was returned to the refrigerator for a four-day period. The mixture was filtered and the crystals washed successively with ether and cold ethyl acetate.

Upon evaporating the mother liquor to a small volume and adding ether, a second crop was obtained, which was washed as before. The ammonium salt of the Guareschi imide amounted to 369 g. (89%). The lumps were broken up and 367 g. (1.76 moles) was added slowly (45 min.) with mechanical stirring, to 880 ml. of cold concentrated sulfuric acid maintained in an ice bath to keep the temperature from rising above 20°C. After all material had dissolved, the bath was removed and the solution was allowed to warm spontaneously to 50°, whereupon it was cooled to 38°. It remained at that temperature for 3 hours before cooling to room temperature. The stirring

was stopped, and the clear golden solution was then transferred to a 5-liter flask, and 795 ml. of water and 20 ml. of concentrated hydrochloric acid were added. The solution was heated to the reflux temperature with a very small flame. Soon, a white solid deposited, whereupon serious foaming ensued. (The frothing seemed to be a function of the amount of white solid present, which apparently decarboxylates and goes into solution). After 48 hours, all solid had gone into solution. The solution was cooled to 0° and the crude dimethylglutaric acid was collected and sucked as dry as possible. The moist crystals were dissolved in chloroform and decanted from the lower layer of sulfuric acid. After clarification and filtration, 330 ml. (3.5 moles) of acetic anhydride was added and chloroform was removed by distillation until a vapor temperature of 120° was reached. After being heated under reflux for a total time of two hours, acetic acid and anhydride were removed at the water pump, and the liquid residue, after being allowed to cool somewhat, was treated with a 50-50 mixture of Skellysolve B and carbon tetrachloride.

The light tan crystals of 3,3-dimethylglutaric anhydride were collected and washed with more of the 50-50 solvent. They weighed 169 g. (60% overall yield from acetone, m.p. 123-4°. Vogel reports m.p. 125°.[91] If a purer, colorless product is desired, distillation in an apparatus designed for the distillation of solids is recommended, as the color is difficult to remove by recrystallization.

4,4-Dimethylpyrrolidone-2.- Liquid ammonia (30 g.) was added to 300 ml. of commercial 2-propanol cooled to -40°C. To this solution was added 85.2 g. (0.6 mole) of the glutaric anhydride in portions. The mixture was allowed to warm to room temperature and Skellysolve A was added to render the slush filterable. The crystals of ammonium 3,3-dimethylglutaramate weighed 103.4 g. (98% yield).

The ammonium salt was dissolved in 100 ml. of water, and 24.1 g. (0.59 mole) of sodium hydroxide was added as a 50% aqueous solution. Boiling expelled ammonia, leaving a solution of the sodium salt. A 0.25 M solution of chlorine was prepared by collecting, in 2,350 ml. of cold 10% sodium hydroxide, the chlorine generated from 37.9 g. of potassium permanganate and 415 ml. of concentrated hydrochloric acid. To this solution was added the glutaramate solution and the mixture was warmed to 40°. Thereupon, the

temperature rose spontaneously to 50°. The beaker was wrapped in newspaper to insulate it and allowed to stand. At the end of 2.5 hours, the temperature had fallen to 38°, and the solution was then neutralized with 455 ml. of concentrated hydrochloric acid, and allowed to stand overnight. Even after being saturated with salt, it was not possible to extract any product from the solution with chloroform, and therefore, the solution was concentrated to a very small volume (the precipitated salts were washed with acetone and the distillate was strongly acidified and evaporated to dryness and the residue was neutralized, so that no product was lost by this operation), and extracted with n-butanol. The butanol solution of the combined products was distilled at 18 mm., yielding ca. 5 g. of very oily, crude crystals (b.p. 150-155°) which were too soluble, even in Skellysolve B, for further purification.

Isopropylidinecyanoacetic ester. - The directions of Cope[92] using ammonium acetate as a catalyst were modified in the first two runs. In the first run, using acetic anhydride to remove water, the starting materials were recovered, no product being isolated. In the second run, using calcium carbide to remove water, a soft golden resin was the sole reaction product. A third run, using a modification of the procedure of Birch and Kon,[93] was successful. A mixture of 81 ml. (1.1 mole) of acetone, 106 ml. (1 mole) of ethyl cyanoacetate and 2.3 g. of ammonium acetate was allowed to stand for three days. The water layer was removed by distilling the mixture until the vapor reached 90°. Benzene was added and the mixture distilled until the vapor reached 100°. One gram of ammonium acetate and 30 ml. of acetone were added and the mixture allowed to stand for two days. The water was removed by the above procedure. This process was repeated twice. The mixture was distilled to give 120 g. of product (78%) pf b.p. 116-132° (20 mm). Crystallization occurred upon standing. Reported b.p. 99-101°C. (9mm).[92]

Ethyl 2-Cyano-3,3-dimethyl-4-nitrobutanoate (XXXIII). A trial run using a catalytic amount of Triton B gave only a 44% yield of product. Since the anion of nitromethane is the reactive species, it was decided to follow the method of Kohler,[94] using the sodium salt of nitromethane.

To a solution of 23.7 g. (0.44 mole) of commercial sodium methoxide in 250 ml. of absolute methanol was added 64 ml. (1.2 mole) of nitromethane.

The mixture was shaken to break up lumps of the sodium salt and 61.2 g. (0.4 mole) of isopropylidine cyanoacetic ester was added. The mixture was shaken until all solid had gone into solution (2 min.). The solution was cooled and 30 ml. of glacial acetic acid was added. After standing for 40 hours, a solution of 10 ml. of concentrated ammonia in 200 ml. water was added and the layers were separated. The aqueous layer was extracted three times with chloroform and the combined organic solutions were dried. The solvent was removed at the aspirator, and the remaining oil was distilled at 2 mm. Material distilling in the range 107-115° was collected. The yield was 63 g. (74%). Bahner reports b.p. 110-111° (1 mm).[95]

Basic Hydrolysis of Ethyl 2-Cyano-3,3-dimethyl-4-nitrobutanoate. (unsuccessful). - In two runs, previous to the development of the synthesis of the nitro-ester as given above, the nitro-ester was prepared according to the method of Kohler,[94] and hydrolyzed without isolation.

To a solution of 5.6 g. (0.24 atom) of sodium in 150 ml. of absolute methanol was added 32 ml. (0.6 mole) of nitromethane. The mixture was shaken to disperse the salt and 30.6 (0.2 mole) of isopropylidine cyanoacetic ester was added. After further shaking for several minutes, all suspended salt had gone into solution. Twenty milliliters of glacial acetic acid was added and the solution was saturated with hydrogen chloride (103 g.). After the mixture had stood for one hour, it was poured into a mixture of ice and 150 g. anhydrous sodium carbonate. The mixture was extracted with benzene and the benzene was removed on the steam bath. The resulting ester was hydrolyzed by adding a solution of 32 g. of sodium hydroxide in 70 ml. of water and refluxing the mixture for 2 hours (immediate evolution of ammonia was noted). After cooling in ice, 70 ml. of concentrated hydrochloric acid was added dropwise with stirring over a 15-minute period, and after standing overnight to insure attainment of equilibrium, the acid was decarboxylated by distilling the mixture to dryness and heating to 200° for 45 minutes. The resulting solid was extracted with ether and the ether solution was then extracted with a sodium carbonate solution. The basic solution was acidified and extracted with ether. After distillation of the ether, toluene and Norite were added and the solution was filtered. After adding Skellysolve A, the solution was chilled, yielding less than one gram of crude pale yellow acid, m.p. 105-8°. It was not felt worthwhile to further characterize or analyze the product in view of the low yield obtained.

To a solution of 8.8 g. (0.22 mole) sodium hydroxide in 50 ml. of water was added 21.4 g. (0.1 mole) of ester. A clear yellow solution was obtained, which was heated under reflux for 19 hours (ammonia was still being evolved and crystals of ammonium carbonate had deposited in the condenser). Since the solution was quite brown by this time, it was felt that it would be best to work it up without completing the hydrolysis. Therefore, 13 ml. (0.22 mole) of glacial acetic acid was added and the solution was allowed to stand overnight to reach equilibrium. After adding 12 ml. each of sulfuric acid and water, a heavy brown sludge was removed by filtration and the solution extracted with ether. After drying and clarification of the extract, the ether was distilled off and toluene and 5 ml. of piperidine were added to effect decarboxylation. After boiling for two hours, the mixture was extracted with sodium carbonate solution and the extract treated with Norite. Acidification, further decolorization, and chilling of the solution deposited only sodium chloride. None of the organic acid with m.p. 105-8° could be isolated.

