



8-1970

**Part I. The Stereochemistry of Carbanions Formed by Base
Catalyzed Decomposition of Azoacetates Part II. Anomalous
Decarbonylation of 4 –Substituted Carboxylic Acids with Thionyl
Chloride**

Tai-shun Lin
Western Michigan University

Follow this and additional works at: <https://scholarworks.wmich.edu/dissertations>

 Part of the Organic Chemistry Commons

Recommended Citation

Lin, Tai-shun, "Part I. The Stereochemistry of Carbanions Formed by Base Catalyzed Decomposition of Azoacetates Part II. Anomalous Decarbonylation of 4 –Substituted Carboxylic Acids with Thionyl Chloride" (1970). *Dissertations*. 3049.

<https://scholarworks.wmich.edu/dissertations/3049>

This Dissertation-Open Access is brought to you for free and open access by the Graduate College at ScholarWorks at WMU. It has been accepted for inclusion in Dissertations by an authorized administrator of ScholarWorks at WMU. For more information, please contact wmu-scholarworks@wmich.edu.



PART I. THE STEREOCHEMISTRY OF CARBANIONS FORMED BY
BASE CATALYZED DECOMPOSITION OF AZOACETATES

PART II. ANOMALOUS DECARBONYLATION OF α -SUBSTITUTED
CARBOXYLIC ACIDS WITH THIONYL CHLORIDE

by

Tai-shun Lin

A Dissertation
Submitted to the
Faculty of the School of Graduate
Studies in partial fulfillment
of the
Degree of Doctor of Philosophy

Western Michigan University
Kalamazoo, Michigan
August 1970

ACKNOWLEDGEMENT

I wish to express my appreciation to the members of my committee, Dr. D. C. Berndt, Dr. R. E. Harmon, Dr. R. H. Anderson and Dr. S. K. Derby for their kindly help and suggestions. But above all, I should like to acknowledge here my debt to Dr. D. C. Iffland for his patient and unfailing guidance in all phases of this work and for his generosity with his time. Finally, I am also grateful for having been appointed to a graduate teaching assistantship by the Department of Chemistry and a School of Graduate Studies associateship so that I could complete this study.

Tai-shun Lin

71-3943

LIN, Tai-shun, 1935-

PART I. THE STEREOCHEMISTRY OF CARBANIONS
FORMED BY BASE CATALYZED DECOMPOSITION OF
AZOACETATES. PART II. ANOMALOUS DECARBONYLATION
OF α -SUBSTITUTED CARBOXYLIC ACIDS WITH THIONYL
CHLORIDE.

Western Michigan University, Ph.D., 1970

Chemistry, organic

University Microfilms, Inc., Ann Arbor, Michigan

THIS DISSERTATION HAS BEEN MICROFILMED EXACTLY AS RECEIVED

TABLE OF CONTENTS

INTRODUCTION	1
------------------------	---

PART I

HISTORICAL	3
----------------------	---

EXPERIMENTAL	8
------------------------	---

Preparation of Hydrazones	9
-------------------------------------	---

Preparation of Azoacetates	23
--------------------------------------	----

Base Catalyzed Decomposition of Azoacetates	26
--	----

RESULTS AND DISCUSSION	41
----------------------------------	----

SUMMARY	55
-------------------	----

PART II

HISTORICAL	57
----------------------	----

EXPERIMENTAL	59
------------------------	----

Preparation of α -Methoxyphenylacetic Acid	60
--	----

Preparation of α -Methoxybenzyl Chloride	62
--	----

Reactions of α -Substituted Carboxylic Acids with Excess Thionyl Chloride	63
--	----

A Comparison of Relative Reactivity of Benzhydrol and Diphenylacetic Acid with Thionyl Chloride	70
RESULTS AND DISCUSSION	73
SUMMARY	81
BIBLIOGRAPHY	82
VITA	86

INTRODUCTION

Although the stereochemical capabilities of carbonium ions have been extensively investigated, the stereochemical fate of carbanions has been subjected relatively little to systematic scrutiny. The fact that only a limited number of clean-cut sources of carbanions are available has added difficulty to such investigations.

The stereochemical capabilities of carbanions has been extensively and thoroughly examined in recent years by Cram and coworkers. However, the carbanion carbon developed in the reactions employed was bonded in every case to an unsaturated (usually aromatic) group. No fully aliphatic carbanion has been subjected to such a stereochemical study.

The reaction of lead tetraacetate with ketohydrazones to form azoacetates has been reported recently by Iffland, Schafer and Salisbury (1). The base catalyzed decomposition of an azoacetate provides a simple way to produce carbanions under mild reaction conditions.

Thus, a potentially advantageous approach is available to develop dissymmetric carbanions from azoacetates having a dissymmetric alkyl group bonded to the azo nitrogen atom. Furthermore, a successful approach to the formation of the necessary optically active azoacetates has been demonstrated (2). The carbanion of special

interest is the methylethyl-n-propyl methyl anion, since this represents one of the simplest potentially dissymmetric fully aliphatic carbanions. For convenience, this ion and the related alkyl group will hereafter be designated as the t-heptyl anion or t-heptyl group.

A number of base catalyzed decomposition reactions of azoacetates which provide information about the stereochemical capabilities of the t-heptyl anion have been investigated and are described in Part I of this dissertation.

The necessary azoacetates were ultimately prepared from resolved t-heptylamine. The determination of the optical purity of the t-heptylamine was desired and its measurement was attempted unsuccessfully by the method of nmr analysis of diastereomeric amide derivatives. Suitable derivatives have been prepared from the acid chloride of O-methylmandelic acid in related situations. However, this led to the discovery of an anomalous decarbonylation reaction of α -substituted carboxylic acids when treated with thionyl chloride. The examination of this reaction is reported in Part II.

PART I

**THE STEREOCHEMISTRY OF CARBANIONS FORMED
BY BASE CATALYZED DECOMPOSITION
OF AZOACETATES**

HISTORICAL

In the simplest view, carbanions are conjugate bases of the corresponding carbon acids. A carbon acid is an organic substance that, when treated with a suitable base, donates a proton to that base by fission of a carbon-hydrogen bond. This definition is made in terms of one of the most important of all chemical reactions, that of proton abstraction from carbon. This definition is profitable because it allows vast number of organic compounds to be classified as to their acid strength, which, in turn is related to the base strength of their conjugate bases and, therefore, to the stability of carbanions.

A thermodynamic acidity scale has been developed by Streitwieser and coworkers (3). They have measured the equilibrium constants between lithium or cesium cyclohexylamide and the carbon acid on the one hand, and cyclohexylamine and the lithium or cesium carbon salt on the other in cyclohexylamine as solvent.

Zimmerman and Thyagarajan (4) metalated a one-to-one mixture of cyclopropylphenyl and isopropylphenyl sulfones with less than an equivalent of phenyllithium, phenylsodium, or phenylpotassium. The resulting mixture was then quenched with D_2O , and the equilibrium constant was calculated from the relative amounts of deuterium in the recovered sulfones.

In contrast to nucleophilic substitution (SN), electrophilic substitution (SE) at saturated carbon has been little studied, particularly with respect to steric course. Similarly, although the stereochemical capabilities of carbonium ions have been extensively investigated, the stereochemical fate of carbanions has been less subjected to systematic scrutiny.

A number of articles have appeared in the literature in which authentic stereospecific electrophilic substitutions at saturated carbon are reported. Letsinger (5) observed that when (-)-2-iodooctane was metalated with secbutyllithium and the product was carbonated (both operations were carried out at -70°), the 2-methyloctanoic acid produced was 20% optically pure and the metalation and carbonation had occurred with predominating overall retention of configuration. Cyclopropyl anions have been studied by Walborsky (6) through decomposition of 1-methyl-2, 2-diphenylcyclopropyllithium with methanol. The reaction occurred with 80% retention of configuration. Nesmeyanov and coworkers (7) mercurated an optically active diastereomer of menthyl 2-bromopropionate, converted this alkylmercuric halide to the dialkylmercury compound and transformed the substance back to the alkylmercuric halide in stereospecific reactions. Cram, et al. (8) have reported that electrophilic substitution that accompanies reverse condensation reactions can occur

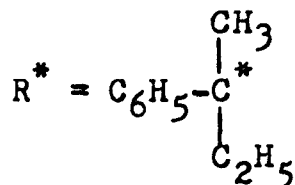
with from 93% predominating retention to 50% predominating inversion. Winstein and coworkers (9) observed better than 99% retention of configuration in the reaction of *cis*-2-methoxycyclohexylneophylmercury with radioactive mercuric chloride to give radioactive *cis*-2-methoxycyclohexylmercuric chloride.

Another indication that electrophilic substitution at saturated carbon can occur with retention is found in the fact that a bromine atom at the bridgehead carbon atom of triptycene can be replaced by lithium, and the triptycyl lithium formed can be carbonated (10). Likewise, 4-camphenylmercury derivatives readily undergo electrophilic substitution reactions (11). In these transformations a tetrahedral configuration must have been maintained at the seat of substitution.

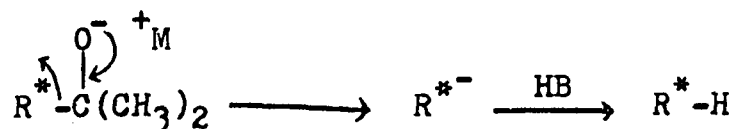
The stereochemical capabilities of the 2-phenyl-2-butyl anion has been investigated by Cram and coworkers in recent years. The reactions studied involved carbon (12, 13), oxygen (14), hydrogen (15) and nitrogen (16) as leaving group and proton and deuteron as electrophile. In these reactions as high as 99% retention, 60% inversion or 100% racemization was observed depending upon the character of the solvent and the cations of the basic catalyst involved. Representative reactions are illustrated in the following chart:

Chart I

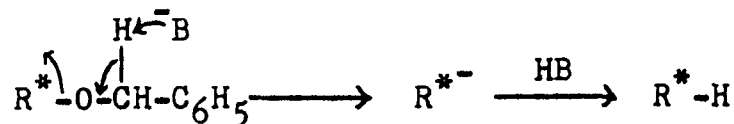
Examples of different leaving group in E₁ reactions.



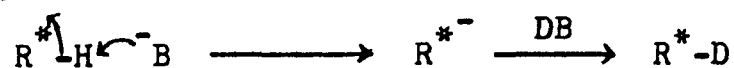
Carbon:



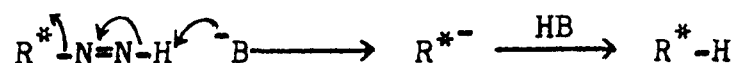
Oxygen:



Hydrogen:



Nitrogen:



Cram has presented the following explanation for variations in the steric behavior of the carbanions. In solvents of low dielectric constants (e.g., t-butyl alcohol, $\epsilon = 10.9$ at 30°) and with metal alkoxides as bases, high retention of configuration is observed. This result is attributed to a favorable orientation of proton donors, which coordinate with the metal cation of an intimate

ion-pair which undergoes cleavage and is favorably solvated from the side of the leaving group by proton donors. In non-protonic solvents with high dielectric constants (e.g., dimethylsulfoxide) the carbanion has sufficient life-time to become symmetrically solvated, and electrophilic substitution gives racemic product. In solvents of high dielectric constants which are good proton donors (e.g., ethylene glycol, $\epsilon = 37$ at 25°), a solvent-separated ion pair undergoes cleavage. The carbanion produced is protonated more rapidly from the side remote from the leaving group and because of the shielding effect of that group, electrophilic substitution gives inversion product.

It should be noted that the carbanion carbon developed in the reactions studied by Cram and Walborsky are bonded to unsaturated (aromatic) or strained (cyclopropyl) groups. No fully aliphatic carbanion has been subjected to such a study.

In view of these observations, a comparison of the stereochemical behavior of the t-heptyl anion generated from an azoacetate with the behavior of ions reported by Cram and Walborsky is of interest and has been completed. The details of this study are summarized in the following sections.

EXPERIMENTAL PART

In the following experimental section all temperatures are expressed as degrees centigrade.

The infrared spectra were obtained with a Beckman Model IR-8 recording spectrophotometer and the assignment of bands was made according to Bellamy (17).

The nmr spectra were obtained with a Varian A-60 spectrometer.

Gas-liquid chromatography was carried out with a F and M Model 720 and a Varian Model 700-"Autoprep" gas chromatograph.

Specific rotations of compounds were measured with a Rudolph Model 62 Polarimeter and a Standard Model D Keston Polarimetric Unit Attached to a Beckman DU-2 Spectrophotometer.

2-Phenylbutane and 3-methylhexane used for comparison work were purchased from Aldrich Chemical Co., Inc.

Elemental analyses were performed by Galbraith Micro-analytical Laboratories, Knoxville, Tennessee.

Preparation of Hydrazones

Acetone 2-phenyl-2-butylhydrazone was obtained in turn from the necessary hydrazine which was prepared and resolved by adapting the procedure described by Cram and coworkers (16). The derivatives in the t-heptyl series were prepared following the procedures by Buu (2).

Preparation of methyl ethyl ketazine

Hydrazine (2 mol, 68 g, 95%) was added slowly with stirring and cooling (ice-water bath) to methyl ethyl ketone (6 mol, 432 g). After the addition was completed, the reaction mixture was cooled to room temperature over a period of one hour. After the water layer was separated, the organic layer was dried with anhydrous potassium carbonate. The excess methyl ethyl ketone was removed by simple distillation and the product was fractionally distilled through a 11 in. Vigreux column. Methyl ethyl ketazine was obtained in 86% yield and had the following properties: bp 165-168° at 749 mm, n_D^{25} 1.4512-1.4520. Literature values (16): bp 168-170° at 750 mm, n_D^{25} 1.4513.

Preparation of methyl ethyl ketone 2-phenyl-2-butylhydrazone

Phenyl magnesium bromide was prepared in the standard manner from 2 mol (340 g) of bromobenzene and 2.3 g at. wt magnesium turnings in absolute ether. Methyl ethyl ketazine

(1 mol, 140 g) was dissolved in 500 ml of absolute ether and was added dropwise with stirring to the Grignard reagent. The resulting mixture was stirred at reflux for 5 days, cooled to 5°, and added to 400 g of ammonium chloride suspended in ice. The organic layer was separated and the aqueous layer was extracted with three 200 ml portions of ether. The combined organic layers were washed with water saturated with sodium bicarbonate, dried with anhydrous potassium carbonate and evaporated under reduced pressure. Distillation of the residue gave methyl ethyl ketone 2-phenyl-2-butylhydrazone: 106.4 g, 50%, bp 174-175° at about 50 mm, n_D^{25} 1.5460. Literature values (16): bp 100-115° at 3 mm.

Three preparations were carried out to produce a total of 161.7 g of the hydrazone.

Preparation of 2-phenyl-2-butylhydrazinium oxalate

Methyl ethyl ketone 2-phenyl-2-butylhydrazone (0.48 mol, 102 g) was added to oxalic acid hydrate (mp 103-106°, 0.83 mol, 102 g) dissolved in a mixture consisting of 300 ml of absolute ethanol, 300 ml of absolute ether and 5 ml of water. A white granular solid was separated from the mixture at room temperature over a period of 36 hours. The crude product was collected and recrystallized from hot ethanol to yield the hydrazine oxalate salt: 88.5 g, 79%, mp 109-111°. Literature value (16): mp 109-110°.

Four similar preparations were carried out to produce a total of 115.4 g of 2-phenyl-2-butylhydrazinium oxalate.

Preparation of (-)-dibenzoyl tartaric acid hydrate

According the procedure reported by Butler and Cretcher (18), tartaric acid (1.2 mol, 180 g) and benzoyl chloride (3.8 mol, 464 g) were slowly heated in a round bottom flask until the temperature reached 150°. The reaction took place mainly between 135 and 140°. The total time of heating was approximately 2 to 3 hours. The contents of the flask were removed and ground in a mortar. Benzoic acid and the excess benzoyl chloride were removed by extracting with benzene in the following manner: 300 ml of solvent was added, the mixture was warmed, with agitation, just short of the boiling point and then cooled to room temperature. The mixture was filtered and the extraction of the solid was repeated. The material was then washed with several portions of cold benzene. The mp of crude dibenzoyl tartaric anhydride was 155 to 160°. The crude benzene extracted product was boiled with 1500 ml of water for one-half hour. Dibenzoyl tartaric acid monohydrate formed as a heavy oil which solidified into a crystalline cake, after standing over night. This solid was removed, air-dried and powdered. Purer product was obtained by recrystallizing from benzene: 207 g, mp 90-92°, $[\alpha]_D^{28.5} -108.5^\circ$ (1, 2 dm; c, 2; ethanol). Literature values (19): mp 88-89°, $[\alpha]_D^{27} -112.5^\circ$ (c, 1.1; ethanol).

Preparation of 2-phenyl-2-butylhydrazine

2-Phenyl-2-butylhydrazinium oxalate (0.13 mol, 34 g) was dissolved in a solution of potassium hydroxide (0.36 g f wt, 20 g) in 240 ml of water. The mixture was extracted three times with 100 ml portions of ether. The combined ether extracts were dried with anhydrous sodium carbonate. The ether was evaporated under reduced pressure and the 2-phenyl-2-butylhydrazine (18.6 g, 87%) was used without further purification.

Resolution of 2-phenyl-2-butylhydrazine

Following the procedure reported by Cram (16). (-)-Dibenzoyl-tartaric acid (0.16 mol, 57.7 g, mp 90-92°), $[\alpha]_D^{28.5}$ -108.5° (1, 2 dm; c, 2; ethanol), was dissolved in a mixture of 300 ml of absolute ethanol and 100 ml of distilled water, and 2-phenyl-2-butylhydrazine (0.11 mol, 18.6 g) was added. The resulting mixture was stirred and allowed to stand for 5 days at 0-5°. The salt that separated was collected. Two successive recrystallizations of the salt were accomplished from 3:1 ethanol-water and the properties of the salt at each stage are listed in Table I.

In a second resolution, 48 g of the 2-phenyl-2-butylhydrazine-(-)-dibenzoyltartaric acid salt was obtained: mp 140-143°, $[\alpha]_D^{23.5}$ -74° (1, 2 dm; c, 1; ethanol). Literature values (16): mp 140-145°, $[\alpha]_D^{25}$ -74.1° (c, 1; ethanol).

Table I

Properties of 2-Phenyl-2-butylhydrazine
(-)-Dibenzoyl-tartaric Acid Salt

Crystallization Number	Weight of Salt	Mp of Salt	Specific Rotation of Salt**
I, Crop 1	29.2 g	141-145	-53°
Crop 2	3.2 g	139-142	-76°
Crop 3	14.5 g	135-140	-72°
Crop 4	2.5 g	142-145	-74°
II,* Crop 1	1.5 g	138-142	-73°
Crop 2	12.0 g	115-120	-73.5°

* Recrystallization from I, Crop 1

**1, 2 dm; c, 1; ethanol

Preparation of racemic acetone 2-phenyl-2-butylhydrazone

2-Phenyl-2-butylhydrazinium oxalate (0.035 mol, 9.2 g) was dissolved in a solution of potassium hydroxide (0.097 g f wt, 5.4 g) in 65 ml of distilled water. The mixture was extracted three times with 60 ml portions of ether. The combined ether extracts were dried with anhydrous sodium carbonate, the ether was evaporated under reduced pressure. The residual hydrazine oil was mixed with acetone (0.21 mol, 11.9 g). The mixture was refluxed on steam bath for four hours, cooled to room

temperature and dried with anhydrous sodium sulfate. The excess acetone was distilled through a 23 cm x 0.6 cm tantalum wire spiral column and the residue was distilled at reduced pressure. The acetone 2-phenyl-2-butylhydrazone was obtained in 80% yield (4.9 g): bp 91-92° at 1 mm, n_D^{25} 1.5220.

The nmr spectrum (in CCl_4) obtained was consisting with the indicated structure and showed the following chemical shifts with assignments noted: 0.68 δ , t, 3H (CH_3-CH_2-); 1.46 δ , s, 3H(CH_3-C); 1.65 δ , s, 3H and 1.85 δ , s, 3H, $(CH_3)_2C=N-$; 1.90 δ , quartet 2H(CH_3-CH_2-C); 4.50 δ , s, 1H(-NH-); 7.25 δ , m, 5H(C_6H_5-).

Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.22; H, 9.96; N, 13.51.

In a second similar preparation, a 76% yield was obtained.

Preparation of (-)-acetone 2-phenyl-2-butylhydrazone

The optically active acetone 2-phenyl-2-butylhydrazone was prepared according to the procedure outlined above, starting with optically active 2-phenyl-2-butylhydrazine liberated from the tartaric acid salt. (-)-2-Phenyl-2-butylhydrazine-dibenzoyltartaric acid salt (0.13 mol, 70 g) was dissolved in a solution of potassium hydroxide (0.65 g f wt, 36.4 g) in 350 ml of distilled water and extracted with three 100 ml portions of ether. The

combined ether extracts were dried with anhydrous sodium carbonate, the ether was evaporated under a vacuum to leave an oil residue consisting of the optically active hydrazine. Reaction with acetone gave 63% (15.5 g) yield of the hydrazone: bp 110-116° at 2 mm, n_D^{25} 1.5224, $[\alpha]_D^{25}$ -0.58° (1, 1 dm; d^{25} 0.939; neat).

Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71.
Found: C, 76.21; H, 9.95; N, 13.51.

Preparation of racemic methyl ethyl ketone t-heptylhydrazone

A solution of n-propyl magnesium bromide was prepared from n-propyl bromide (4.4 mol, 542 g) and magnesium turnings (4.6 g at. wt, 112 g) in 1000 ml of dry ether. Methyl ethyl ketazine (1 mol, 140 g) dissolved in 500 ml of dry ether was added dropwise with stirring to the Grignard reagent. The resulting mixture was stirred at reflux for two days, cooled to 5°, and added to 400 g of ammonium chloride suspended on ice. The organic layer was separated, and the aqueous layer was extracted three times with 200 ml portions of ether. The combined organic layers were washed with water saturated with sodium bicarbonate, dried and the solvent was evaporated under reduced pressure. Distillation of the residue gave 37.1 g of racemic methyl ethyl ketone t-heptylhydrazone: bp 91-94° at 14 mm, n_D^{25} 1.4488.

The nmr spectrum (neat) showed a complex pattern of

overlapping and unfactorable multiplets in the 0.5 to 2.5 δ range characteristic of the t-heptyl compounds. In addition, singlets at 1.3 δ and 4.2 δ were observed and apparently assignable to $\text{CH}_3-\overset{|}{\text{C}}=\text{N}-$ and $-\text{NH}-$ respectively.

Preparation of 3-methyl-3-hexanol

3-Methyl-3-hexanol was prepared in 60-70% yield by reacting 2-pentanone with ethyl magnesium bromide: bp $141-142^\circ$, n_D^{25} 1.4200. Literature values (2): bp 143° , n_D^{20} 1.4231.

Preparation of t-heptylamine

A solution of 750 g of sulfuric acid (sp gr 1.84) in 400 ml of glacial acetic acid was added slowly, with stirring, to a solution of 3-methyl-3-hexanol (3 mol, 348 g) and sodium cyanide (3 g f wt, 149.2 g, 98.4%) in 380 ml of glacial acetic acid. The temperature of the reaction mixture was maintained between $40-60^\circ$ by the use of an ice-water bath. The reaction mixture was allowed to stand over night. A solution of 1280 g of sodium hydroxide in 1300 ml of water was then added slowly, with stirring and cooling (in ice-water bath) to the mixture. The reaction mixture was refluxed for eight hours and then steam distilled. Sodium carbonate was added to the distillate to salt out the amine layer. The amine layer was separated and the aqueous layer was extracted with three 100 ml

portions of pentane. The combined organic portions were dried over anhydrous potassium carbonate. Distillation yielded colorless t-heptylamine: 249 g, 73%, bp 128-130°, n_D^{25} 1.4170. Literature values (2): bp 129.5-130.5° at atmospheric pressure, n_D^{25} 1.4171.

Seven similar preparations were completed. A total of 862 g of t-heptylamine was obtained.

Resolution of t-heptylamine

Over a period of 2 hours, racemic t-heptylamine (4 mol, 460 g) was added slowly with stirring to a solution of (+)-tartaric acid (5.2 mol, 600 g), $[\alpha]_D^{26} +13.1^\circ$ (1, 2 dm; c, 10; water), in 2000 ml of water. The mixture was heated over a steam bath for an hour and allowed to cool to room temperature. The solution, after being stored over night in the refrigerator, yielded white crystalline tartrate salt: 507 g, mp 116-118°.

Two resolutions were carried out and the combined tartrate salt was recrystallized twice from water.

t-Heptylamine-(+)-tartrate salt (2.4 mol, 632.1 g) was dissolved in 700 ml of water. A solution of 208 g of potassium hydroxide dissolved in 300 ml of water was added slowly to the tartrate salt solution. In order to avoid loss of the amine by evaporation, the reaction flask was cooled in an ice-water bath. Sodium carbonate was added to salt out the amine. The amine layer was separated and

the aqueous layer was extracted three times with 100 ml portions of pentane. The pentane extracts were combined with the organic layer, dried over anhydrous potassium carbonate and distilled through a 23 cm x 0.6 cm tantalum wire spiral column. The distillation gave optically active t-heptylamine: 243.4 g, 90%, bp 129-130°, n_D^{25} 1.4170, $[\alpha]_D^{25}$ -0.065° (1, 4 dm; d^{25} 0.776; neat). Literature values (2): bp 129.5-131.5°, $[\alpha]_D^{25}$ -0.041° (1, 4 dm; d^{25} 0.776; neat)*.

The properties of the amine tartrate salt and the corresponding t-heptylamine at each stage are listed in Table II.

Preparation of (+)-N-methylene-t-heptylamine

Over a period an hour, formaldehyde solution (1.94 mol, 245 ml, 37%) was added with stirring and cooling (ice-water bath) to (-)-t-heptylamine (1.94 mol, 222.6 g, $[\alpha]_D^{25}$ -0.065°), contained in a 1000 ml 3-neck round bottom flask equipped with an addition funnel, motor stirrer and reflux condenser. The mixture was stirred for an hour after addition had been completed. On standing the reaction mixture separated into two layers. The aqueous

*The reported value is not as indicated as the reference, since our observed density was distinctly different from that designated in the reference. The reported specific rotation is believed in error because of error in this density value and accordingly all reported values are "corrected" by recalculation using the currently measured densities. Such "corrected" values are designated by an asterisk.

(lower) layer was made alkaline with potassium hydroxide and extracted with three 50 ml portions of pentane. The pentane extracts were combined with the organic layer, dried over anhydrous potassium carbonate and distilled through a 23 cm x 0.6 cm tantalum wire spiral column. The distillation yielded a lachrymatory liquid: 219.1 g, 90%, bp 140-141°, n_D^{25} 1.4340, $[\alpha]_D^{25} +1.02^\circ$ (1, 2 dm; d^{25} 0.815; neat). Literature values (2): bp 140-145°, n_D^{25} 1.4277, $[\alpha]_D^{25} +0.72^\circ$ (1, 2 dm; d^{25} 0.815; neat)*.

Table II

Properties of Diastereomeric Salt and
Amine in Resolution of t-Heptylamine

Crystallization Number	Weight of Salt	Mp of Salt	Specific Rotation of Salt*	Specific Rotation of Amine**
I, Crop 1	1197.2 g	116-118	+15.2°	
II, Crop 1	370.3 g	116-118	+15.0°	-0.078°
Crop 2	301.8 g	116-118	+15.3°	-0.052°

* 1, 2 dm; $c, 4$; water

**1, 2 dm; d^{25} 0.776; neat. Optical activity measured using a Standard Model D Keston Polarimetric Unit Attached to a Beckman DU-2 Spectrophotometer.

Preparation of (+)-N-methyl-t-heptylamine

Using a parr low pressure hydrogenation apparatus,

a solution of (+)-N-methylene-t-heptylamine (0.88 mol, 111.8 g, $[\alpha]_D^{25} +1.02^\circ$), dissolved in 100 ml of methanol was reduced with the aid of 0.5 g of PtO_2 . After filtering and removing the solvent, the residue was distilled. Two reductions were completed and combined to give (+)-N-methyl-t-heptylamine with the following properties: 184.5 g, 84%, bp 145-155°, n_D^{25} 1.4240, $[\alpha]_D^{25} +0.14^\circ$ (1, 2 dm; d^{25} 0.780; neat). Literature values (2): bp 142-155°, n_D^{25} 1.4218, $[\alpha]_D^{25} +0.19^\circ$ (1, 2 dm; d^{25} 0.780; neat)*.