Acid Hydrolysis of Ethyl 2-Cyano-3,3-dimethyl-4-nitrobutanoate. (Unsuccessful). - A mixture of 21.3 g. (0.1 mole) of the ester, 25 ml. of hydrochloric acid, and 25 ml. of methanol was refluxed for nineteen hours. The mixture was diluted with water and extracted with ether. The ether solution was extracted with sodium carbonate solution (evaporation of the ether left 8.4 g. of neutral oil which may have been the unreacted ester). The carbonate solution was acidified and extracted with ether. After removal of the ether, the material was heated to 170° for 0.5 hour to effect decarboxylation. Toluene was added and the solution was extracted with sodium carbonate solution. The ether was displaced with toluene on the steam bath. After adding Skellysolve A and chilling, 3 grams of white crystals were deposited (m.p. 136-8°). This compound proved to be as-dimethylsuccinic acid, m.p. 138-9°.[88]

The toluene solution of the decarboxylation products after the carbonate extraction was heated under vacuum to remove the toluene, leaving 2 g. of neutral oil. This is presumably 2,2-dimethyl-4-nitrobutyronitrile, since hydrolysis with concentrated hydrochloric acid gave a product of m.p. 139-41° showing no depression when mixed with as-dimethylsuccinic acid from the decarboxylation.

Another run, using concentrated hydrochloric acid, dioxane and 21.4 g. of the ester, after refluxing for 100 hours, yielded several grams of ammonium chloride and 0.8 g. of crude as-dimethylsuccinic acid, m.p. 131-6°.

The Curtius Reaction of 3,3-Dimethylglutaric Anhydride. (Unsuccessful) A mixture of 7.2 g. (0.11 mole) of sodium azide, 14.2 g. (0.1 mole) of the anhydride, and 100 ml. of dry n-butyl ether was stirred in a water bath which was rapidly heated from 60° to 100°C. No gas evolution was observed, so the mixture was cooled and 5.7 ml. (0.1 mole) of glacial acetic acid was added. The mixture was again heated. Vigorous gas evolution began at 85°C. The mixture was maintained at 100°C for 0.5 hour, and then was heated to the reflux temperature and held there for 0.5 hour. Water and 5 g. of sodium hydroxide were added and the butyl ether was steam distilled. The aqueous solution was neutralized, saturated with salt and extracted with ether. Evaporation of the ether left 1 g. of crude oily product, m.p. 50-55°C. Because of the low yield, this product was not further characterized.

The Preparation and Hofmann Degradation of 3,3-Dimethylglutaramic Acid. - Fifty milliliters of 2-butanol were cooled to -40° and 5 g. of liquid ammonia was added, followed by 14.2 g. (0.1 mole) of 3,3-dimethylglutaric anhydride. The mass was allowed to come to room temperature. After one hour, the solid was collected and washed with Skellysolve A. The yield was 17.3 g. (98% yield) of ammonium salt.

One-third of a solution of 20.4 g. (0.885 atom) of sodium in 450 ml. of absolute methanol was added to a solution of 52 g. (0.295 mole) of the ammonium salt in 300 ml. of absolute methanol, and the solution was boiled for 15 minutes to expel the ammonia. The solution was cooled and the remainder of the methoxide solution was added, immediately followed by 15.1 ml. (0.195 mole) of bromine. The solution was placed on the steam bath for 15 minutes to complete the reaction. The bulk of the methanol was removed in vacuo, 100 ml. of water was added, and the mixture was extracted with benzene. Removal of the benzene from the solution left 55.8 g. (quantitative

yield) of a pale yellow highly viscous oil. Distillation at 2 mm gave 59 g. of a distillate with b.p. 130-58°C and 6.5 g. of residual tar. The distillate partially crystallized upon standing. The neutral fraction of 3,3-dimethylglutarimide m.p. 144-5° was removed by ether extraction from a slightly alkaline solution. Acidification of the basic solution followed by extraction and distillation yielded a colorless and extremely viscous oil b.p. 140-5° (2 mm), which did not crystallize. A low neutralization equivalent of 171 was obtained for this purified material. It was found impossible to prepare insoluble mercury, lead, silver or S-benzylthiuronium salts. The sodium salt prepared in absolute butanol separated as an oil after the alcohol was completely displaced with anhydrous toluene by distillation, and the solution cooled in dry ice. The oil eventually turned into an oily semi-solid mass, which could not be successfully recrystallized because of its high solubility.

A derivative was prepared by hydrolysis of the urethane function. Thus, 5.7 g. was refluxed for 4 hours with 33 ml. of 30% sodium hydroxide. To the solution was added 50 ml. of water and 6 ml. of benzoyl chloride. The mixture was shaken until the reaction was over and then acidified. The oily precipitate was found to be only partially soluble in sodium bicarbonate and therefore, all neutral material was removed by ether extraction from alkaline solution. After acidification, the solid was collected and recrystallized twice from aqueous methanol and once from chloroform-hexane. The acid melted at 117-120°C, and gave a neutralization equivalent of 239. (Calcd. for $C_6H_5CONHCH_2C(CH_3)_2CH_2CO_2H$ is 235).

Preparation and Hofmann Degradation of Methyl 3,3-Dimethylglutaramate. (Unsuccessful) - A solution of 80 g. (0.56 mole) of 3,3-dimethylglutaric anhydride in 50 ml. (1.24 mole) of absolute methanol was refluxed for 4 hours. Distillation gave 9.5 g. (98% yield) of the monomethyl ester, b.p. 146-56°C (18 mm).

A mixture of 56.6 g. (0.325 mole) of the monomethyl ester and 38.5 ml. (0.49 mole) of thionyl chloride was allowed to stand overnight at room temperature. After heating on the steam bath for 10 minutes, the bulk of the excess thionyl chloride was removed under reduced pressure. Dry benzene

was added and distilled off at reduced pressure to remove the last traces of thionyl chloride.

The crude acid chloride was dropped slowly into 100 ml. of concentrated ammonia with stirring. The temperature was maintained below 20°C, with a salt-ice bath. Extraction and distillation gave 46.5 g. (83% overall) of the amide, b.p. 110-15° (2 mm). A solution of 12.4 g. (0.54 atom) of sodium in 390 ml. of absolute methanol was added to a solution of 46.5 g. (0.27 mole) of the amide in 240 ml. of absolute methanol. Immediately, 15.5 ml. (0.27 mole) of bromine was added and the solution was heated for 15 minutes on the steam bath. The solution was neutralized with acetic acid. The bulk of the methanol was removed in vacuo and sufficient water was added to dissolve precipitated salts and induce crystallization of the water insoluble product. Twenty grams of oily crystals were thus collected (fraction 1). A second component which remained in solution despite the addition of more water, was isolated in the form of oily crystals by saturating the solution with salt, and extracting the solution with chloroform. After displacing the chloroform with Skellysolve C and cooling, 13 g. of oily crystals were collected (crude 3,3-dimethylglutarimide).

Fraction 1, after several recrystallizations from aqueous methanol and several subsequent recrystallizations from chloroform, was obtained in the form of asbestos-like fibers with m.p. 269°C. This neutral compound contained bromine and gave the following results upon analysis.

Found:	C, 28.2; H, 3.1; N, 4.3
Calcd. for $C_7H_2Br_2NO_2$	C, 28.1; H, 3.0; N, 4.7
Calcd. for $C_8H_{11}Br_2NO_4$	C, 27.8; H, 3.2; N, 4.1

Since this compound failed to depress the melting point of camphor, a Rast molecular weight could not be determined. The identity of the compound was not further established.

2,2-Dimethylbutanediol-1,4 (XXXVI). - A solution of 64 g. (0.5 mole) of as-dimethylsuccinic anhydride in 100 ml. of ether was slowly added to a refluxing slurry of 23.7 g. (0.625 mole) of lithium aluminum hydride in one liter of ether. The mixture was heated under reflux for one hour after the addition. The mixture was cooled in ice and decomposed with 191 ml. (2.5 mole) of 2-propanol. After adding 156 ml. of saturated salt solution, the mixture was filtered and the filter cake was washed with

ether. The filtrate was distilled, giving 44.8 g. (76%) of glycol, b.p. 229-33°. The reported b.p. is 123° (10 mm).[96]

1,4-Dibromo-2,2-dimethylbutane (XXXVII) was prepared by adding 70.3 g. (0.595 mole) of the glycol XXXVI in 31.4 ml. (0.4 mole) of dry pyridine dropwise to 114 ml. (1.2 mole) of phosphorus tribromide at room temperature. After the addition, the mixture was stirred at 130° in an oil bath for 2.5 hours. The reaction mixture was cooled, poured onto ice and extracted with chloroform. The chloroform solution was filtered to remove solid material and extracted with 1% sodium hydroxide until the aqueous layer remained basic. The chloroform solution was then extracted with concentrated sulfuric acid to remove unreacted glycol and bromohydrin, and then washed with water and dried. Distillation afforded 20.5 g. of product (14.5%), b.p. 108-12° (22 mm).