Preparation of (+)-N-nitrosomethyl-t-heptylamine

The method of Heath and Mattocks (20) was adapted for this preparation of (+)-N-nitrosomethyl-t-heptylamine. Sodium nitrite (2.82 mol, 196 g f wt) dissolved in 350 ml of water was added slowly with stirring to (+)-N-methyl-t-heptylamine (1.41 mol, 182.3 g, $[\alpha]_D^{25} +0.14^\circ$), and 278.4 ml (4.68 mol) of acetic acid at 25-35°. The mixture was cooled in ice-water bath and made alkaline by adding potassium hydroxide (4 g f wt, 224 g) dissolved in 250 ml of water. The nitrosoamine was extracted with three 100 ml portions of ether, dried with anhydrous potassium carbonate and the solvent was removed by distillation. The residue was fractionated at reduced pressure and six fractions of yellow oil were collected. Fractions 4-6 totalled 153.8 g, 70%, gave the following range of properties: bp 107-112 at 10 mm, n_D^{25} 1.4560-1.4578,

$[\alpha]_D^{25} + 2.08^\circ$ (1, 2 dm; d^{25} 0.931; neat). Literature values (2): bp 128-135° at 28 mm, n_D^{25} 1.4538-1.4553, $[\alpha]_D^{25} + 1.50^\circ$ (1, 2 dm; d^{25} 0.931; neat)*.

Preparation of (+)-N-methyl-t-heptylhydrazine

Zinc dust (1.36 g at. wt, 85.6 g) was added slowly in small portions to a solution of (+)-N-nitrosomethyl-t-heptylamine (0.34 mol, 54.3 g, $[\alpha]_D^{25} + 2.08^\circ$) dissolved in 326 ml (1.36 mol) of glacial acetic acid and 330 ml of water. The addition time was about two hours. The reaction mixture was stirred for eighteen hours. The temperature of the solution was maintained between 0-10° during the entire process. Since no phase separation was observed after the solution was made alkaline with concentrated sodium hydroxide solution, the mixture was steam distilled. The distillate was extracted several times with large portions of pentane. The pentane extracts were combined and dried over anhydrous potassium carbonate. The solvent was removed by distillation through a 23 cm x 0.6 cm tantalum wire spiral column. Three reductions were completed and the combined crude hydrazine was distilled at reduced pressure. Six fractions of a clear liquid were collected; 90.6 g, 65%, bp 63-70° at 10 mm, n_D^{25} 1.4432-1.4470, $[\alpha]_D^{25} + 0.27^\circ$ (1, 2 dm; d^{25} 0.844; neat). Literature values (2): bp 59-60° at 10 mm, n_D^{25} 1.4425-1.4458, $[\alpha]_D^{25} + 0.19^\circ$ (1, 2 dm; d^{25} 0.844; neat)*.

Preparation of (+)-acetone methyl-t-heptylhydrazone

A mixture of (+)-methyl-t-heptylhydrazine (0.62 mol, 89.3 g, $[\alpha]_D^{25} +0.27^\circ$) and acetone (6.2 mol, 455 ml) was refluxed for three hours on steam bath. The reaction mixture was cooled to room temperature and separated into two layers after the addition of water. The organic layer was separated and the aqueous layer was extracted three times with 50 ml portions of pentane. The pentane extracts were combined with the organic layer and dried over anhydrous potassium carbonate. The solvent was removed by distillation through a 23 cm x 0.6 cm tantalum wire spiral column and the residue was distilled at reduced pressure. Optically active acetone methyl-t-heptylhydrazone was collected: 103 g, 90%, bp $80-85^\circ$ at 14 mm, n_D^{25} 1.4460-1.4472, $[\alpha]_D^{25} +0.40^\circ$ (1, 2 dm; d^{25} 0.843; neat). Literature values (2): bp $79-91^\circ$ at 14 mm, n_D^{25} 1.4432-1.4458, $[\alpha]_D^{25} +0.27^\circ$ (1, 2 dm; d^{25} 0.843; neat)*.

Preparation of Azoacetates

Preparation of racemic 2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane

A solution of lead tetraacetate (0.017 mol, 7.6 g) dissolved in 75 ml of dry methylene chloride was added dropwise to a stirred solution of racemic acetone 2-phenyl-2-butylhydrazone (0.015 mol, 3.06 g) dissolved in 20 ml of dry methylene chloride. The temperature of the reaction mixture was maintained between 0 to 5° by immersing the reaction flask in an ice-water bath. After a few milliliters of the hydrazone had been added turbidity and a yellow color developed. The reaction mixture was stirred for an additional thirty minutes at room temperature before 100 ml of water was added. The methylene chloride layer was separated, washed successively with 100 ml of water, 100 ml of saturated sodium bicarbonate solution and then dried over anhydrous sodium sulfate. The solvent was evaporated and the dark yellow residual oil was distilled at reduced pressure. Distillation gave the azo compound appearing as a light yellow colored liquid: 2.0 g, 51%, bp 98-99° at 1 mm, n_D^{25} 1.4935, λ_{\max} 367 mμ, $\log \epsilon_{\max}$ 1.45 (ethanol).

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.75; H, 8.45; N, 10.59.

A second preparation gave 5.6 g, 56%, of product having the same properties.

Preparation of (-)-2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane

Optically active 2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane was prepared according to the procedure outlined above, starting with (-)-acetone 2-phenyl-2-butylhydrazone (0.071 mol, 14.5 g, $[\alpha]_D^{25} -0.58^\circ$) and lead tetraacetate (0.078 mol, 34.7 g) in dry methylene chloride solution.

The reaction yielded the light yellow azo compound: 10.5 g, 57%, bp $93-94^\circ$ at 1 mm, $n_D^{25} 1.4935$, $[\alpha]_D^{25} -0.26^\circ$ (1, 1 dm; $d^{25} 0.982$; neat).

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.89; H, 8.51; N, 10.71.

Preparation of racemic 2-acetoxy-2-t-heptylazobutane

Racemic 2-acetoxy-2-t-heptylazobutane was prepared according to the procedure outlined above, starting with methyl ethyl ketone t-heptylhydrazone (0.15 mol, 27.6 g) and lead tetraacetate (0.18 mol, 80.1 g) in dry methylene chloride solution. The temperature of the reaction mixture was maintained between -40 to -50° during the entire process by use of an 2-propanol-dry ice bath.

The reaction gave a light yellow liquid: bp $48-49^\circ$ at 0.2 mm, $n_D^{25} 1.4336$.

Anal. Calcd for $C_{13}H_{26}N_2O_2$: C, 64.42; H, 10.81; N, 11.56. Found: C, 64.39; H, 10.67; N, 11.76.

Conduction the reaction at $0-10^\circ$ as in the previous

oxidation, led to a reaction mixture that afforded only a low yield of the azo compound (15%) and a product difficult to purify. Such product gave high refractive index value and rapidly developed intense violet color on exposure to air even though initially it had a pale yellow color when freshly distilled.

Preparation of (-)-2-acetoxy-2-t-heptylazopropane

(-)-2-Acetoxy-2-t-heptylazopropane was prepared according to the procedure outlined above, starting with (+)-acetone methyl-t-heptylhydrazone (0.15 mol, 27.6 g, $[\alpha]_D^{25} +0.40^\circ$) and lead tetraacetate (0.33 mol, 146.9 g) in dry methylene chloride. In this preparation, the hydrazone was added dropwise to the lead tetraacetate solution at -40 to -50° . Three preparations were completed and the combined crude azoacetate was distilled twice at reduced pressure to yield the light yellow azo compound: 31.6 g, 42%, bp $50-54^\circ$ at 8 mm, n_D^{25} 1.4315, $[\alpha]_D^{25} -0.17^\circ$ (1, 2 dm; d^{25} 0.908; neat). Literature values (2): bp $75-100^\circ$ at 14 mm, n_D^{25} 1.4413-1.4425.

Anal. Calcd for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.59; N, 12.27. Found: C, 63.22; H, 10.61; N, 12.39.

Base Catalyzed Decomposition of Azoacetates

Formation of 2-phenylbutane from racemic 2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane

Racemic 2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane, (0.004 mol, 1.05 g) was mixed with a solution of potassium hydroxide (0.04 g f wt, 2.24 g) dissolved in 4.0 ml of water and diluted with 16 ml of methanol. The mixture was placed in an Erlenmeyer flask equipped with a reflux condenser and magnetic stirrer. The reaction occurred slowly as indicated by the evolution of nitrogen gas. The solution was warmed to 35° for thirty minutes and then let stand over night with stirring. The reaction mixture was extracted three times with 10 ml portions of pentane. The combined pentane extracts were washed twice with 15 ml portions of water and then dried over anhydrous potassium carbonate. The solvent was removed by distillation through a 14 mm x 360 mm heli-pak variable reflux column. The presence of 2-phenylbutane in the residue was demonstrated by vapor phase chromatography in a two foot SE 30 column. The hydrocarbon was identified by comparison with authentic 2-phenylbutane (Aldrich Chem. Co. Inc. # B9040-8). The yield (88%) of the 2-phenylbutane was determined quantitatively by vapor phase chromatography using internal reference method with isopropyl benzene as internal standard.

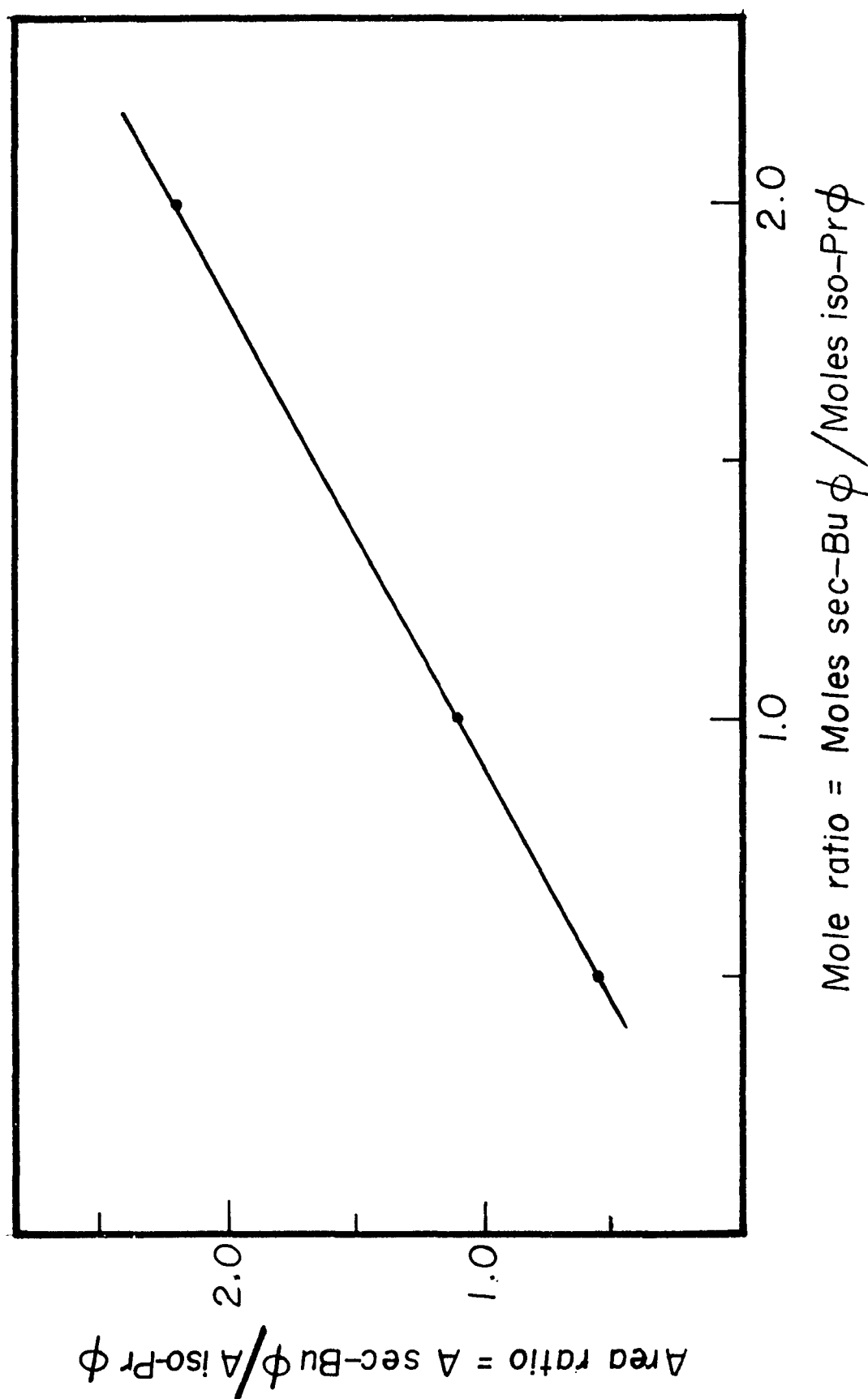


Figure 1 Analytical work curve for determination of 2-phenylbutane

Experiment 1. Base decomposition of racemic 2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane in 3 mole% of water-97 mole% of t-butanol at 40°

A solution of potassium metal (0.08 g at. wt, 3.132 g) dissolved in 142.5 ml (1.53 mol) of t-butanol and 0.82 ml (0.046 mol) of water was placed in a 3-neck round bottom flask equipped with a motor stirrer, an addition funnel and a reflux condenser topped with tubing leading to a calibrated gas burette. Nitrogen gas formed was measured by displacement of water from the burette. The reaction flask was immersed in a constant temperature water-bath ($40 \pm 0.1^\circ$). The entire system was flushed with nitrogen gas. Racemic 2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane (0.011 mol, 2.896 g) was introduced into the base solution through the addition funnel. The reaction occurred as indicated by the evolution of nitrogen gas. The reaction mixture was stirred for one hour. By this time the volume of the nitrogen gas collected had become constant: 244 ml at 737.7 mm, 24.2° , 211 ml dry at STP, 86%. The reaction flask was cooled, diluted with 200 ml of water and the mixture was extracted with 100 ml of pentane. The pentane layer was separated and the aqueous layer was extracted additionally with three 50 ml portions of pentane, the combined pentane layers were washed several times with water, dried, and concentrated by distillation using a 23 cm x 0.6 cm tantalum wire spiral column and collecting only the

distillate boiling below 37°. The residual liquid (about 15 ml) was chromatographed on 50 g of 80-200 mesh alumina and eluted with pentane. The first 150 ml of column eluant was concentrated by distillation as above. The residual liquid was distilled at reduced pressure to give racemic 2-phenylbutane: 1.20 g, 82%, bp 81-83° at 50 mm, n_D^{25} 1.4865. This 2-phenylbutane provided a retention time and ir spectrum identical with those of the authentic hydrocarbon (Aldrich Chem. Co. Inc. # B9040-8).

Experiment 2. Base decomposition of (-)-2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane in 3 mole% of water-97 mole% of t-butanol at 30°

(-)-2-Acetoxy-2-(2'-phenyl-2'-butylazo)-propane (0.0115 mol, 3.023 g, $[\alpha]_D^{25}$ -0.26°) was added to a solution of potassium metal (0.102 g at. wt, 3.969 g) dissolved in a solution of 0.82 ml (0.046 mol) of water and 142.5 ml (1.53 mol) of t-butanol. This reaction was conducted according to the procedure outlined in Experiment 1 except that the reaction temperature was adjusted to 30°. The following volume of nitrogen gas was collected: 212 ml, 746.8 mm, 23.2°, 186 ml dry at STP, 72%. The reaction yielded (+)-2-phenylbutane: 1.21 g, 76%, n_D^{25} 1.4842 $[\alpha]_D^{25}$ +1.00° (1, 1 dm; d_D^{25} 0.853; neat), 72% retention*. Literature value (16); n_D^{25} 1.4878.

*Based on the value of the specific rotation of the optically pure hydrocarbon and the absolute configuration as reported by Cram, et al. (16)

Experiment 3. Duplication of Experiment 2

To a solution of potassium metal (0.102 g at. wt, 3.979 g) dissolved in a mixture of 0.82 ml (0.046 mol) of water and 142.5 ml (1.53 mol) of t-butanol, (-)-2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane (0.0115 mol, 3.024 g, $[\alpha]_D^{25} -0.26^\circ$) was added. This reaction was conducted identically to Experiment 2. The volume of nitrogen gas collected after one hour was as follows: 230 ml at 744 mm, 23.8°, 201 ml at STP, 78%. The yield of (+)-2-phenylbutane: 1.12 g, 70%, bp 79-81° at 45 mm, $n_D^{25} 1.4870$, $[\alpha]_D^{25} +0.95^\circ$ (1, 1 dm; $d^{25} 0.853$; neat), 68% retention. Literature value (16): $n_D^{25} 1.4878$.

Experiment 4. Base decomposition of (-)-2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane in water at 100°

Optically active 2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane (0.0153 mol, 4.022 g, $[\alpha]_D^{25} -0.26^\circ$) was introduced to a solution of potassium hydroxide (0.0765 g f wt, 4.284 g) dissolved in 256.7 ml of distilled water. The reaction mixture was refluxed at 100° with constant stirring for four hours. The volume of nitrogen gas collected was as follows: 350 ml, 736.5 mm, 23.2°, 304 ml dry at STP, 89%. The procedures for isolation and identification of the (-)-2-phenylbutane were the same as noted in Experiment 1. The reaction gave (-)-2-phenylbutane: 1.601 g, 80%, bp 83-87° at 45 mm, $n_D^{25} 1.4865$, $[\alpha]_D^{25} -0.44^\circ$ (1, 1 dm; $d^{25} 0.853$;

neat), 32% inversion. Literature value (16): n_D^{25} 1.4878.

Experiment 5. Base decomposition of racemic 2-acetoxy-2-t-heptylazobutane in 3 mole% of water-97 mole% of t-butanol at 50°

Racemic 2-acetoxy-2-t-heptylazobutane (0.0206 mol, 4.997 g) was introduced to a solution of potassium metal (0.204 g at. wt, 7.968 g) dissolved in 1.64 ml (0.091 mol) of water and 285 ml (3.04 mol) of t-butanol. This reaction was made according to the procedure outlined in Experiment 1 except that the reaction was run at 50°. By the time (3 hours) the volume of nitrogen gas collected had become constant: 520 ml at 737.8 mm, 25.4°, 446 ml dry at STP, 97%, the reaction was stopped and the reaction mixture was extracted with three 70 ml portions of pentane. The combined pentane extracts were concentrated by distillation through a 14 mm x 360 mm heli-pak variable reflux column and collecting only the distillate boiling below 37°. The residual liquid (about 15 ml) was chromatographed on 50 g of 80-200 mesh alumina and eluted with pentane. The first 150 ml of eluant was concentrated by distillation using the above column. Racemic 3-methylhexane was isolated from the concentrate using a twenty foot SE 30 column on a Varian Model A-700 "Autoprep" Automatic Preparative Gas Chromatograph: 1.13 g, 46%, n_D^{25} 1.3862. This 3-methylhexane provided a retention time and refractive index identical with those of the authentic hydrocarbon (Aldrich Chem. Inc. # M4980).

Experiment 6. Base decomposition of (-)-2-acetoxy-2-t-heptylazopropane in 3 mole% of water-97 mole% of t-butanol at 50°

The base catalyzed decomposition reaction was carried out according to the procedure outlined in Experiment 1 by introducing (-)-2-acetoxy-2-t-heptylazopropane (0.0255 mol, 5.812 g, $[\alpha]_D^{25} -0.17^\circ$) to a solution of potassium metal (0.204 g at. wt, 7.973 g) dissolved in a mixture of 1.64 ml (0.091 mol) of water and 285 ml (3.04 mol) of t-butanol. The volume of nitrogen gas collected after three hours was as follows: 600 ml at 746 mm, 24.5°, 517 ml dry at STP, 90%. The product was isolated and identified using the same procedure as indicated in Experiment 5. The yield of optically active 3-methylhexane was as follows: 1.69 g, 55%; $n_D^{25} 1.3870$, $[\alpha]_D^{25} +1.09^\circ$ (1, 1 dm; $d^{25} 0.682$; neat). est 22% retention*.

Experiment 7. Decomposition of (-)-2-acetoxy-2-t-heptylazopropane in water at 100° in the presence of base

In this reaction no organic solvent was added to the reaction mixture. (-)-Acetoxy-2-t-heptylazopropane (0.0251

*Values for retention or inversion in the reactions producing optically active 3-methylhexane are based on the maximum $[\alpha]_D^{25} = \pm 9.1^\circ$ reported for optically pure hydrocarbon (21) and acceptance of $[\alpha]_D^{25} = -0.12^\circ$ reported by Buu as the value for optically pure t-heptylamine. This leads to a minimum value for optical purity of the azo-compound used in the decomposition reactions and minimum values for the steric course of the reaction. The correlation is based on an assumption of a parallel course of reaction in similar solvents to the correlation established by Cram et al. (16)

mol, 5.719 g, $[\alpha]_D^{25} -0.17^\circ$) was introduced to a solution of potassium hydroxide (0.127 g f wt, 7.089 g) dissolved in 417 ml of distilled water. The reaction mixture was refluxed for three hours with vigorous stirring. Since this azoacetate was insoluble in water, the reaction was heterogeneous. The volume of nitrogen gas collected after three hours was as follows: 605 ml at 736.8 mm, 27.8° , 511 ml dry at STP, 91%. The product was isolated and identified using the same method as indicated in Experiment 5. 3-Methylhexane was isolated as follows: 1.55 g, 52%, $n_D^{25} 1.3862$, $[\alpha]_D^{25} 0.00$ (1, 1 dm; $d^{25} 0.682$; neat; $a=0.00$), 100% racemization.

Experiment 8. Base decomposition of (-)-2-acetoxy-2-t-heptylazopropane in methanol at 40°

In this experiment no water was introduced to the reaction mixture. (-)-2-Acetoxy-2-t-heptylazopropane (0.0241 mol, 5.490 g, $[\alpha]_D^{25} -0.17^\circ$) was added to a solution of potassium metal (0.241 g at. wt, 9.384 g) dissolved in 286.6 ml of absolute methanol. The experimental procedure followed that in Experiment 1. The volume of nitrogen gas collected after six hours was as follows: 512 ml at 742 mm, 21° , 452 ml dry at STP, 84%. The product was isolated and identified using the same method indicated in Experiment 5. The reaction yielded optically active 3-methylhexane: 1.028 g, 36%, $n_D^{25} 1.3875$, $[\alpha]_D^{25} -0.013^\circ$ (1, 1 dm; $d^{25} 0.682$; neat), est 0.27% inversion.

Experiment 9. Base decomposition of (-)-2-acetoxy-2-t-heptylazopropane in 20% by volume of water-80% by volume of methanol at 40°

(-)-2-Acetoxy-2-t-heptylazopropane (0.024 mol, 5.478 g, $[\alpha]_D^{25} -0.17^\circ$) was added to a solution of potassium metal (0.240 g at. wt, 9.371 g) dissolved in a mixture of 57.3 ml (20% by volume) of water and 229.3 ml (80% by volume) of methanol. The experiment was made using the same procedures as mentioned in Experiment 1. The volume of nitrogen gas collected after three hours was as follows: 585 ml at 749 mm, 21.5°, 520 ml dry at STP, 97%. The product was isolated and identified as indicated in Experiment 5. The yield of (-)-3-methylhexane was 1.263 g (44%): $n_D^{25} 1.3860$, $[\alpha]_D^{25} -0.035^\circ$ (1, 1 dm; $d^{25} 0.682$; neat), est 0.72% inversion.

Experiment 10. Base decomposition of (-)-2-acetoxy-2-t-heptylazopropane in 35% by volume of water-65% by volume of methanol at 40°

This experiment was carried out according to the procedures as indicated in Experiment 1 and Experiment 5, starting with (-)-2-acetoxy-2-t-heptylazopropane (0.022 mol, 5.012 g, $[\alpha]_D^{25} -0.17^\circ$) and potassium hydroxide (0.250 g f wt, 13.994 g) dissolved in 525 ml of water and 975 ml of methanol. The volume of nitrogen gas collected after two hours was as follows: 550 ml at 743 mm, 22.8°, 482 ml dry at STP, 98%. The reaction was completed and yielded optically active 3-methylhexane: 0.868 g, 31%,

n_D^{25} 1.3882, $[\alpha]_D^{25}$ -0.044° (1, 1 dm; d^{25} 0.682; neat), est 0.90% inversion.

The lower yield of this reaction may be due to additional losses incurred in the work up operation with the larger volume of reaction mixture.

Experiment 11. Decomposition of racemic 2-acetoxy-2-t-heptylazobutane in water at 100° in the absence of base

Racemic 2-acetoxy-2-t-heptylazobutane (0.003 mol, 0.723 g) was added to 50 ml of water. The entire system was flushed with nitrogen gas and the reaction mixture was refluxed at 100°. The volume of nitrogen gas evolved from the reaction was collected and measured in an interval of every five minutes. A plot of the volume of nitrogen gas evolved versus reaction time appears in Figure 2*. The half time of the reaction was found to be thirty five minutes. No effort was made to isolate the 3-methylhexane.

Experiment 12. Decomposition of racemic 2-acetoxy-2-t-heptylazobutane in water at 100° in the presence of base

This reaction was conducted in exactly the same way as indicated in Experiment 11 except that potassium

*The initial deviation of experimental values from the extrapolated curve may be the consequence of either an induction period for the free radical process or supersaturation of nitrogen gas in the pure water reaction medium

hydroxide (0.015 g f wt, 0.841 g) was introduced to the reaction mixture. The volume of nitrogen produced versus reacting time is shown in Figure 3. The half time of the reaction was determined to be thirty-six minutes.

Table III

Base Decomposition of
 $(-)-(CH_3)_2C(OAc)-N=N-C(CH_3)(C_2H_5)(C_6H_5)$

Experiment	2	3	4
Substrate concn (mol/l)	0.078	0.080	0.060
Water (mol%)	3	3	100
Organic solvent	t-BuOH	t-BuOH	none
Base K ^o concn (m)	0.49	0.71	-
KOH	-	-	0.30
Time (hr)	1	1	4
t (°C)	30	30	30
Steric course	72% ret	68% ret	32% inv

Table IV

Base Decomposition of $(-)-(CH_3)_2C(OAc)-N=N-t-C_7H_{15}$

Experiment	6	7	8	9	10
Substrate concn (mol/l)	0.089	0.06	0.084	0.084	0.015
Water (vol%)	57×10^{-4}	100	none	20	35
Organic solvent	t-BuOH	none	CH ₃ OH	CH ₃ OH	CH ₃ OH
Base K ^O concn (m) KOH	0.71 -	- 0.3	0.84 -	- 0.84	- 0.17
Time (hr)	3	3	6	3	2
t (°C)	50	100	40	40	40
Steric course	22% ret (est)	100% rac	0.27% inv (est)	0.72% inv (est)	0.90% inv (est)

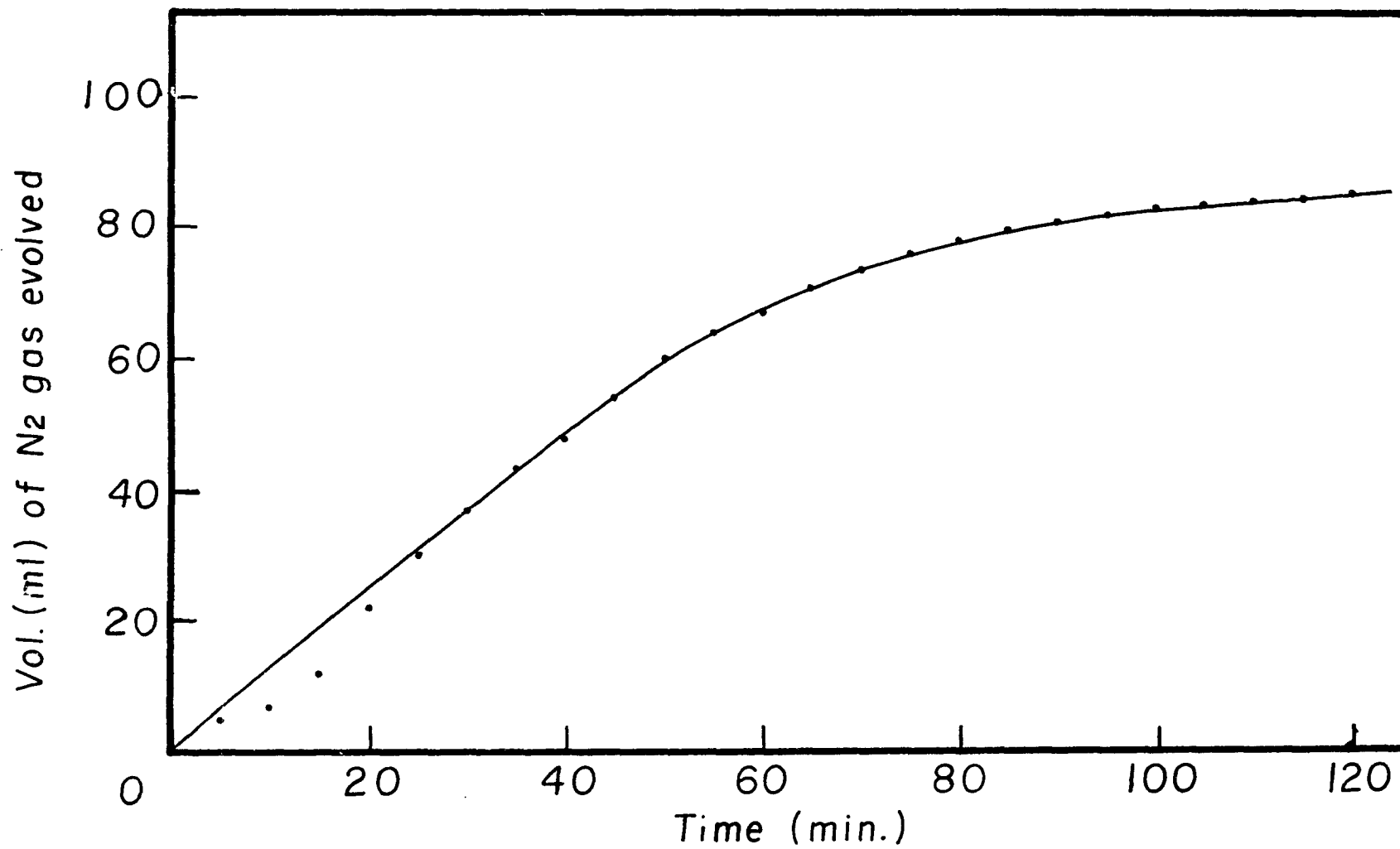


Figure 2 The volume of nitrogen gas evolved versus reaction time (Experiment 11)