1-Bromo-2,2-dimethyl-4-phthalimidobutane (XXXVIII) was prepared by adding 10 g. (0.055 mole of potassium phthalimide[97] to a solution of 13.3 g. (0.055 mole) of the dibromide XXXVII in 60 ml. of dimethylformamide. The solution was heated on the steam bath for 1.5 hours, and then 45 ml. of chloroform was added and the solution was poured into 100 ml. of water. The aqueous phase was separated and extracted with chloroform. The combined chloroform solutions were washed with dilute sodium hydroxide and water, and dried. The chloroform was removed on the steam bath and the residue was distilled at the water pump to remove 4.6 g. of an oil which passed over around 65°. This oil was unsaturated to bromine and to permanganate and, because of the boiling point, must be a bromo hexene. The residue solidified upon cooling and was crystallized from Skellysolve B to give 9.0 g. (52.9%) of product, m.p. 60-1°.

Anal. Calcd. for $C_{14}H_{16}BrNO_2$: C, 54.20; H, 5.20; N, 4.52. Found: C, 54.41; H, 5.09; N, 4.35.

4-Bromo-3,3-dimethylbutylamine Hydrobromide (XXXIX) was prepared by boiling a mixture of 9 g. (0.029 mole) of the Gabriel product XXXVIII, 29 ml. of concentrated hydrobromic acid, and 29 ml. of acetic acid for 5 hours. The solution was chilled and the phthalic acid was collected and washed with a minimum quantity of acetic acid. The filtrate was evaporated to dryness in vacuo on the steam bath and the residual traces of solvent were removed in a desiccator over potassium hydroxide. The product was

crystallized from acetonitrile (12 ml. per g.) to give 4.5 g. (60%) of pure material, m.p. 245-6° d.

Anal. Calcd. for $C_6H_{15}Br_2N$: C, 27.61; H, 5.79. Found: C, 27.54; H, 5.56.

Treatment with benzenesulfonyl chloride and aqueous sodium hydroxide gave N-benzenesulfonyl-3,3-dimethylpyrrolidine, m.p. 49-50°. The mixed melting point with authentic material was undepressed.

Hydroxypivalaldehyde (XL) was prepared from formaldehyde, isobutyraldehyde and potassium carbonate using the procedure of Kapp.[100]

2,2-Dimethyl-4-nitro-3-butenol-1 Various procedures for condensing hydroxypivalaldehyde with nitromethane were tried, using sodium hydroxide and methoxide and diethylamine as condensing agents. The best procedure follows. The aldehyde (48.3 g., 0.473 mole), 25.4 ml. (1 equiv.) of redistilled nitromethane and 48.7 ml. (1 equiv.) of dry diethylamine were allowed to stand for 5 hours at room temperature. The mixture was acidified with acetic acid and partioned between ethyl acetate and saturated salt solution. Distillation afforded 51 g. (66%) of nitro glycol, b.p. 80-180° (2 mm). Dehydration was accomplished by heating 12.4 g. (0.076 mole) with 16.2 ml. (0.167 mole) of acetic anhydride to a temperature of 120°, whereupon an exothermic reaction set in, raising the temperature to 151°. In 5 minutes the solution had cooled to 120°. This temperature was maintained by external heating for an additional 10 minutes. The mixture was taken up in ether and extracted with water. Distillation gave 10.4 g. (73%) of nitroalkene, b.p. 103-115° (2 mm).

3,3-Dimethyl-4-hydroxybutylamine (XLIII). - A solution of 10.3 g. (0.05 mole) of the nitroalkene in 25 ml. of tetrahydrofuran was added to a slurry of 6.3 g. (0.165 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran over a 15 minute period with cooling in a water bath. After an 0.5 hour reflux period the reaction was worked up in the usual manner to give 4.1 g. (64%) of product, b.p. 122-7° (24 mm). This material formed an oxalate, m.p. 214° d.

4-Bromo-3,3-dimethylbutylamine Hydrobromide (XXXIX). (Unsuccessful). Thionyl bromide was prepared from thionylchloride and hydrogen bromide by the procedure of Elderfield.[101] Thus, 0.2 g. of the amino alcohol (XLIII) in 5 ml. of dry benzene was treated with an equivalent of thionyl bromide

in 5 ml. of dry benzene over a 3-hour period. The mixture was stirred for an additional 3 hours. The solution was evaporated in vacuo, giving a gummy dark-colored solid. This was treated with sodium hydroxide and benzenesulfonyl chloride, giving a trace of N-benzenesulfonyl-3,3-dimethylpyrrolidine (m.p. and mixed m.p.).

Acetoxypivaldehyde was prepared on a 4-mole scale by adding toluene to the methylene chloride solution of hydroxypivalaldehyde, as obtained in the previously used procedure, and codistilling off the water. Next, 410 ml. of acetic anhydride was added over a period of 30 minutes to the boiling solution. The heating was continued for an additional hour and the excess anhydride was decomposed by the addition of alcohol. The solution was extracted with water and dilute base. Distillation gave 305 g. (53%) of product b.p. 85-105° (18 mm) and a considerably effervescing residue. The material was redistilled twice at atmospheric pressure to give 120 g. (21%) b.p. 180-8° (lit. b.p. 182°)[107] a considerable low boiling forerun and residue. The low boiling material was fractionated to give isobutyl acetate, b.p. 111-114°. Basic hydrolysis gave isobutyl alcohol, b.p. 105-8°, which was treated with phenyl isocyanate to give the phenyl urethane of isobutyl alcohol, m.p. 86°.

The attempted condensation of acetoxypivalaldehyde with nitromethane was conducted by adding 0.22 mole of nitromethane to a solution of 0.2 atom of sodium in 150 ml. of absolute methanol, followed by the addition of 0.2 moles of the aldehyde in 50 ml. of absolute methanol over a period of 15 minutes, keeping the temperature around 10° by cooling. The white salt of nitromethane soon went into solution giving a golden color. The solution was cooled to 0° and 0.4 mole of acetic acid was added dropwise. The solution was allowed to stand overnight and then partitioned between water and chloroform. At 18 mm., material distilled continuously up to 110°. At 1 mm the residue distilled continuously from 95° to 140° giving only 16 g. of a mixture.

Opening of As-dimethylsuccinic Anhydride With Amines. - A solution of 12.8 g. (0.1 mole) of as-dimethylsuccinic anhydride in 50 ml. of ether was added to 5 g. (0.3 mole) of liquid ammonia in 50 ml. of ether with dry ice cooling. The precipitate (16.0 g., 99%) was collected, powdered, and slowly added as a suspension in 100 ml. of tetrahydrofuran to a refluxing

slurry of 12 g. (0.316 mole) of lithium aluminum hydride in 200 ml. of tetrahydrofuran. Violent evolution of ammonia occurred. After 11 hours of heating, 250 ml. more of tetrahydrofuran was added, but the voluminous solid failed to dissolve. After a total reflux time of 24 hours, the reaction was worked up by adding 2-propanol and a minimum amount of water (no hydrogen came off). The slush was centrifuged and the supernatent liquid was distilled, giving 1.85 g. (16%) of amino alcohol, b.p. 117-121° (21 mm). The nickel tests were positive for a primary amine and negative for a secondary amine.

The Hinsberg reaction gave N-benzenesulfonyl-3,3-dimethylpyrrolidine (m.p. and mixed m.p. with authentic material) and a trace of a base-soluble sulfonamide, m.p. 93-4°.

The amino-alcohol (0.5 g.) was added to 10 ml. of concentrated hydrobromic acid and the solution was distilled from an oil bath at 150° until 7 ml. of distillate had been collected. The remaining liquid was removed <u>in vacuo</u> and the residue was extracted with ethylene chloride, leaving a gum. The ethylene chloride solution was chilled and the crystalline product was recrystallized from acetone several times, decreasing the initial m.p. from 186-7° d. to 182-4°d. This compound gave no m.p. depression when mixed with authentic 4-bromo-2,2-dimethylbutylamine hydrobromide, m.p. 188-9° d., in varying proportions. That these compounds were identical was proved both by the fact that both gave the same Hinsberg product, and also by the Debye-Scherrer powder technique. Thus, 6.8 hour exposures to an X-ray source operating at 30 kv and 15 ma with a copper target and nickel filter gave powder diagrams which were completely superimposable.