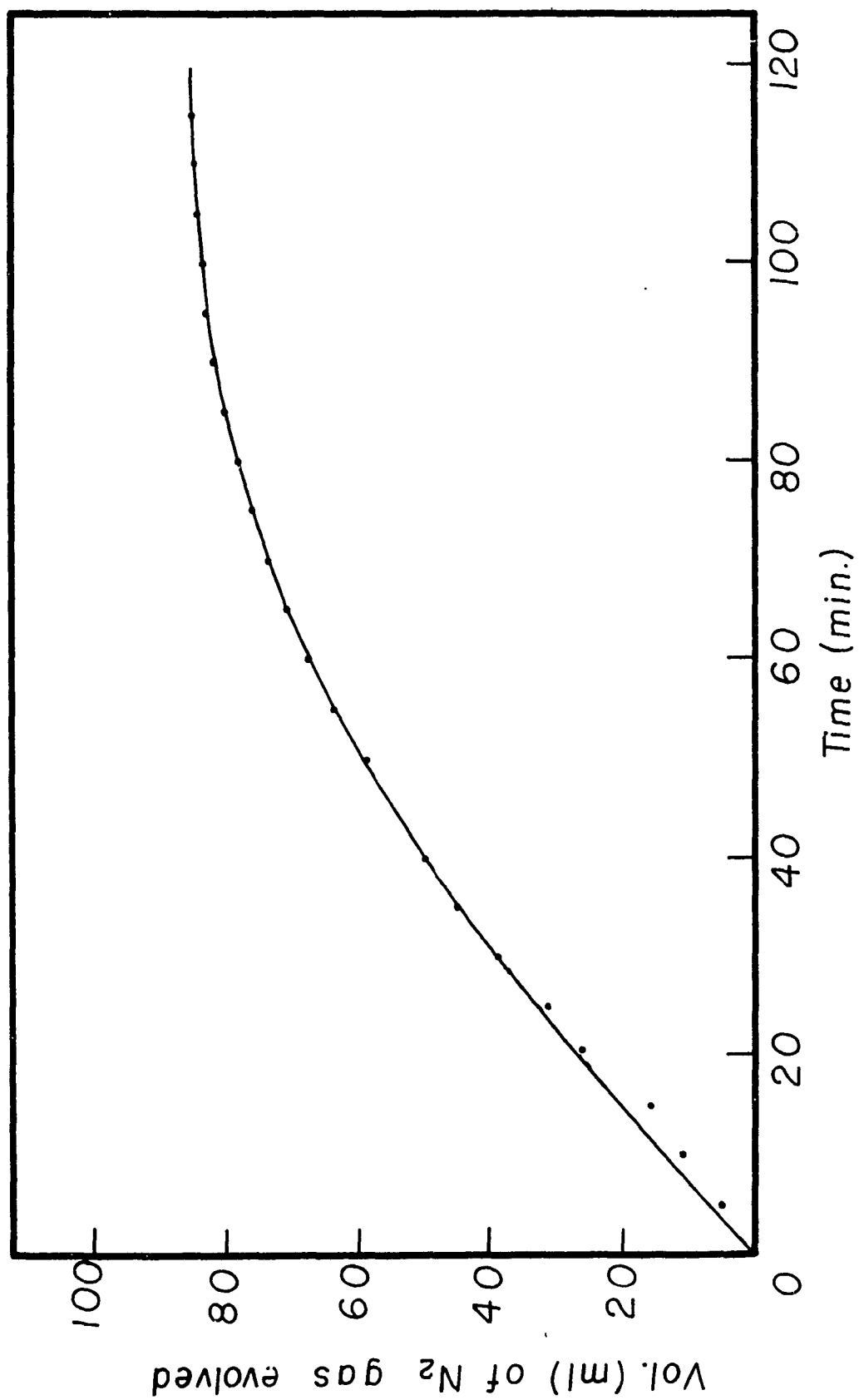


Figure 3 The volume of nitrogen gas evolved versus reaction time (Experiment 12)

RESULTS AND DISCUSSION

Preparation of (-)-2-Acetoxy-2-(2'-Phenyl-2'-Butylazo)-Propane from (+)-2-Phenyl-2-Butylhydrazine

The preparation of 2-phenyl-2-butylhydrazine followed the procedure reported by Cram and Bradshaw (16). The hydrazine was stored until used as its oxalate salt, since the free base was subject to air oxidation. Resolution of this hydrazine was accomplished by the reported manner through fractional crystallization of its (-)-dibenzoyl tartrate salt to give (+)-2-phenyl-2-butylhydrazine. This optically active hydrazine was converted to the hydrazone in high yield (80%) by reaction with acetone. The hydrazone was in turn oxidized by lead tetraacetate at 0-10° to give the (-)-2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane in about 60% yield. This optically active azoacetate was stored for extended period of time without decomposition or change in color.

Preparation of (-)-2-Acetoxy-2-t-Heptylazopropane from (-)-t-Heptylamine

(-)-2-Acetoxy-2-t-heptylazopropane was prepared from (-)-t-heptylamine by adapting the procedures described by Buu (2). This indirect route via the unsymmetrical disubstituted hydrazine was necessary as a consequence of earlier difficulties in the preparation

of t-heptylhydrazine (22). The feasibility of the sequence involving the oxidative removal of the methyl substituent was earlier demonstrated (23). This synthetic sequence does not modify the C-N bond at the t-heptyl group and retention may be concluded with assurance. The absolute configuration of active 3-methylhexane has been established (24); thus, completion of the preparation sequence providing the active azoacetate will permit assignment of absolute configuration to the amine once the stereochemical course of the azoacetate decomposition is determined. Alternately, if the absolute configuration of amine becomes known and independent demonstration of the stereochemistry of the decomposition process becomes available.

3-Methyl-3-hexanol was obtained from a Grignard reaction using ethyl magnesium bromide and 2-pentanone. Conversion of the tertiary alcohol to t-heptylamine was accomplished by adapting the procedures reported by Ritter and Kalish (25). This tert-carbinylamine was resolved by fractional crystallization of its (+)-tartrate salt. Development of the secondary amine proceeded smoothly by the formation of (+)-N-methylene-t-heptylamine followed by catalytic hydrogenation. The next reaction, a nitrosation of methyl-t-alkyl secondary amines, has been described by Heath and Mattocks (20).

The (+)-N-methyl-t-heptylhydrazine was prepared by

reaction of the corresponding N-nitroso secondary amine with zinc and acetic acid. It was found that the nature of the solvent and the temperature of the reaction play a significant role in affecting the yield of the hydrazine. It was finally discovered reduction in dilute acetic acid (50 : 50) with the reaction temperature maintained between 0-10° during the entire process gave the highest yield (65%). It was initially observed that under more vigorous condition at higher reaction temperature (25-30°) extensive N-N bond cleavage occurred to form (+)-N-methyl-t-heptylamine with a reduction in yield of the derived hydrazine (30%). Such reduction of the hydrazine has been reported in literature (26).

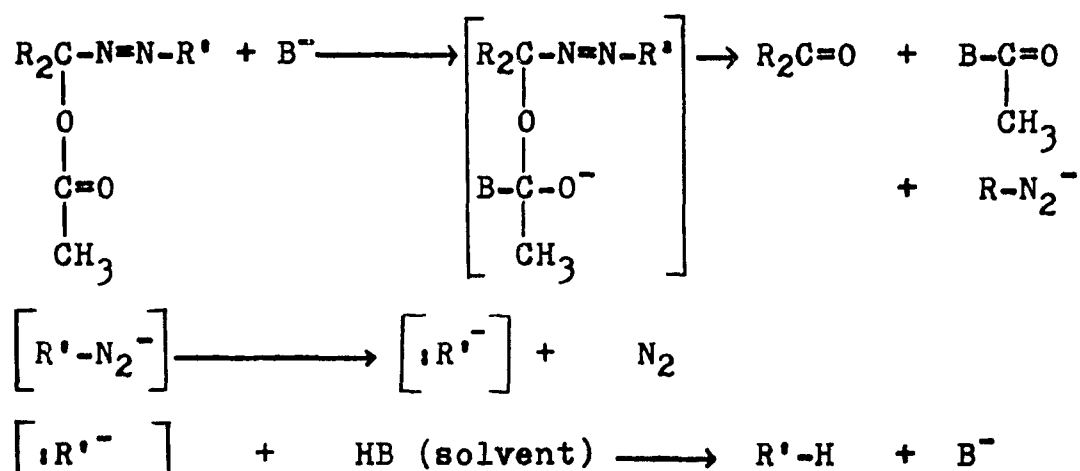
Conducting the oxidation of (+)-acetone methyl-t-heptylhydrazone with lead tetraacetate at 0-10° in the usual way led to a reaction mixture that afforded only a low yield of the azo compound (15%) and a product difficult to purify. This product invariably gave abnormally high refractive index value and rapidly developed intense violet color on exposure to air even though initially a pale yellow liquid was collected in the distillation. It was believed that the temperature of the reaction played a key role in affecting the yield and the purity of the azoacetate. Accordingly, a reaction eventually as low as -50° was completed and produced a pale yellow product in improved yield (42%). This

azoacetate product exhibited no change in color during a six months storage in a refrigerator and the refractive index was significantly lower than the value reported by Buu. Elemental analysis was in good agreement with calculated values for expected azoacetate.

Base Catalyzed Decomposition Reactions of Azoacetates

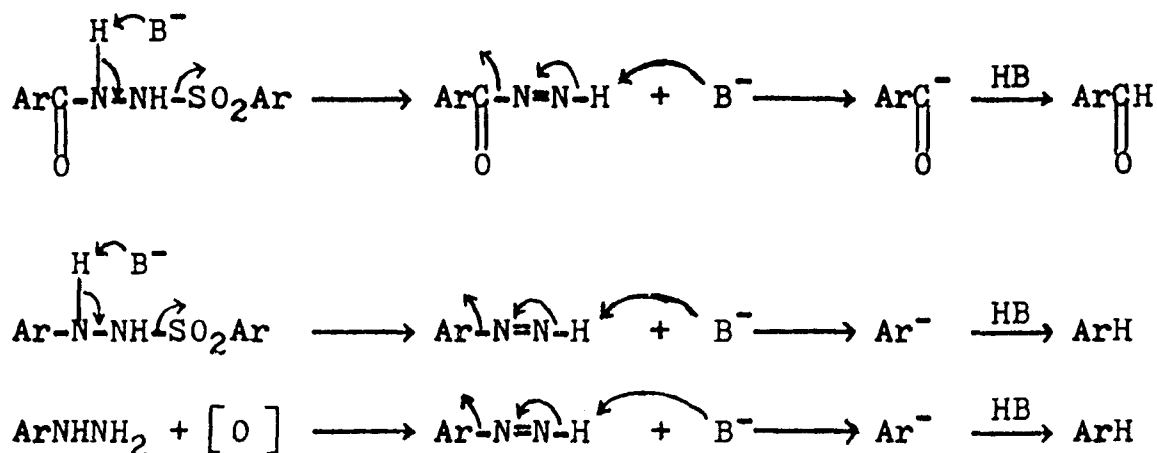
The base catalyzed decomposition of azoacetate to hydrocarbon was suggested to proceed by initial base promoted saponification of the ester to form the RN_2^- anion which spontaneously loses nitrogen to give a carbanion (2). Subsequently the anion captures a proton from the solvent to form the hydrocarbon which can be isolated. In part, this sequence is analogous to the last steps in the Wolff-Kishner reduction (16) and is summarized in Scheme I.

Scheme I



The formation of this RN_2^- anion intermediate from materials other than hydrazones has been suggested. In the McFadyen-Stevens reaction (27), an arenesulfonhydrazide is treated with base to give ultimately an aldehyde, nitrogen serving as leaving group. Also the treatment of sulfonamides of arylhydrazine with base has in some cases provided the aromatic hydrocarbon (28). An additional approach involves the oxidation of an arylhydrazine to form a hydrocarbon (29). These reactions are illustrated in Scheme II.

Scheme II



Initially racemic azoacetates, 2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane, 2-acetoxy-2-t-heptylazopropane and 2-acetoxy-2-t-heptylazobutane were shown to react with base to give 2-phenylbutane and 3-methylhexane. Because of its greater ease of preparation, racemic 2-acetoxy-2-t-heptylazobutane was used in a number of the exploratory experiments in the t-heptyl series. It was assumed that

its reactivity would be closely similar to the reactivity of propane derivative. The identity of the product was established by comparison of the retention time, ir and refractive index with those of the authentic hydrocarbons.

A total of eight base catalyzed decomposition reactions of optically active azoacetates were completed. The reaction conditions and results are collected in Tables III and IV.