A preliminary run in which both succinamic acids were obtained (subsequent runs failed to afford any more than one isomer) was carried out by adding a solution of 6.4 g. (0.05 mole) of the anhydride in 25 ml. of ether to 3 g. of liquid ammonia in 25 ml. of tetrahydrofuran in a dry ice bath. After removal of excess ammonia by boiling on the steam bath for a short while, water and 4.2 ml. of concentrated hydrochloric acid were added. The three-phase system (solid plus 2 liquid phases) was filtered to remove the lower melting solid, and the organic layer was separated and evaporated to dryness to give crude higher melting solid. Both materials

were found to be insoluble in all solvents except water and alcohols, in which they are quite soluble. Both were recrystallized from 2-propanol, (a, m.p. 124-5°; b, m.p. 136-7°). Both of these compounds are cyclized to the known succinimide, m.p. 106-8°, by brief heating. Both acids depressed each others melting point as well as the m.p. of the succinic acid (m.p. 136-8°). The major product was the low melting isomer. Other runs were made in which the ammonium succinimate was treated with methanolic sodium hydroxide to give the sodium salt, which was recrystallized several times from methanol. The free acid was liberated by treatment with the theoretical quantity of sulfuric acid in 2-propanol. Yields were low, perhaps because of acid catalysed cyclization. Recrystallization losses were also great. It would seem that an ion exchange column would be the only satisfactory method of separating these acids.

Phenylhydrazine in benzene at room temperature converts the anhydride to the hydrazide-acid, m.p. 185-6° d., in 95% yield. This material is homogeneous. Heat converts it to the cyclic hydrazide, m.p. 132-3°. Levy and Englander report m.p. 131-2° for this compound.[102]

The hydrazide (23.6 g., 0.1 mole) suspended in 100 ml. of tetrahydrofuran was slowly added to a stirred refluxing slurry of 17.1 g. (0.45 mole) of lithium aluminum hydride and 400 ml. of tetrahydrofuran. All organic matter remained in solution. After the addition, the mixture was heated under reflux for 1 hour, and then decomposed with 2-propanol and a minimum of water. After removing the inorganic precipitate by centrifuging, the solution was distilled at 27 mm. Almost all of the material passed over in the range 116-128°. The material was taken up in acetone and oxalic acid was added. Only a very small quantity of material, m.p. 185°, precipitated. This was slightly soluble in acetone, in contradistinction to the oxalates of aniline and phenylhydrazine, and reduced Benedicts solution, as does phenylhydrazine. This salt is perhaps a substituted hydrazine oxalate.

2,2-Dimethylpropanediol-1,3 (XLVIII). - The procedure of Meyersbury[103] was modified slightly. To a solution of 5 moles isobutyraldehyde and 850 ml. of 35% formaldehyde (10.7 moles), was slowly added with cooling a solution of 213 g. (3.3 mole) of potassium hydroxide in 1700 ml. of 95% ethanol. After standing for 16 hours, the alcohol was distilled off, the

solution was saturated with sodium chloride and extracted with n-butanol. The solution was distilled and the fraction of b.p. 120-93° was collected and treated with a mixture of carbon tetrachloride and chloroform. The crystals were collected and recrystallized twice from carbon tetrachloride-chloroform to give 243 g. (47%) of m.p. 129-31°. Meyersburg lists m.p. 130°.[103] The low yield was due to the use of old formaldehyde.

2,2-Dimethylpropanediol-1,3 Monotosylate (XLIX). - Commercial tosylchloride was purified by dissolving 200 g. in 250 ml. of benzene. The solution was decanted from insoluble solids into a separatory funnel and washed with 50 ml. of sodium hydroxide, followed by 50 ml. of saturated sodium chloride. The solution was dried with potassium carbonate and decolorized with a small quantity of charcoal. The solution was evaporated to a small volume. Skellysolve B was added and the solution was chilled, giving 170 g. (80%) of colorless needles.

The procedure of Sekers and Marvel[104] was used. A solution of 10.4 g. (0.1 mole) of the glycol in 32.2 ml. (0.4 mole) of dry pyridine was cooled to 20° while a solution of 19 g. (0.1 mole) of tosyl chloride in 50 ml. of dry ether was added over a period of 0.5 hr. After the mixture had been stirred for 3 hours at room temperature, the pyridine was removed by neutrallizing with 30 ml. of concentrated hydrochloric acid and washing the ether solution with water. The ether was displaced with methanol on the steam bath and water was added to the point of cloudiness. Chilling deposited 5.4 g. of oily crystals of the ditosylate (unaffected by acetic anhydride) which was recrystallized from aqueous acetone, m.p. 116-120°. Addition of more water to the mother liquor gave the monotosylate as an oil which was used directly in the next step.

The oil was dissolved in 65 ml. of 95% ethanol and a solution of 7.9 g. (0.12 mole) of potassium cyanide in 21 ml. of water was added. After a 14-hour reflux period, the mixture was extracted with benzene and the benzene solution was distilled at the aspirator. No volatile material passed over at the expected temperature of 100°, and at a bath temperature of 200°, pyrolysis of the unchanged tosylate commenced.

2,2-Dimethyl-3-methoxypropanol-1. - Sodium (11.5 g., 0.5 atom) was dissolved in a solution of 57.3 g. (0.55 mole) of 2,2-dimethylpropanediol-1,3 in 300 ml. of absolute t-amyl alcohol. The solution was cooled and

46 ml. (0.75 mole) of methyl iodide was added and the mixture was stirred for 3 hours at room temperature. Water was added and the organic layer was separated and dried. Distillation gave 30.3 g. of product, b.p. 150-60°, and 14.2 g. of unreacted glycol. The yield was 73%, based on unrecovered glycol.

2,2-Dimethyl-4-methoxybutyronitrile (LI). - A solution of 49 g. (0.256 mole) of tosyl chloride was added to a solution of 30.3 g. of the above alcohol (0.256 mole) in 129 ml. (1 mole) of pyridine and after 1 hour on the steam bath, the mixture was treated with water and 75 ml. of concentrated hydrochloric acid and extracted with Skellysolve B. The Skellysolve was removed on the steam bath and the 32 g. of residue was taken up in 200 ml. of ethylene glycol. After the addition of 11.8 g. (1.5 equivalents) of potassium cyanide, the solution was distilled until the distillate was no longer cloudy. The 2-phase distillate was partitioned between water and Skellysolve A. The organic solution was separated and distilled, giving 3.1 g. (10%) of oil of b.p. about 170°.

2,2-Dimethyl-4-methoxybutylamine (LII). (Unsuccessful) - The total quantity of nitrile, plus forerun and residue in 20 ml. of 2-butanol was added to a stirred slurry of 4 g. of molten sodium in 20 ml. of toluene. After decomposition with ethanol, water and 20 ml. of concentrated hydrochloric acid were added and the solvent was distilled off. After treatment with charcoal, the solution was made basic and the amine extracted with benzene. The benzene solution was extracted with dilute hydrobromic acid and the extract was evaporated in vacuo, giving about 5 g. (60%) of very hygroscopic crystals of the hydrobromide. The nickel tests were positive for a primary amine and negative for a secondary amine. The Hinsberg test gave a base-soluble oil, which resisted crystallization. Concentrated hydrobromic acid was distilled from the salt to give a hygroscopic solid resembling the original salt. A small portion was treated with the nickel reagent after prior neutrallization with sodium bicarbonate and gave a strong test for a primary amine. Therefore, not much 3,3-dimethyl-4-bromobutylamine hydrobromide was formed, if any. The salt was boiled with anhydrous hydrogen bromide in acetic acid for 16 hours, and after removal of the solvent in vacuo, the dark residue was treated with benzenesulfonyl chloride and aqueous base to give a black oil insoluble in base. (Acidi-

fication of the reaction mixture precipitated nothing, so no primary amine had survived the hydrolysis). The black oil was chromatographed on alumina from 3:7 carbon tetrachloride-Skellysolve B to give a crude yellowish solid, which was fractionally oiled from carbon tetrachloride-Skellysolve B to give a colorless but still impure solid, m.p. 52-64°. This material liquified when mixed with authentic N-benzenesulfonyl-3,3-dimethyl pyrrolidine.