Stereochemistry of 2-Phenyl-2-Butyl Anion Derived from (-)-2-Acetoxy-2-(2'-Phenyl-2'-Butylazo)-Propane

In the base catalyzed cleavages of (+)-R*-NHNHSO₂Ar in t-butanol-water mixture, the stereospecificity of the reaction was reported by Cram to vary with the concentration of water in the reaction mixture (16). The percentage of retention in the hydrocarbon product decreased as the reaction mixture became progressively richer in water and ranged from 80% retention to 5% inversion as water concentration changed from 0 to 95 mole% in the reaction mixture. In a second set of reactions, oxidative cleavage of (+)-2-phenyl-2-butylhydrazine in aqueous potassium hydroxide solution at 100° using bromine as oxidizing agent, gave as high as 33% inversion.

In the formation of (+)-2-phenylbutane from the base decomposition reaction of (-)-2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane in 3 mole% of water-97 mole% of t-butanol

at 30° (Experiments 2 and 3), the net steric course was found to average 70% retention (see Scheme III). However, as the base catalyzed decomposition reaction was carried out in water without organic solvent at 100° (Experiment 4) the steric course of the reaction was 32% inversion. This correspondence in steric course for the reactions used to form the hydrocarbon by Cram and in this study permit the conclusion that the carbanion behavior and solvent effects are largely independent of the reaction used for its formation. Furthermore, the stereochemical course of new carbanions formed from azoacetates could be reasonably concluded by analogy with the course established under the various solvent situations by Cram's experiments, i.e., decompositions of active azoacetates in solvents having a high mole percent of t-butanol will result in configuration retention.

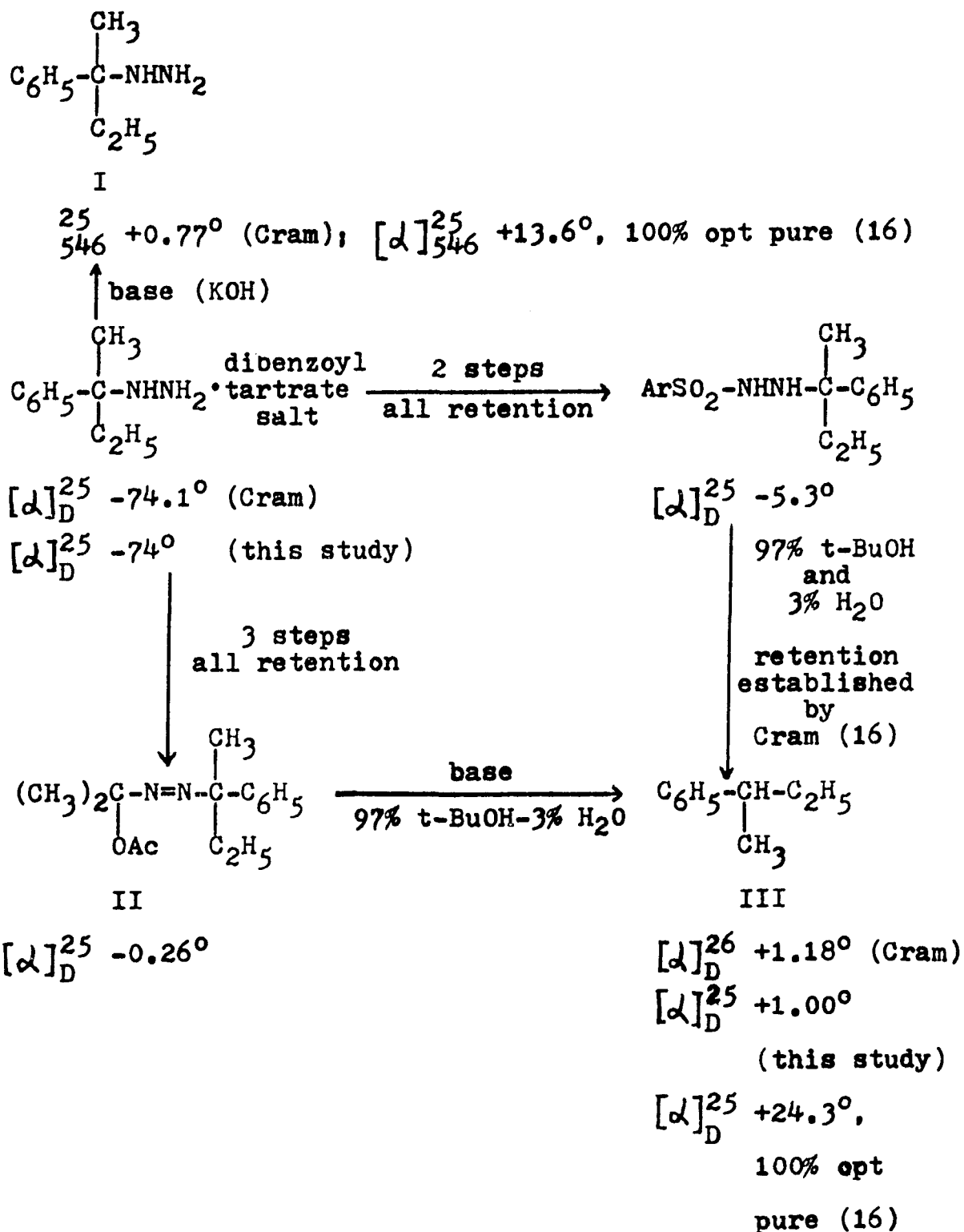
Stereochemistry of t-Heptyl Anion

The base catalyzed decomposition reaction of (-)-2-acetoxy-2-t-heptylazopropane in 97 mole% of t-butanol and 3 mole% of water at 50° produced (+)-3-methylhexane (Experiment 6). The steric course of this reaction was 22% retention.

In absolute methanol, 80% methanol-20% water and 65% methanol-35% water mixtures, the base decomposition of this optically active azoacetate gave (-)-3-methyl-

Scheme III

Stereochemical Correlation in 2-Phenyl-2-butyl Series



hexane with a stereochemical course corresponding to 0.27%, 0.72% and 0.90% inversion (Experiments 8, 9, and 10).

The values for retention or inversion in the reactions producing optically active 3-methylhexane are based on the maximum $[\alpha]_D^{25} = \pm 9.1^\circ$ reported for optically pure hydrocarbon (21) and acceptance of $[\alpha]_D^{25} = -0.12^\circ$ reported by Buu (2) as the value for optically pure t-heptylamine. This leads to a minimum value for optical purity of the (-)-2-acetoxy-2-t-heptylazopropane used in the decomposition reactions and minimum values for the steric course of the reactions.

The configurational correlation is based on the assumption of a parallel course of reaction in similar solvents to the correlation established by Cram and Bradshaw (16) and the parallel to the 2-phenyl-2-butyl series in this study.

It was first considered that the t-heptyl anion would be more reactive (less resonance stabilized) than the 2-phenyl-2-butyl anion and greater stereochemical inversion would follow. The reduced retention in 97% butanol-3% water (32% for t-heptyl series versus 70% for 2-phenyl-2-butyl series) is consistent with this expectation. However, the demonstration of high net inversions was not realized.

It is to be noted that as water concentration increased from 0% in absolute methanol to 35% in

methanol-water mixture, the percentage of inversion increased from 0.27% to 0.90%. These results show a small but uniform relationship between the steric course of the base catalyzed decomposition reaction of an azoacetate and the dielectric constant of the solvent.

In view of these observations, it was anticipated that greater inversion would result if the base decomposition reactions could be achieved in a solvent system with higher water concentration. For methanol-water system, 35% of water in the mixture is a limit beyond which a homogeneous solution can not be obtained with reasonable reaction volumes. Other organic solvent-water systems with a variety of organic solvents such as the following were examined qualitatively: dioxane, pyridine, n-butylamine, ethylene glycol, diethylene glycol, glyme, diglyme, dimethylformide, dimethylsulfoxide, hexamethylphosphoramide, acetonitrile and acetone. These combinations were abandoned as possible reaction mixtures for the decomposition reaction due to the insolubility of the azoacetate in these mixtures when appreciable water was employed (greater than 20-25%). Hence, these systems offered no apparent advantage over the methanol-water system with 35% water.

Gram and coworkers reported that the base catalyzed cleavage of (+)-R*-NHNHSO₂Ar in absolute methanol and in 95% water-5% methanol mixture gave respectively steric

courses of 40% retention and 7% inversion (16). However, the base catalyzed decomposition reaction of optically active azoacetate gave inversion even in absolute methanol as well as lower retention (greater inversion) in 97% t-butanol-3% water. The reason for this variance between results obtained in this study and those reported by Cram is not clear. It should be recognized that the carbanion included in this study is the first fully aliphatic carbanion examined. This difference in behavior may be related to difference in solvation capacity of the two type of ions.

Since the decomposition of 2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane was accomplished with 32% inversion in aqueous base (no organic solvent) at 100°, it was also expected that a similar high inversion would result with the t-heptyl derivative. Surprisingly racemic hydrocarbon was found (Experiment 7). The reaction intermediate leading to the hydrocarbon involved in the base catalyzed azoacetate decomposition process is believed to be $R^{\cdot}-N_2^{\cdot-}$. An alternate and independent free radical process which may produce the same hydrocarbon is expected to be non-stereospecific and lead to racemic hydrocarbon.

Two experiments with a racemic azoacetate were designed to compare the rate of the non-stereospecific free radical type reaction with the rate of the base catalyzed anionic reaction (Experiments 11 and 12).

It was observed that the half times for the decomposition of racemic 2-acetoxy-2-t-heptylazobutane (as indicated by volume of nitrogen collected) in water at 100° was independent of the presence or absence of base. It is concluded that under these conditions the reaction mixture is heterogeneous and the decomposition of undissolved azo compound is occurring thermally via the free radical pathway. Accordingly, the failure to obtain inversion in the decomposition of (-)-2-acetoxy-2-t-heptylazopropane may be explained by a complete lack of anionic process. Nevertheless, the great difference in relative rates of anionic and radical process for the 2-phenylbutyl and t-heptyl series (32% inversion vs 100% racemization) is surprising.

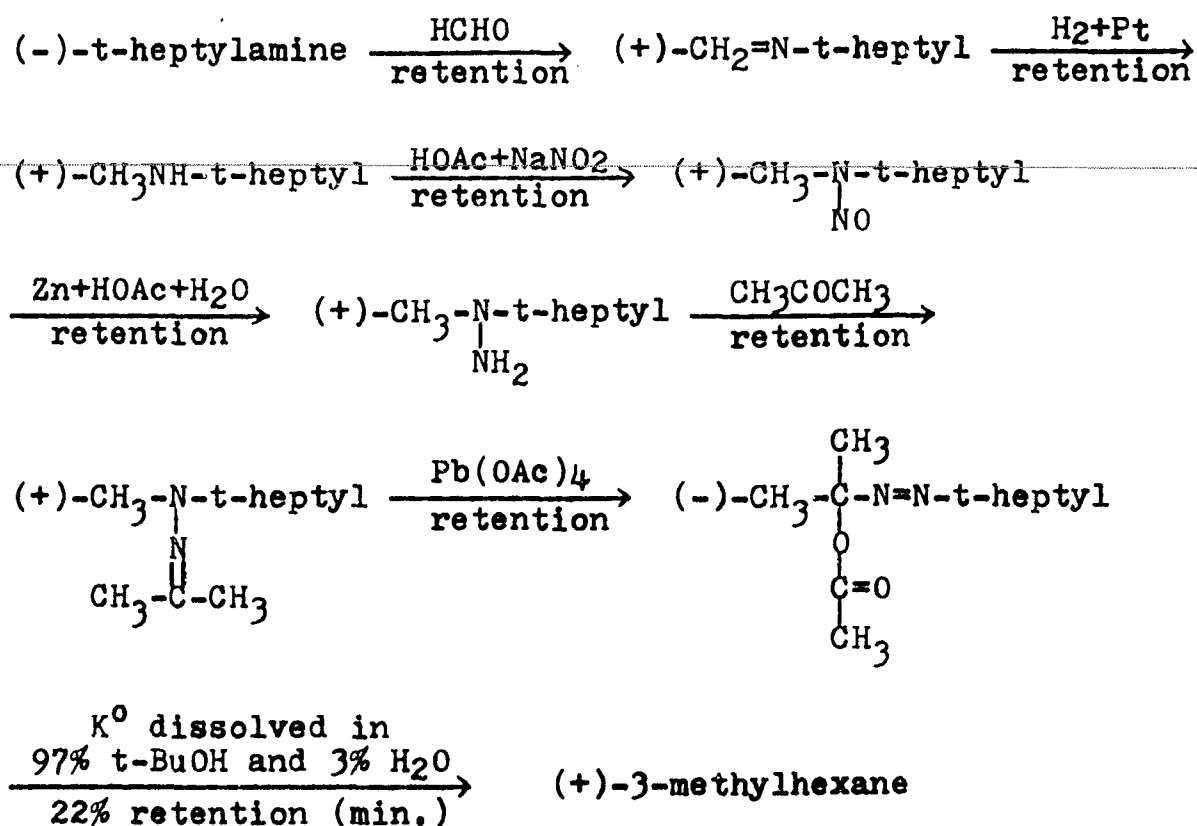
Configuration Correlation

The maximum rotation and configuration of (+)-2-phenyl-2-butylhydrazine (I) were demonstrated and established by Cram and coworkers (16). Since (-)-2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane (II) was derived from (I) via its hydrazone with retention of configuration at each reaction step, the configuration of (II) was also established by its correlation with (I).

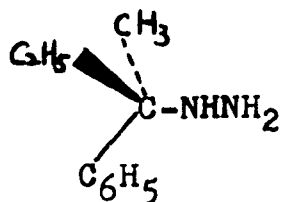
In the base catalyzed decomposition reaction of (-)-2-acetoxy-2-t-heptylazopropane (V) in 97 mole% of t-butanol and 3 mole% of water at 50°, the steric course

of the formation of (+)-3-methylhexane (IV) was established as 22% retention based on the assumption of a parallel course of this reaction in similar solvents and the correlations established by Cram and Bradshaw (16). Since the configuration of (+)-3-methylhexane (IV) has been unequivocally established (24), the configurational correlation between the azoacetate and the hydrocarbon was known and the configuration of (-)-2-acetoxy-2-t-heptylazopropane (V) was thus established. The formation of (+)-3-methylhexane (IV) starting from (-)-t-heptylamine via (-)-azoacetate (V) is outlined in the following synthetic Scheme:

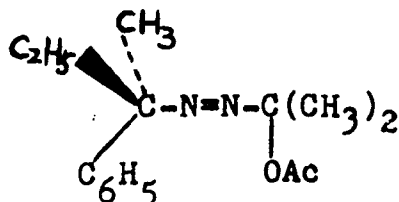
Scheme IV



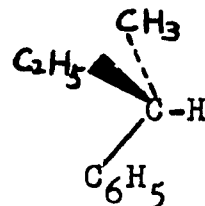
Hence, the configuration of (-)-t-heptylamine (VI) becomes established via this correlation of configurations with (+)-3-methylhexane (IV) and (-)-2-acetoxy-2-butylazo-propane (V). The diagrams below illustrate these relationship.