Methyl alpha-bromoisobutyrate was prepared in 83% yield by the Hell-Volhard-Zelinsky method, using the directions of Saunders.[105] An attempt to alkylate acetonitrile with this halide on an 0.5 mole scale using the lithium diethylamide method as outlined previously failed. The addition of the bromide to the white suspension of metalated nitrile was an initially vigorous reaction, but the vigor soon subsided and the contents of the flask progressively turned to a black tar which stopped the stirrer. The tar and the clear supernatent ether solution were worked up separately. The tar was separated into acidic, basic, and neutral fractions, but these fractions were just as black and tarry as the original tar. Distillation of the ether fraction left a small solid residue after removal of unreacted bromide. This residue was crystallized from Skellysolve E, and recrystallized from aqueous methanol. Sublimation at 140° (20 mm) gave 2 g. of a neutral compound, m.p. 153-4°. Analysis gave C, 42.32; H, 5.23; N, 12.65, corresponding to $C_{3.9}H_{5.7}NO_{2.8}$.

Kinetic Studies - All chemicals and reagents were reagent grade. All volumetric ware was calibrated.

To carry out a run, an excess of buffer solution was prepared by weighing out the required components, making up almost to volume with distilled water, and placing the volumetric flask in a well-stirred thermostat, adjusted to 30.00° ± 0.01. After coming to temperature, the volume was adjusted to the mark. The proper bromoamine hydrobromide was weighed out roughly to give 100 ml. of approximately 0.01 M solution, transferred to a 100 ml. volumetric flask, and placed in the thermostat. After coming to temperature, the buffer solution was added almost to the mark; the flask was shaken until the solution was homogeneous, and returned to the bath. The first sample taken was used as the initial point. Five ml. samples were withdrawn with a pipet for analysis and discharged (the time was taken at the mid point of the discharge) into 1 ml. of 8 N nitric

acid (to stop the reaction) and 5 drops of a saturated solution of ferric ammonium sulfate in 1N nitric acid added. Immediately before titration, 5 ml. of approximately 0.021 N silver nitrate was added, and the excess silver nitrate titrated with potassium thiocyanate solution (approximately 0.012 N). The infinite time values were obtained by averaging the titer of three samples each of which had been allowed to stand with 1 ml. of 8 N sodium hydroxide for about 10 seconds before 2 ml. of 8 N nitric acid had been added and which had been treated thereafter as described above.

The rate constants were calculated by averaging the slopes calculated from the initial point to each successive point. Points obviously in error were discarded. The data for each run are given, all at 30°C.

Run No. 1 — 4-Bromo-2,2-dimethylbutylamine hydrobromide, MW = 261.03
Buffer: CH_3COONa = 1.000; CH_3COOH = 1.000; KNO_3, none.
V_∞ = 0.556 ± .002 ml., KSCN.
First point at 3'45" after mixing.

$t_{sec.}$	V_t	V_t-V_∞	$\log(V_t-V_\infty)$	$\log\frac{V_0-V_\infty}{V_t-V_\infty}$	$k_{exp.} \times 10^4 (sec.^{-1})$
0	4.496	3.940	0.59550	0	--
1218	3.651	3.095	0.49066	0.10484	1.98
2475	2.920	2.364	0.37365	0.22185	2.06
4230	2.218	1.662	0.22063	0.37487	2.04
6735	1.568	1.012	0.00518	0.59032	2.02
9305	1.121	0.565	-0.24795	0.84345	2.08
					ave 2.04 ± 0.06

Run No. 2 — 4-Bromo-2,2-dimethylbutylamine hydrobromide, MW = 261.03
Buffer: CH_3COONa = 0.500; CH_3COOH = 1.000; KNO_3 = 0.500
V_∞ = 0.576 ± 0.0 ml., KSCN
First point at 5'10" after mixing.

0	4.561	3.985	0.60043	0	--
1815	3.913	3.337	0.52336	0.07707	0.977
3617	3.383	2.807	0.44824	0.15219	0.971
5395	2.949	2.373	0.37530	0.22513	0.961
7090	2.589	2.013	0.30384	0.29659	0.963
9060	2.269	1.693	0.22866	0.37177	0.944$^\Delta$
11010	1.976	1.400	0.14613	0.45430	0.950
12850	1.735	1.159	0.06408	0.53635	0.961
14615	1.560	0.984	-0.00700	0.60743	0.956
					ave 0.963 ± 0.014

$^\Delta$Denotes points rejected in averaging.

$t_{sec.}$	V_t	V_t-V_∞	$\log(V_t-V_\infty)$	$\log\frac{V_o-V_\infty}{V_t-V_\infty}$	$k_{exp.} \times 10^4 (sec.^{-1})$

Run No. 3 — 4-Bromo-2,2-dimethylbutylamine hydrobromide, MW = 261.03
Buffer: CH_3COONa = 1.000; CH_3COOH = 1.000; KNO_3 = 1.000
V_∞ = 0.566 ± 0.002 ml., KSCN
First point at 15' 47" after mixing.

0	3.962	3.396	0.53097	0	--
398	3.698	3.132	0.49582	0.03515	2.03
1405	3.110	2.544	0.40552	0.12545	2.06
2271	2.699	2.133	0.32899	0.20198	2.05
3187	2.335	1.769	0.24773	0.28324	2.04
4081	2.053	1.487	0.17231	0.35866	2.02
4945	1.809	1.243	0.09447	0.43650	2.03
5883	1.603	1.037	0.01578	0.51519	2.02
6783	1.430	0.864	-0.06349	0.59446	2.02
7853	1.261	0.695	-0.15802	0.68899	2.02
					ave 2.03 ± 0.02

Run No. 4 — 4-Bromo-2,2-diisopropylbutylamine hydrobromide, MW = 317.13
Buffer: CH_3COONa = 0.500; CH_3COOH = 1.000; KNO_3 = 0.500
V_∞ = 0.916 ± 0.007 ml., KSCN
First point at 1' 00" after mixing.

0	3.276	2.360	0.37291	--	--
66	2.536	1.620	0.20952	0.16239	56.7
135	2.006	1.090	0.03743	0.33548	57.2
205	1.700	0.784	-0.10568	0.47859	53.7
398	1.264	0.348	-0.45842	0.83133	48.1$^\Delta$
					ave 55.9 ± 2.2

Run No. 5 — 4-Bromobutylamine hydrobromide, MW = 232.98
Buffer: CH_3COONa = 2.000; CH_3COOH = 0.500; KNO_3, none.
V_∞ = 0.545 ± 0.006 ml., KSCN
First point at 5' 30" after mixing.

0	4.666	4.121	0.61500	--	--
3595	4.535	3.990	0.60097	0.01403	0.0899$^\Delta$
25965	4.001	3.456	0.53857	0.07643	0.0678
69870	3.155	2.610	0.41664	0.19836	0.0654
					ave 0.0666 ± 0.0012

$t_{sec.}$	V_t	V_t-V_∞	$\log(V_t-V_\infty)$	$\log\frac{V_0-V_\infty}{V_t-V_\infty}$	$k_{exp.} \times 10^4 (sec.^{-1})$

Run No. 6 | 4-Bromo-2,2-dimethylbutylamine hydrobromide, MW = 261.03
Buffer: CH_3COONa = 0.500; CH_3COOH = 0.500; KNO_3 = 0.500
V_∞ = 0.531 ± 0.002 ml., KSCN
First point at 2' 45" after mixing.

0	4.548	4.017	0.60390	--	--
895	3.948	3.417	0.53364	0.07026	1.81
1680	3.504	2.973	0.47319	0.13071	1.79
3095	2.824	2.293	0.36040	0.24350	1.81
3857	2.530	1.999	0.30081	0.30309	1.81
4817	2.218	1.687	0.22712	0.37678	1.80
5975	1.896	1.365	0.13513	0.46877	1.81
6903	1.697	1.166	0.06670	0.53720	1.79
7786	1.529	0.998	-0.00087	0.60477	1.79
8861	1.357	0.826	-0.08302	0.68692	1.79
					ave 1.80 ± 0.01

Run No. 7 | 4-Bromo-2,2-dimethylbutylamine hydrobromide, MW = 261.03
Buffer: CH_3COONa = 1.000; CH_3COOH = 1.000; KNO_3, none
V_∞ = 0.660 ± 0.004 ml., KSCN
First point at 5' 05" after mixing.

0	4.463	3.803	0.58013	--	--
1060	3.728	3.068	0.48686	0.09327	2.02
1885	3.244	2.584	0.41229	0.16784	2.05
2665	2.850	2.190	0.34044	0.23969	2.07
3478	2.536	1.876	0.27323	0.30690	2.03
4423	2.208	1.548	0.18977	0.39036	2.03
5290	1.934	1.274	0.10517	0.47496	2.06
6232	1.721	1.061	0.02572	0.55441	2.05
7100	1.565	0.905	-0.04335	0.62348	2.02
					ave 2.04 ± 0.02

Run No. 8 tabulated on p. 87 (unbuffered).

$t_{sec.}$	V_t	V_t-V_∞	$\log(V_t-V_\infty)$	$\log\frac{V_0-V_\infty}{V_t-V_\infty}$	$k_{exp.} \times 10^4 (sec.^{-1})$

Run No. 9 4-Bromo-2,2-dimethylbutylamine hydrobromide, MW = 261.03
Buffer: CH_3COONa = 0.250; CH_3COOH = 0.250; KNO_3 = 0.750
V_∞ = 0.651 ± 0.012 ml., KSCN
First point at 5' 48" after mixing.

0	4.470	3.819	0.58195	--	--
805	3.970	3.319	0.52101	0.06094	1.74
1590	3.567	2.916	0.46479	0.11716	1.70
2333	3.192	2.541	0.40500	0.17695	1.75
3123	2.889	2.238	0.34986	0.23209	1.71
3997	2.580	1.929	0.28533	0.29662	1.71
4933	2.291	1.640	0.21484	0.36711	1.71
5797	2.063	1.412	0.14983	0.43212	1.72
6724	1.867	1.216	0.08493	0.49702	1.70
7875	1.666	1.015	0.00647	0.57548	1.68
					ave 1.71 ± 0.03

Run No. 10 4-Bromo-2,2-dimethylbutylamine hydrobromide, MW = 261.03
Buffer: CH_3COONa = 0.250; CH_3COOH = 0.500; KNO_3 = 0.750
V_∞ = 0.588 ± 0.006 ml., KSCN
First point at 2' 45" after mixing.

0	4.597	4.009	0.60304	--	--
1507	4.118	3.530	0.54777	0.05527	0.844[Δ]
3136	3.632	3.044	0.48344	0.11960	0.877
4632	3.249	2.661	0.42504	0.17800	0.885
6080	2.943	2.355	0.37199	0.23105	0.875
7655	2.624	2.036	0.30878	0.29426	0.885
9881	2.264	1.676	0.22427	0.37877	0.883
11749	2.004	1.416	0.15106	0.45198	0.886
13741	1.781	1.223	0.08743	0.51561	0.865
15837	1.574	1.016	0.00689	0.59615	0.867
					ave 0.878 ± 0.010

$t_{sec.}$	V_t	V_t-V_∞	$\log(V_t-V_\infty)$	$\log\frac{V_0-V_\infty}{V_t-V_\infty}$	$k_{exp.} \times 10^4 (sec.^{-1})$
Run No. 11	4-Bromo-2,2-dimethylbutylamine hydrobromide, MW = 261.03 Buffer: CH_3COONa = 0.250; CH_3COOH = 0.250; KNO_3, none. V_∞ = 0.596 ± 0.003 ml., KSCN First point at 3' 23" after mixing.				
0	4.468	3.872	0.58794	--	--
1009	3.716	3.120	0.49415	0.09379	2.14
2423	2.891	2.295	0.36078	0.22716	2.16
3188	2.570	1.974	0.29535	0.29259	2.12
4479	2.107	1.511	0.17926	0.40868	2.10
5603	1.819	1.223	0.08743	0.50051	2.06
6446	1.607	1.011	0.00475	0.58319	2.08
7475	1.435	0.839	-0.07624	0.66418	2.05
					ave 2.10 ± 0.05

$t_{hrs.}$					$k_{exp.} \times 10^4 (hrs.^{-1})$
Run No. 12	4-Bromobutylamine hydrobromide, MW = 232.98 Buffer: CH_3COONa = 0.500; CH_3COOH = 0.250; KNO_3, none. V_∞ = 0.156 ± 0.001 ml., KSCN. First point at 5' 00" after mixing.				
0	4.452	4.296	0.63306	--	--
12.62	3.967	3.811	0.58104	0.05202	94.6
32.63	3.281	3.125	0.49485	0.13821	97.4
46.67	2.877	2.721	0.43473	0.19833	97.6
59.67	2.556	2.400	0.38021	0.25285	97.3
70.40	2.344	2.188	0.34005	0.29301	95.8
82.16	2.113	1.957	0.29159	0.34147	95.6
94.96	1.887	1.731	0.23830	0.39476	95.5
123.53	1.496	1.340	0.12710	0.50596	94.2
					ave 96.0 ± 1.8

$$k_{exp.}(sec.^{-1}) = .00960 \times \frac{1}{3600} = 0.00000266 \pm 0.00000005$$

$$k_{exp.}(sec.^{-1}) \times 10^4 = 0.0266 \pm 0.0005$$

$t_{sec.}$	V_t	V_t-V_∞	$\log(V_t-V_\infty)$	$\log\frac{V_o-V_\infty}{V_t-V_\infty}$	$k_{exp.} \times 10^4 (sec.^{-1})$

Run No. 13 4-Bromo-1,1-dimethylbutylamine hydrobromide, MW = 261.03
Buffer: CH_3COONa = 0.500; CH_3COOH = 0.250; KNO_3, none.
V_∞ = 0.473 ± 0.001 ml., KSCN.
First point at 3' 12" after mixing.

0	4.600	4.127	0.61563	--	--
505	4.598	4.125	0.61542	0.00021	0.0090$^\Delta$
12675	4.323	3.850	0.58546	0.03017	0.0548
28633	3.987	3.514	0.54580	0.06983	0.0561
					ave 0.0554 ± 0.0006

Run No. 14 4-Bromo-3,3-dimethylbutylamine hydrobromide, MW = 261.03
Buffer: CH_3COONa = 0.500; CH_3COOH = 0.250; KNO_3, none.
V_∞ = 0.662 ± 0.002 ml., KSCN.
First point at 3' 02" after mixing.

0	4.652	3.990	0.60097	--	---
909	4.650	3.988	0.60076	0.00021	0.00531$^\Delta$
9413	4.635	3.973	0.59912	0.00185	0.00452
73948	4.511	3.849	0.58535	0.01562	0.00486
154858	4.458	3.796	0.57933	0.02164	0.00322
					ave 0.0042 ± 0.0001

Run No. 15 not done.

Run No. 16 4-Bromo-2,2-dimethylbutylamine hydrobromide, MW = 261.03
Buffer: HCOONa = 0.500; HCOOH = 1.000; KNO_3, none.
V_∞ = 0.593 ± 0.001 ml., KSCN
First point at 14' 00" after mixing.

$t_{hrs.}$					$k_{exp.} \times 10^4 (hrs.^{-1})$
0	4.644	4.051	0.60756	---	--
4.96	4.112	3.519	0.54642	0.06114	284
11.05	3.539	2.946	0.46923	0.13833	288
16.50	3.106	2.513	0.40019	0.20737	289
21.48	2.764	2.171	0.33666	0.27090	290
26.37	2.490	1.897	0.27807	0.32949	288
31.55	2.233	1.640	0.21484	0.39272	287
36.75	1.994	1.401	0.14644	0.46112	289
42.00	1.809	1.216	0.08493	0.52263	286
46.45	1.673	1.080	0.03342	0.57414	285
					ave 287 ± 3

$$k_{exp.}(sec.^{-1}) = .0287 \times \frac{1}{3600} = .00000796$$

$$k_{exp.}(sec.^{-1}) \times 10^4 = 0.0796 \pm 0.0008$$

$t_{hrs.}$	V_t	V_t-V_∞	$\log(V_t-V_\infty)$	$\log\frac{V_0-V_\infty}{V_t-V_\infty}$	$k_{exp.} \times 10^4 (hrs.^{-1})$

Run No. 17 — 4-Bromo-1,1-dimethylbutylamine hydrobromide, MW = 261.03
Buffer: CH_3COONa = 0.500; CH_3COOH = 0.250; KNO_3, none.
V_∞ = 0.583 ± 0.010 ml., KSCN
First point at 32' 10" after mixing.