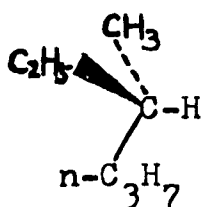
R(+)-I



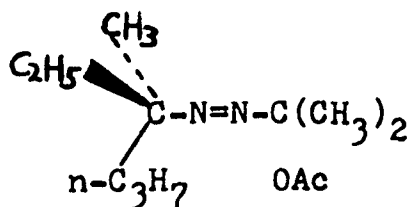
R(-)-II



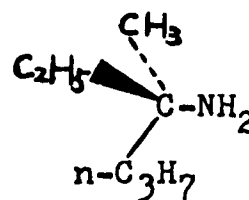
S(+)-III



S(+)-IV



R(-)-V



R(-)-VI

SUMMARY

2-Phenyl-2-butylhydrazine was prepared and resolved through fractional crystallization of its (-)-dibenzoyl tartrate salt. This optically active hydrazine was then converted to its hydrazone derivative and oxidized with lead tetraacetate to give (-)-2-acetoxy-2-(2'-phenyl-2'-butylazo)-propane. Base catalyzed decomposition of this optically active azoacetate in 97% of t-butanol and 3% of water resulted in production of (+)-2-phenylbutane with a steric course of 70% retention. On the other hand, the same substrate was decomposed in aqueous potassium hydroxide solution at 100° to give (-)-2-phenylbutane with 32% inversion. These steric courses correspond to those observed for the 2-phenyl-2-butyl anion derived from other substrates by Cram (16).

In a second series, a reaction sequence was completed which enabled the first development and study of a fully aliphatic carbanion from an optically active source. The preparation of 3-methylhexane from optically active methylethyl-n-propyl carbonylamine via an azoacetate was completed. Since all steps except the last required retention of configuration, this sequence permitted an examination of the stereochemistry of the carbanion precursor of the hydrocarbon. Four base

catalyzed decomposition reactions of (-)-2-acetoxy-2-butyl-azopropane were completed with a stereochemical course that varied between 22% retention to 0.90% inversion depending on solvent. In methanol solvent systems, significantly greater inversion was observed in the t-heptyl series than any series previously reported by Cram and a regular increase in inversion with increase in water composition of the mixed solvent was noted. In aqueous potassium hydroxide solution at 100° the decomposition of this optically active azoacetate gave racemic 3-methylhexane. This is presumably formed by non-stereospecific free radical reaction competing exclusively with the ionic decomposition because of the extremely low solubility of the azo substrate in the aqueous base.

The configuration of (-)-methylethyl-n-propyl-carbinylamine was established via the correlation of configurations with (+)-3-methylhexane and optically active azoacetate.

PART II

ANOMALOUS DECARBONYLATION OF α -SUBSTITUTED CARBOXYLIC ACIDS WITH THIONYL CHLORIDE

HISTORICAL

The conversion of carboxylic acids to acid chlorides using thionyl chloride reagent has become accepted as a first class and routine process. Nevertheless, a number of irregular examples have been reported and renewed attention to this reaction appears to be developing.

In 1901, H. Meyer described the treatment of mandelic and benzilic acids with excess thionyl chloride and reported the formation of benzaldehyde and benzophenone as abnormal reaction products (30).

Recently, M. S. Simon and coworkers suggested an abnormal reaction of thionyl chloride with 4-nitro-2,5-dimethoxyphenylacetic acid to give a sulfenyl chloride proceeded by a process which oxidized the benzylic position (31).

In a related situation, A. J. Krubsack and T. Higa reported that treatment of 3-phenylpropanoic and 2-methyl-3-phenylpropanoic acids with excess thionyl chloride led to the corresponding sulfenyl chlorides. In this case, the oxidation occurred at the α -carbon atom of the carbonyl group rather than at a benzylic position and the reaction was of a much more general and consequential nature. A mechanism for this reaction and for the further reactions of the sulfenyl chloride under these reaction conditions was suggested.

A newly described application of this thionyl chloride reaction is the preparation of acid chlorides from optically active acids, such as O-methylmandelic acid, to be used in preparation of diastereomeric amides from optically active or optically impure amines. From an examination of the nmr spectra of the amide mixture so formed, it is frequently possible to determine the ratio of diastereomers. This provides one of the simplest methods of measuring optical purity.

In this part, an anomalous decarbonylation reaction of α -methoxy, α -hydroxy and α -chlorocarboxylic acids analogous to the example first reported by Meyer are described and the possible pathways of the reactions are suggested.

EXPERIMENTAL PART

In the following experimental section all temperatures are expressed in centigrade units.

The nmr spectra were produced with a Varian A-60 spectrometer.

The infrared spectra were obtained on a Beckman IR-8 spectrophotometer with a 10 cm sodium chloride-window gas cell.

Reaction products were analysed with F and M Model 720 gas-liquid chromatograph using authentic samples as reference.

Chloromethyl methyl ether, benzophenone, acetophenone and benzaldehyde used for comparison work were purchased from Eastman Organic Chemicals, Fisher Scientific Co., and Matheson Coleman & Bell Co.

Preparation of α -Methoxyphenylacetic Acid

α -Methoxyphenylacetic acid was prepared by adapting the procedure according to Reeve and Christoffel (32).

Sodium acid salt of α -methoxyphenylacetic acid

dl-Mandelic acid (0.33 mol, 50 g) was added to a hot solution containing sodium hydroxide (4.43 mol, 177 g) dissolved in 580 ml of water. The reaction was carried out in a 2 l-beaker to accommodate the foaming which occurred during the methylation. After cooling to 45-50°, freshly distilled dimethyl sulfate (1.83 mol, 230 g) was added to the reaction mixture over a period of two hours, no significant temperature change developed. After cooling to room temperature, the precipitate which formed (mixture of normal sodium salts of mandelic and α -methoxyphenylacetic acids and inorganic salts) was filtered and dissolved in 250 ml of hot distilled water. The sodium acid salt was precipitated by adding concentrated hydrochloric acid to adjust the solution to a pH of 3. The mixture was cooled to 20° and filtered. An additional portion of product was obtained by adding 30 g of sodium chloride to the filtrate. The combined crude products were dissolved in ten times their weight of boiling distilled water, cooled to 20° and the recrystallized sodium acid salt of α -methoxyphenylacetic acid was collected and air dried: 24 g, 41%.

Conversion of sodium acid salt of α -methoxyphenylacetic acid to α -methoxyphenylacetic acid

Sodium acid salt of α -methoxyphenylacetic acid (0.065 mol, 22.8 g) was dissolved in 200 ml of hot water and 2.5 ml of concentrated hydrochloric acid was added slowly with stirring to the solution. The addition of a large excess of hydrochloric acid to the hot solution was avoided. After the solution was cooled to room temperature, an additional 7 ml of concentrated hydrochloric acid was added. The oily α -methoxyphenylacetic acid which separated was extracted with three 30 ml portions of ether. The combined ether extracts were washed with water, dried, and the solvent was removed by distillation. The residue which solidified was recrystallized from 500 ml of petroleum ether (bp 90-100°) to give α -methoxyphenylacetic acid: 19.5 g, 90%, mp 70-70.5°. Literature value (32): mp 70.5-71°.

Preparation of α -Methoxybenzyl Chloride

Preparation of benzaldehyde dimethylacetal

Benzaldehyde dimethylacetal was prepared by adapting the procedure reported by Langvad (33). A mixture of benzaldehyde (0.8 mol, 84.8 g), methanol (16 mol, 512 g) and dimethyl sulfate (1 mol, 126 g) was refluxed for half an hour and slowly added with vigorous stirring to a mixture of 500 ml 2N sodium hydroxide and 300 g of cracked ice. The acetal was extracted with three 100 ml portions of ether, dried over potassium carbonate and distilled at reduced pressure: 99.5 g, 80%, bp 81-82° at 15 mm, n_D^{25} 1.4920.

Conversion of benzaldehyde dimethylacetal to α -methoxybenzyl chloride

α -Methoxybenzyl chloride was prepared according to the procedure described by Straus and Heinze (34). Benzaldehyde dimethylacetal (0.1 mol, 15.2 g) was mixed with freshly distilled acetyl chloride (0.22 mol, 16.3 g) and 0.5 ml of thionyl chloride. The reaction mixture was warmed to 55° on a hot water bath for thirty minutes and then cooled to room temperature. After standing over night, the reaction mixture was distilled at reduced pressure to give α -methoxybenzyl chloride: 13.4 g, 85%, bp 59-61° at 0.1 mm, n_D^{25} 1.5260. Literature value (34): 71-72° at 0.1 mm.

Reactions of α -Substituted Carboxylic Acids with Excess Thionyl Chloride

These reactions were completed on a small scale sufficient to provide a gas sample for qualitative ir carbon monoxide analysis and glc analysis of liquid or solid products. A 20 ml reaction flask was attached to a reflux condenser connected to a gas train including in order the following components: a tube containing solid potassium hydroxide, a tube containing drierite, a gas collecting balloon. The collected gas was transferred to the evacuated 10 cm ir gas cell. The ir spectrum was examined for the CO stretching absorption at 2140 cm^{-1} . The reaction mixture was concentrated by distillation of the excess thionyl chloride and the residue analyzed by glc and nmr. Retention times were compared to authentic compounds. The following reagent amounts are typical of the reactions studied. Methoxyacetic acid (0.01 mol, 1 g) and excess thionyl chloride (0.06 mol, 7.14 g) was introduced into the reaction flask. The reaction mixture was refluxed for thirty minutes, cooled and allowed to stand for twenty minutes. Reaction products were demonstrated as noted above.

Reactions of O-methylmandelic acid, atrolactic acid, mandelic acid, benzilic acid and α -chlorophenylacetic acid with excess thionyl chloride were examined. In all

these reactions, carbon monoxide gas was detected and identified as one of the reaction products.

The nmr spectra of the reaction mixtures and appropriate reference compounds were obtained. The chemical shift values observed are summarized in Table V. The yields of decarbonylation products were determined from the integration ratio of isolated signals characteristic of the decarbonylation product and the expected acid chloride.

Examination of the following acids failed to produce detectable carbon monoxide: citric acid, monochloro-, dichloro-, trichloro- and trifluoroacetic acids.

A summary of the reactions is indicated in Table VI.

Table V

Summary of Nmr Spectra of Decarbonylation
Reaction Mixture and Reference Compounds

<u>Sample</u>	<u>Acid Chloride</u>	<u>Decarbonylation Product</u>
1. O-Methylmandelic acid reaction mixture	CH ₃ 3.65δ(s) - 3H - 3.76δ(s) CH 5.04δ(s) 0.60H; 6.62δ(s) 0.34H Ar 7.62δ(m) - 5H - 7.62δ(m)	
2. C ₆ H ₅ CH(OCH ₃)Cl	CH ₃ CH Ar	3.76δ(s) 3H 6.62δ(s) 1H 7.62δ(m) 5H
3. Methoxyacetic acid reaction mixture	CH ₃ 3.46δ(s) - 3H - 3.52δ(s) CH ₂ 4.36δ(s) 1.02H; 5.49δ(s) 1.04H	
4. CH ₃ OCH ₂ Cl	CH ₃ CH ₂	3.52δ(s) 3H 5.49δ(s) 2H
5. Artolactic acid reaction mixture	CH ₃ 2.13δ(s) 2.40H; 2.54δ(s) 0.60H Ar 7.45δ(m) - 5H - 7.45δ(m)	

Table V (continued)

<u>Sample</u>	<u>Acid Chloride</u>	<u>Decarbonylation Product</u>
6. $C_6H_5COCH_3$	CH_3	2.54 δ (s) 3H
	Ar	7.45 δ (m) 5H
	<u>Acid</u>	<u>Decarbonylation Product</u>
7* Mandelic acid reaction mixture	$-CO_2H$ 9.56 δ (s) 0.46H; CHO 9.96 δ (s) 0.55H	
8. C_6H_5CHO		CHO 9.96 δ (s) 1H

*The nmr spectrum was taken after hydrolysis. No benzal chloride was detected by glc before hydrolysis. The retention time determined from authentic benzal chloride was available for comparison.

Table VI

Summary of Anomalous Reactions of
 α -Substituted Acids with Thionyl Chloride

<u>Acid</u>	<u>CO Formation</u>	<u>Decarbonylation Prod. Observed</u>
1. O-Methyl- mandelic acid	2140 cm^{-1} band observed	$\text{C}_6\text{H}_5\text{CH}(\text{OCH}_3)\text{Cl}$
2. Methoxy- acetic acid	"	$\text{CH}_3\text{OCH}_2\text{Cl}$
3. Atrolactic acid	"	$\text{C}_6\text{H}_5\text{COCH}_3$
4. Mandelic acid	"	$\text{C}_6\text{H}_5\text{CHO}$
5. Benzilic acid	"	$\text{C}_6\text{H}_5\text{COC}_6\text{H}_5$
6. α -Chlorophenyl- acetic acid	"	$\text{C}_6\text{H}_5\text{CHO}$

Table VI (continued)

<u>Analysis Method</u>			
<u>Yield(%)</u>	<u>Glc</u>	<u>Nmr</u>	
1. 36	-	Comparison with authentic $C_6H_5(OCH_3)Cl$	
2. 50	-	Comparison with authentic CH_3OCH_2Cl	
3. 20	Comparison of retention time	Comparison with authentic $C_6H_5COCH_3$	
4. 54.5	"	Comparison with authentic C_6H_5CHO	
5. 73.	"	Comparison with authentic $C_6H_5COC_6H_5$	
6. trace	"	-	