0	4.613	4.030	0.60531	---	-
8.27	3.988	3.405	0.53212	0.07319	170$^\Delta$
14.51	3.546	2.963	0.47173	0.13358	219
22.02	3.135	2.552	0.40688	0.19843	216
29.89	2.758	2.175	0.33746	0.26785	208
36.21	2.499	1.916	0.28240	0.32291	209
43.88	2.242	1.659	0.21985	0.38546	206
50.14	2.044	1.461	0.16465	0.44066	212
57.84	1.835	1.252	0.09760	0.50771	208
65.62	1.687	1.104	0.04297	0.56234	201
					ave 210 ± 9

$$k_{exp.}(sec.^{-1}) = .0210 \times \frac{1}{3600} = .00000584$$

$$k_{exp.}(sec.^{-1}) \times 10^4 = 0.0584 \pm 0.0025$$

Run No. 18 — 4-Bromo-2,2-diphenylbutylamine hydrobromide, MW = 385.16
Buffer: CH_3COONa = 0.500; CH_3COOH = 0.250; KNO_3, none.
V_∞ = 0.878 ± 0.001 ml., KSCN
First point at 3' 47" after mixing.

$t_{sec.}$					$k_{exp.} \times 10^4 (sec.^{-1})$
0	1.844	0.966	-0.01502	---	-
223	.915	0.037	-1.43180	1.41678	146
307	.897	0.019	-1.72125	1.70623	128
413	.894	0.016	-1.79588	1.78086	99$^\Delta$
					ave 137 ± 9

$t_{sec.}$	V_t	V_t-V_∞	$\log(V_t-V_\infty)$	$\log\frac{V_0-V_\infty}{V_t-V_\infty}$	$k_{exp.} \times 10^4 (sec.^{-1})$
Run No. 19	4-Bromo-2,2-diethylbutylamine hydrobromide, MW = 289.08 Buffer: HCOONa = 0.500; HCOOH = 1.000; KNO_3, none. V_∞ = 0.646 ± 0.001 ml., KSCN First point at 3' 00" after mixing.				
0	4.682	4.036	0.60595	---	--
1258	4.547	3.901	0.59118	0.01477	0.270$^\Delta$
2433	4.414	3.768	0.57611	0.02984	0.282
3666	4.270	3.624	0.55919	0.04676	0.294
4761	4.168	3.522	0.54679	0.05916	0.286
5978	4.020	3.374	0.52815	0.07780	0.299
7138	3.889	3.243	0.51095	0.09500	0.306
8347	3.787	3.141	0.49707	0.10888	0.300
9587	3.653	3.007	0.47813	0.12782	0.307
10907	3.535	2.889	0.46075	0.14520	0.306
12408	3.397	2.751	0.43949	0.16646	0.309
					ave 0.299 ± 0.017

The one unbuffered run was carried out as described for the buffered cases. However, the derived equation requires the initial concentration at time of mixing. This was obtained in terms of V_0-V_∞ by calculation from the known volumes and concentrations. The experimental rate constant [$k'_{exp.}(sec.^{-1}) \times 10^4$ = 0.0047] was found to be relatively invariant considering that it is calculated as the difference of two large terms.

Run No. 8 — 4-Bromo-2,2-dimethylbutylamine hydrobromide, MW = 261.03
Buffer: NONE; KIO_3 = 1.000.
V_∞ = 0.558 ± 0.005 ml., KSCN
First point at 3' 26" after mixing.
Initial concentration, 0.2501 g. in 99.92 ml.; or M = 0.009589
(V_0-V_∞)calc.: 5.168 ml. sample, with 0.01211 N, KSCN gives
V_0-V_∞ = 4.092 ml.

$t_{sec.}$	V_t-V_∞	$\log\frac{V_0-V_\infty}{V_t-V_\infty}$	$\frac{2.303}{t}\log\frac{V_0-V_\infty}{V_t-V_\infty}$ x10^4	$\left(\frac{V_t-V_\infty}{V_0-V_\infty}-1\right)$	$\frac{1}{t}\left(\frac{V_t-V_\infty}{V_0-V_\infty}-1\right)$ x 10^4	$k'_{exp.}(sec.^{-1})$ x 10^4
0	4.092	---	---	0	0	--
206	4.091	0.00011	0.0123	-.00025	-.01212	0.0002$^\Delta$
313	4.046	0.00491	0.361	-.01102	-.352	0.009$^\Delta$
1225	3.956	0.01468	0.276	-.03324	-.271	0.005
4196	3.850	0.02648	0.1452	-.05915	-.1410	0.0042
21435	3.546	0.06220	0.0669	-.13344	-.0622	0.0047
150900	2.702	0.18025	0.0275	-.33969	-.0225	0.0050
						ave 0.0047 ± 0.0005

IV. SUMMARY

Although the reasons are not well understood, it is well-known that the introduction of geminal alkyl groups into a suitably chosen bifunctional compound strikingly enhances the cyclization tendency of that compound. In order to elucidate the nature of this phenomenon, a series of geminally substituted 4-bromobutylamine hydrobromides were prepared. More specifically, the compounds prepared were the hydrobromides of 4-bromobutylamine, 4-bromo-1,1-dimethylbutylamine, 4-bromo-2,2-dimethylbutylamine, 4-bromo-2,2-diethylbutylamine, 4-bromo-2,2-diisopropylbutylamine, 4-bromo-2,2-diphenylbutylamine, 4-bromo-2,2-di-p-tolylbutylamine, and 4-bromo-3,3-dimethylbutylamine. In successfully meeting the synthetic challenge implicit in the preparation of these difficulty accessible compounds, it is felt that a valuable contribution was made to the chemistry of quaternary carbon compounds.

4-Bromobutylamine hydrobromide was prepared by the cleavage of 4-phenoxybutylamine with hydrobromic acid and alternatively by the hydrobromic acid treatment of 4-hydroxybutylamine, which is available by a bifunctional reduction of the Michael addition product of hydrogen cyanide and methyl acrylate. The Delepine synthesis was not found practical, since the adduct of tetramethylene dibromide and hexamethylenetetramine could not be successfully hydrolyzed with hydrobromic acid.

4-Bromo-1,1-dimethylbutylamine hydrobromide was prepared successfully by the hydrobromic acid treatment of 1,1-dimethyl-4-hydroxybutylamine which is available from the bifunctional reduction of the Michael addition product of 2-nitropropane and methyl acrylate with lithium aluminum hydride. A superior procedure was developed for hydrolysing lithium aluminum hydride reduction mixtures with a limited quantity of saturated aqueous sodium chloride. All inorganic matter settles out in an easily filterable condition, leaving the product in a nearly anhydrous ethereal solution. This procedure is especially useful for working up highly water soluble amino alcohols. 4-Bromo-1,1-dimethylbutylamine hydrobromide was found to cyclize in aqueous solution in contrast to 4-bromobutylamine hydrobromide, thus establishing the "geminal alkyl effect" in this series. The structure of 4-bromo-1,1-dimethylbutylamine hydrobromide was proved by preparing known derivatives

of the product of cyclization, 2,2-dimethylpyrrolidine.

1,1-Dimethyl-4-ethoxybutylamine is also a suitable precursor of 4-bromo-1,1-dimethylbutylamine hydrobromide and may be prepared by alkaline hydrolysis of N-formyl-1,1-dimethyl-4-ethoxybutylamine, the product of treating 1,1-dimethyl-4-ethoxybutanol with sodium cyanide and sulfuric acid. The alternate possibility of preparing 1,1-dimethyl-4-ethoxybutylamine by Hofmann rearrangement of 2,2-dimethyl-5-ethoxypentanamide was not realized, since this amide could not be prepared by conventional cleavage of 2,2-dimethyl-5-ethoxyvalerophenone with sodamide. Instead, the sole isolable product from the attempted cleavage was 3,3,5-trimethylpyrrolidone-2. It is postulated that beta elimination of the ethoxyl group occurs concomitantly with cleavage of the ketone to give 2,2-dimethyl-4-pentenamide, which then cyclized to the pyrrolidone in the basic medium. The unprecedented novelty of this overall transformation is discussed.

The possibility of establishing the skeleton of 4-bromo-1,1-dimethylbutylamine hydrobromide via Beckmann rearrangement was investigated. Thus, while rearrangement of pivalophenone oxime, a model compound, with phosphorus pentachloride is known to give benzonitrile, and rearrangement with hydrogen chloride in acetic acid is known to give pivalanilide, it was found that rearrangement with benzene-sulfonyl chloride in a basic medium gave the desired N-t-butylbenzamide. In view of this, 2,2-dimethyl-5-phenoxyvalerophenone was prepared by the alkylation of isobutyrophenone with 3-phenoxypropyl bromide and converted to the oxime which was then rearranged under the same conditions to give N-benzoyl-1,1-dimethyl-4-phenoxybutylamine. This amide proved resistant to alkaline hydrolysis, even under drastic conditions, as only traces of the desired 1,1-dimethyl-4-phenoxybutylamine were produced, the starting material being recovered in substantial yield. Hydrolysis of the amide with hydrobromic acid, which was expected to give 4-bromo-1,1-dimethylbutylamine hydrobromide directly, took another course as the C-N bond was cleaved also, giving ammonium bromide, phenol, benzoic acid, and presumably dibromo-2-methylpentane. Since N-t-butylbenzamide was found to yield ammonium bromide, benzoic acid, and t-butylbromide upon similar treatment, this appears to be a general reaction of the amides of tertiary carbinamines and is entirely analogous to the known behavior of the esters of tertiary carbinols, which, upon attempted acid catalysed alcoholysis, yield

the free acid and a mixed ether.

Dimethyl-, diethyl-, and di-p-tolylacetonitriles were prepared by dehydration of the corresponding amides, which in turn were prepared from the corresponding acids *via* the acid chlorides. The overall conversion of the acids to the nitriles was carried out by a procedure specifically developed to be superior to the established procedures, both with respect to manipulative simplicity, and to the yields attainable. Di-p-tolylacetic acid was prepared by acid catalysed hydrolysis of the carbitol acetal of di-p-tolylketene, which was obtained by sodium carbitoxide treatment of 1,1-di-p-tolyl-2,2,2-trichloroethane, the condensation product of toluene and chloral. Diisopropylacetonitrile was prepared in high yield by fusion of potassium hydroxide and diisopropylcyanoacetic ester, which was in turn prepared in near quantitative yield by the alkylation of cyanoacetic ester with isopropyl iodide in the presence of sodium isopropoxide. The utilization of the base sodium isopropoxide is therefore seen to be potentially useful for the introduction of hindered groups into cyanoacetic ester in unprecedented yield.

2,2-Dimethyl-, -diethyl-, -diisopropyl-, -diphenyl-, and -di-p-tolyl-4-phenoxybutyronitriles were prepared by the alkylation of the corresponding disubstituted acetonitriles with phenoxyethyl bromide in the presence of lithium diethylamide. In addition, 2,2-diisopropyl-4-methoxybutyronitrile was prepared by the alkylation of diisopropylacetonitrile with methoxyethyl bromide. These alkylations set a precedent and serve to illustrate the variety of "prohibitively hindered" nitriles which have now become available through the use of lithium diethylamide. Upon reduction of the substituted butyronitriles with lithium aluminum hydride, and hydrolysis of the reaction mixtures, the corresponding substituted butylamines were obtained except for the case of 2,2-diisopropyl-4-phenoxybutyronitrile, which is so hindered that reduction proceeded slowly to give perhaps the expected dinegatively charged anion of 2,2diisopropyl-4-phenoxybutylamine, an inordinately unstable intermediate, which spontaneously cyclized with the elimination of phenoxide ion, thus demonstrating the phenomenal activity of the geminal diisopropyl grouping over that of methyl, ethyl, or phenyl, etc. However, the reduction of 2,2-diisopropyl-4-methoxybutyronitrile proceeded normally, giving the

expected methoxy amine in excellent yield. The limitations of other methods of reducing tertiary nitriles are discussed. 4-Bromo-2,2-dimethyl-, -diethyl-, and -diisopropylbutylamine hydrobromides were obtained by hydrolysis of the phenoxy and methoxy amines with hydrobromic acid. The 4-bromo-2,2-diphenyl and di-p-tolylbutylamine hydrobromides were obtained in very low yield and low purity by the same method. Since the principal by-products were the cyclized materials, the 3,3-disubstituted pyrrolidines, the course of the elimination of the phenoxy grouping needs more study, and it is suggested that, as in the diisopropyl case, the methoxy group will be easier to displace. These bromoamine hydrobromides are unstable in aqueous solution and cyclize rapidly with the elimination of hydrogen bromide. The structures of the bromo amine salts were proved by an unequivocal and independent synthesis of one cyclization product, 3,3-dimethylpyrrolidine, and by conversion of another cyclization product, 3,3-diphenylpyrrolidine, to its hydrochloride, a known compound.

Other methods for establishing the essential skeleton of 4-bromo-2,2-dimethylbutylamine were investigated. It was found that, although neither nitromethane nor hydrogen cyanide would add to ethyl 3-methyl-2-butenoate, nitromethane added smoothly to ethyl 2-cyano-3-methyl-2-butenoate, but the resulting Michael addition product could not be hydrolysed to 2,2-dimethyl-4-nitrobutyric acid because of preferential complex decompostion. Hofmann rearrangement of 3,3-dimethylglutaramic acid and its methyl ester was also unsatisfactory due to extensive cyclization of the starting materials to give 3,3-dimethylglutarimide.

4-Bromo-3,3-dimethylbutylamine hydrobromide was prepared by hydrobromic acid hydrolysis of 4-bromo-3,3-dimethyl-1-phthalimidobutane. The product of the Gabriel reaction between potassium phthalimide and 1,4-dibromo-2,2-dimethylbutane which, was in turn prepared from the corresponding glycol as obtained by lithium aluminum hydride reduction of <u>as</u>-dimethylsuccinic anhydride. This novel synthesis makes full use of the fact that neopentyl halides are inert to displacement reactions such as the Gabriel synthesis. Although the halogen of 4-bromo-3,3-dimethylbutylamine is inert to intermolecular displacement, the molecular geometry is such as to allow intramolecular displacement as evidenced by the fact that the free amine cyclizes

readily. The product, 3,3-dimethylpyrrolidine is also the cyclization product of 4-bromo-2,2-dimethylbutylamine, thus establishing the structure of the bromo amine as correct.

Other methods for establishing the 4-bromo-3,3-dimethylbutylamine skeleton were completely unsatisfactory. 3,3-Dimethyl-1-nitrobutanediol was prepared by condensation of nitromethane and hydroxypivalaldehyde in very low and unreproducible yields. Furthermore, purification of this nitro glycol was impossibly difficult. Condensation of nitromethane and acetoxypivalaldehyde was also unfeasible because of low yields. The unexpected inherent instability of acetoxypivaldehyde is discussed. The nitro glycol was dehydrated with acetic anhydride to give 2,2-dimethyl-4-nitro-3-butenyl acetate which was then reduced with lithium aluminum hydride to 3,3-dimethyl-4-hydroxybutylamine. Reduction of the product of opening as-dimethylsuccinic anhydride with ammonia was also investigated as an alternate route to the latter amino alcohol. However, it was found that a mixture of the desired amino alcohol and 2,2-dimethyl-4-hydroxybutylamine was formed since treatment with hydrobromic acid gave a mixture of gummy material and 4-bromo-2,2-dimethylbutylamine hydrobromide. Therefore, ammonia opens as-dimethylsuccinic anhydride to give substantial quantities of a sterically and electronically unexpected succinamate. Phenylhydrazine does open this anhydride unilaterally, but the resulting product could not be reduced to the desired amino alcohol in spite of the fact that N-N bonds suffer facile hydrogenolysis. Cyanohydrin esters are known to undergo hydrogenolysis to give nitriles. However, the diacetate of hydroxypivalaldehyde cyanohydrin failed to undergo this reaction. Although the monotosylate of 2,2-dimethylpropanediol-1,3 failed to react with potassium cyanide, 3,3-dimethyl-3-methoxypropanol tosylate reacted smoothly under forcing conditions to give the corresponding nitrile, which was reduced to 3,3-dimethyl-4-methoxybutylamine. Disappointingly, cleavage of this compound with hydrogen bromide gave rearranged products. Finally, an attempted alkylation of acetonitrile with methyl alpha-bromo-isobutyrate gave tarry products.

Limitations in the standard methods of distinguishing among primary, secondary, and tertiary amines are discussed.

Time was available to allow only enough kinetic runs to be made to outline the scope of the problem. Primary and secondary salt effects were

observed, the rate of the ring closure was found to be extraordinarily sensitive to the hydrogen ion concentration. Once standardized, the rate of reaction will prove to be a very sensitive method for the measurement of pH of buffer solutions on the acidic side of neutrality.

The effect of substitution of methyl groups on the rate of cyclization was found to be small in the 1,1 position; large in the 2,2 position; and to depress the rate when in the 3,3 position. Increasing the size of the groups to ethyl to isopropyl in the 2,2-position increased the rate still more, but less so than did the original substitution of methyl.

The effect is probably almost completely steric since phenyl and isopropyl had similar large effects on the rate despite the disparity in electronic effects of these groups. A speculation on the large steric effects noted has been presented and discussed; and the need for further work on this problem was pointed out.

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