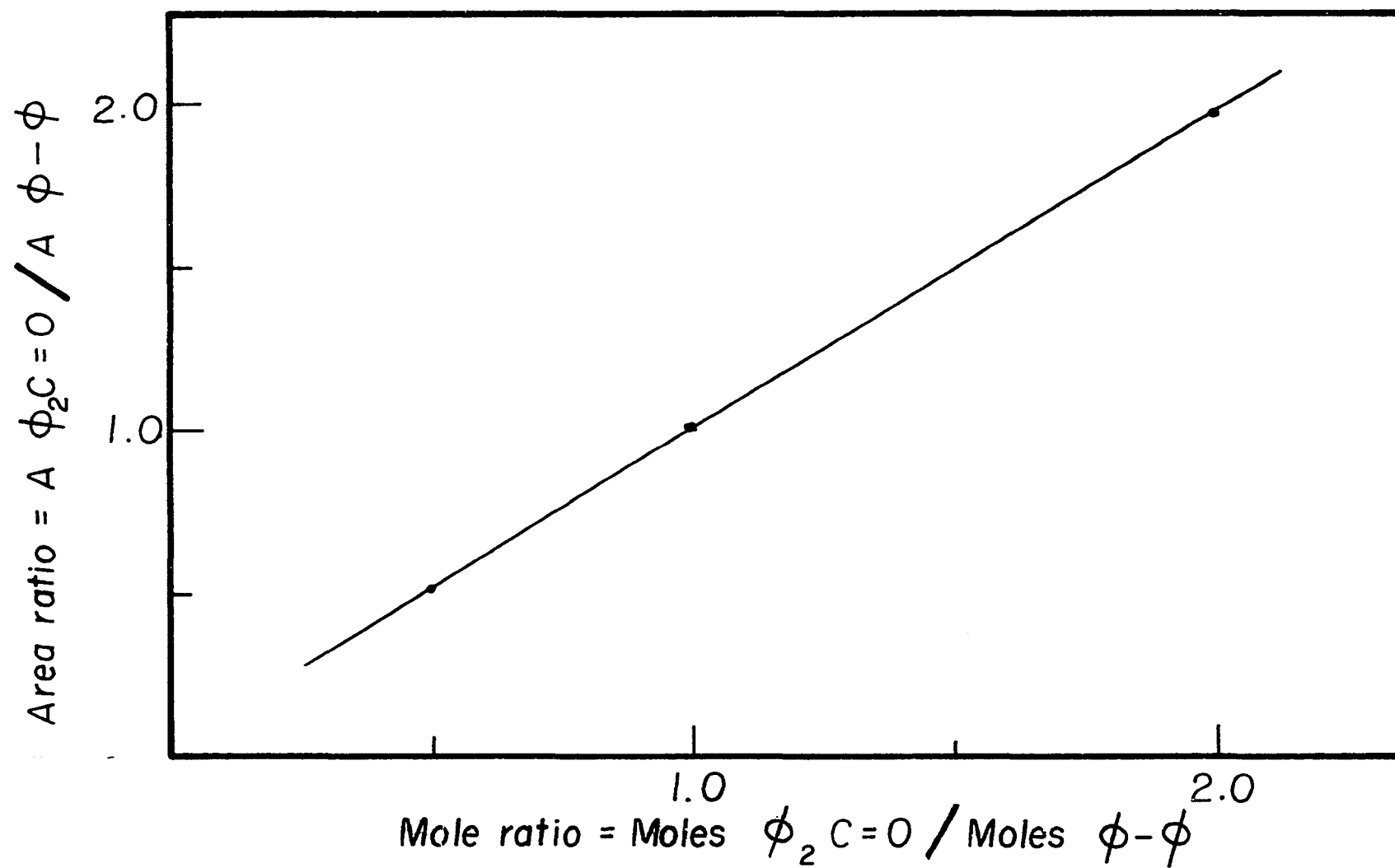


Figure 4 Analytical work curve for determination of benzophenone

A Comparison of Relative Reactivity of Benzhydrol
and Diphenylacetic Acid with Thionyl Chloride

A solution was prepared by dissolving benzhydrol (0.01 mol, 1.84 g) and diphenylacetic acid (0.01 mol, 2.12 g) in 8 ml of chloroform. Thionyl chloride (0.01 mol, 1.19 g) was added and the mixture was refluxed for thirty minutes, cooled to room temperature and concentrated under reduced pressure. The nmr spectrum of the residue (in CDCl_3 solution) was obtained and summarized in Table VII.

Composition of the mixture was measured by relative intensity of the methine proton signals. Assignment of signals was obtained using authentic benzhydrol, diphenylacetic acid. The reaction of these compounds individually with thionyl chloride gave spectral values for the reaction products: benzhydryl chloride and diphenylacetyl chloride. Nmr chemical shift values for these compounds (in CDCl_3 solution) are also included in Table VII. Many of these chemical shifts are concentration and solvent dependent (this is especially true for benzhydrol). For the competitive reaction described, the spectra exhibited signals for the benzhydryl chloride and diphenylacetic acid methine protons and of almost equal intensity. No signals assignable to benzhydrol or diphenylacetyl chloride were observed. The minimum relative reactivity of the two compounds may be estimated from the essentially

complete reaction of benzhydrol and essentially non-reaction of the diphenylacetic acid as follows:

$$\frac{\text{reactivity of benzhydrol}}{\text{reactivity of diphenylacetic acid}} = \frac{\text{amt benzhydrol reacted}}{\text{amt diphenylacetic acid reacted}}$$

$$= \frac{\text{amt benzhydryl chloride formed}}{\text{amt diphenylacetyl chloride formed}} = \frac{1H}{(1 - 0.90)H} = \frac{10}{1}$$

The possibility that diphenylacetyl chloride interacts with benzhydrol to form the alkyl chloride and regenerate the carboxylic acid was eliminated as follows: A reaction mixture was prepared by refluxing diphenylacetic acid (0.01 mol, 1.12 g) and thionyl chloride (0.03 mol, 3.57 g) for thirty minutes in 5 ml of chloroform. The solvent and unreacted thionyl chloride were removed under reduced pressure. The nmr spectrum of the residue indicated a mixture of diphenylacetic acid and diphenylacetyl chloride in the ratio of 11 to 6. Benzhydrol was added in small portions to the nmr sample until identifiable signals of benzhydrol were observed (2.0 δ and 5.68 δ). The diphenylacetyl chloride methine signal remained (5.48 δ). The sample was heated to reflux and observed after thirty minutes and after twenty hours at room temperature. The acid chloride signal was essentially unchanged during this time.

Table VII

Summary of Nmr Spectra for Competitive
Reaction Mixture and Reference Compounds

<u>Sample</u>		<u>Nmr Resonance</u>		
1. Competitive reaction mixture	$(C_6H_5)_2CHCl$	6.18 δ (s)	1H	
	$(C_6H_5)_2CHCO_2H$	5.08 δ (s)	0.9H	
2.	$(C_6H_5)_2CHCO_2H$	CH	5.16 δ (s)	
3.	$(C_6H_5)_2CHOH$	CH	5.68 δ (s)	
		OH	2.0-2.67 δ (s)	
4.	$(C_6H_5)_2CHCl$	CH	6.30 δ (s)	
5.	$(C_6H_5)_2CHCOCl$	CH	5.48 δ (s)	

RESULTS AND DISCUSSION

Thionyl chloride is widely used as a reagent to transform carboxylic acids to the corresponding acid chlorides in a simple procedure with good yields. Specifically, the application to prepare optically active O-methylmandelyl chloride has recently been suggested as a simple and convenient pathway to amides which are useful in the determination of the optical purity of the dissymmetric amines (35). This method was recommended as a suitable laboratory experiment for undergraduate students (36).

An anomalous course of the reaction or the formation of side reaction products is not commonly encountered and rarely expected. Nevertheless, instances are known in which formation of the acid chloride is not clean-cut.

In two recent papers different authors have reported the abnormal reaction of thionyl chloride with 4-nitro-2,5-dimethoxyphenylacetic acid (31) and 3-phenylpropanoic acid (37) to give sulfenyl chlorides.

A recent desire in this laboratory to measure the optical purity of t-heptylamine led to the preparation of O-methylmandelyl chloride to be used in forming diastereomeric amides. In this laboratory, treatment of excess thionyl chloride with O-methylmandelic acid gave a mixture consisting of the expected acid chloride and unexpectedly an α -chloroether, α -methoxybenzyl chloride

(36%), and a small amount of benzaldehyde. The distilled product (bp 57-68° at 0.2 mm) provided an nmr spectrum which was readily interpreted as a mixture of these compounds. For comparison purpose an authentic sample of α -methoxybenzyl chloride was prepared from benzaldehyde dimethylacetal (33) according to the procedure reported by Straus and Heinze (34).

It was believed that the formation of benzaldehyde in the reaction mixture was due to the trace hydrolysis of α -methoxybenzyl chloride. This was demonstrated by the decomposition of the authentic α -methoxybenzyl chloride in the presence of thionyl chloride to give benzaldehyde. In each case the benzaldehyde was established by comparison of its retention time with authentic benzaldehyde and the formation of a 2,4-dinitrophenylhydrazone derivative (38).

In order to establish whether this decarbonylation reaction might be more general than this one example, additional α -substituted acids were reacted with excess thionyl chloride. An examination of the reaction products for carbon monoxide and decarbonylation products was made. Methoxyacetic acid produced carbon monoxide and a product mixture containing 50% of the decarbonylation product, α -chloromethyl ether. The following acids also produced carbon monoxide and a related aldehyde or ketone: mandelic acid, atrolactic acid, benzilic acid and α -chlorophenyl-

acetic acid. Of these compounds, only benzilic acid and mandelic acid have been reported to form decarbonylation products in unspecified yields (30). The production of carbon monoxide has not been established previously in any example. A 73% yield of benzophenone from benzilic acid was measured by quantitative glc using biphenyl as an internal standard.

The following acids failed to produce a detectable amount of carbon monoxide and the reaction mixtures were not further examined for anomalous products: citric acid, chloro-, dichloro-, trichloroacetic acids and trifluoroacetic acid.

The formation of aldehydes and ketones from the α -hydroxy acids and α -chlorophenylacetic acid was unexpected following the experience with the α -methoxy acids which gave chloro-decarbonylation products. Gem-dichloro compounds were expected; however, careful examination of the reaction mixture for such compound was in vain. It is noteworthy that the carbonyl compounds were observed in the original anhydrous reaction mixture and not compounds formed following a hydrolysis step. It might be reasoned that the carbonyl compound would form by decomposition of a gem-chlorohydroxy decarbonylation product provided the decarbonylation step was fast compared to replacement of the α -hydroxy group by chlorine. Thus, in order to compare these reaction rates, a

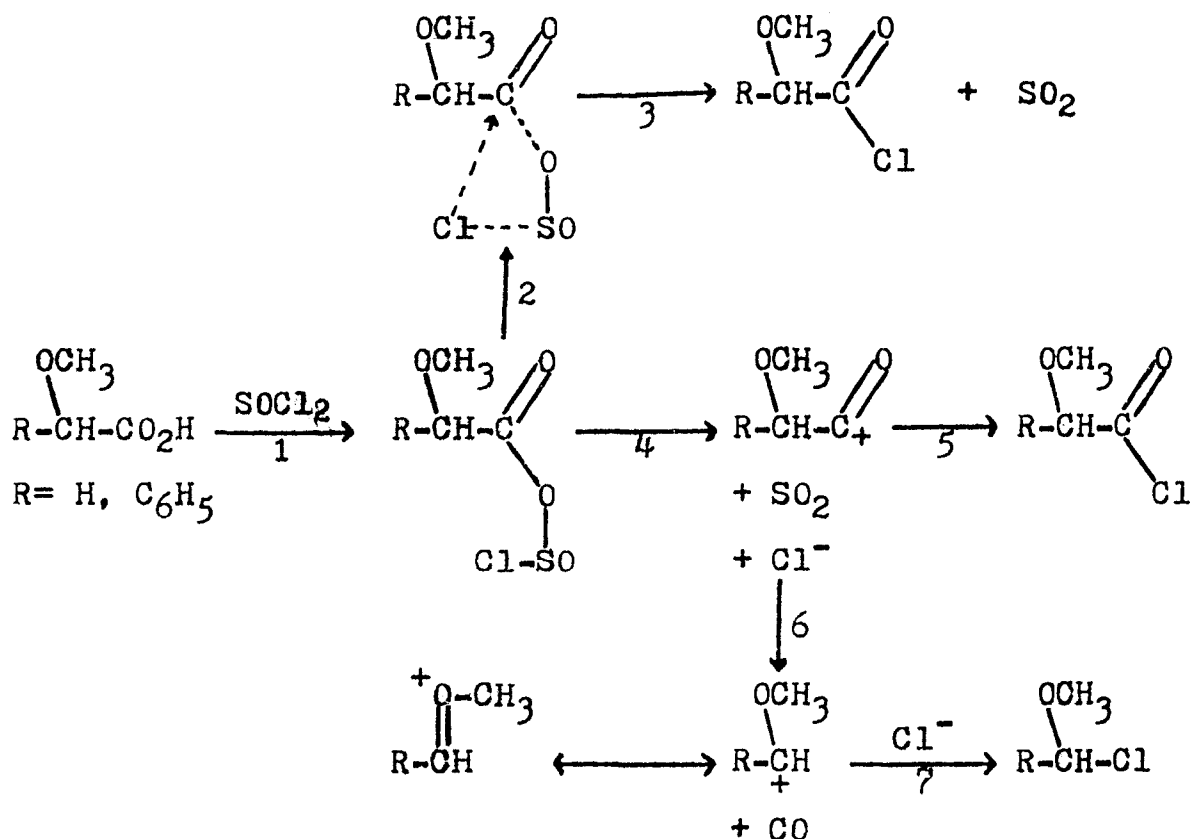
competitive reaction with equal molar amounts of diphenylacetic acid, benzhydrol and thionyl chloride was made. Examination of the nmr spectra of the reaction mixture indicated that all of the benzhydrol had reacted but not more than 10% of diphenylacetic acid had been consumed. The relative reactivity of the hydroxy and carboxylic groups taken from the reactivity of these model compounds was about 10 to 1. The possibility of an exchange reaction between benzhydrol and diphenylacetyl chloride was eliminated. Based on this reaction and decarbonylation results, the possible pathway for the formation of decarbonylation products from the α -substituted acids and excess thionyl chloride may proceed as shown in Schemes V and VI.

The formation of acid chlorides from carboxylic acids with thionyl chloride is reported (39, 40) to proceed from an initially formed mixed anhydride (Scheme V, step 1) via an S_Ni type of mechanism involving a pseudo-four atom ring transition state (Scheme V steps 2 and 3). A second but yet unproven path (Scheme V, steps 4 and 5) may be the dissociation of the mixed anhydride forming an acylium ion, sulfur dioxide and chloride ion and avoid the high energy inherent in the strained cyclic transition state. Ion recombination forms the observed acid chloride (Scheme V, step 5).

The decarbonylation reactions may be most readily explained via the carbonium ion pathway. The presence

of an α -alkoxy substituent permits the initially formed acylium ion to undergo decarbonylation to form the more stable resonance hybrid carbonium ion (Scheme V, step 6). Ion recombination at this point provides the observed product, the chloromethyl ether (Scheme V, step 7).

Scheme V

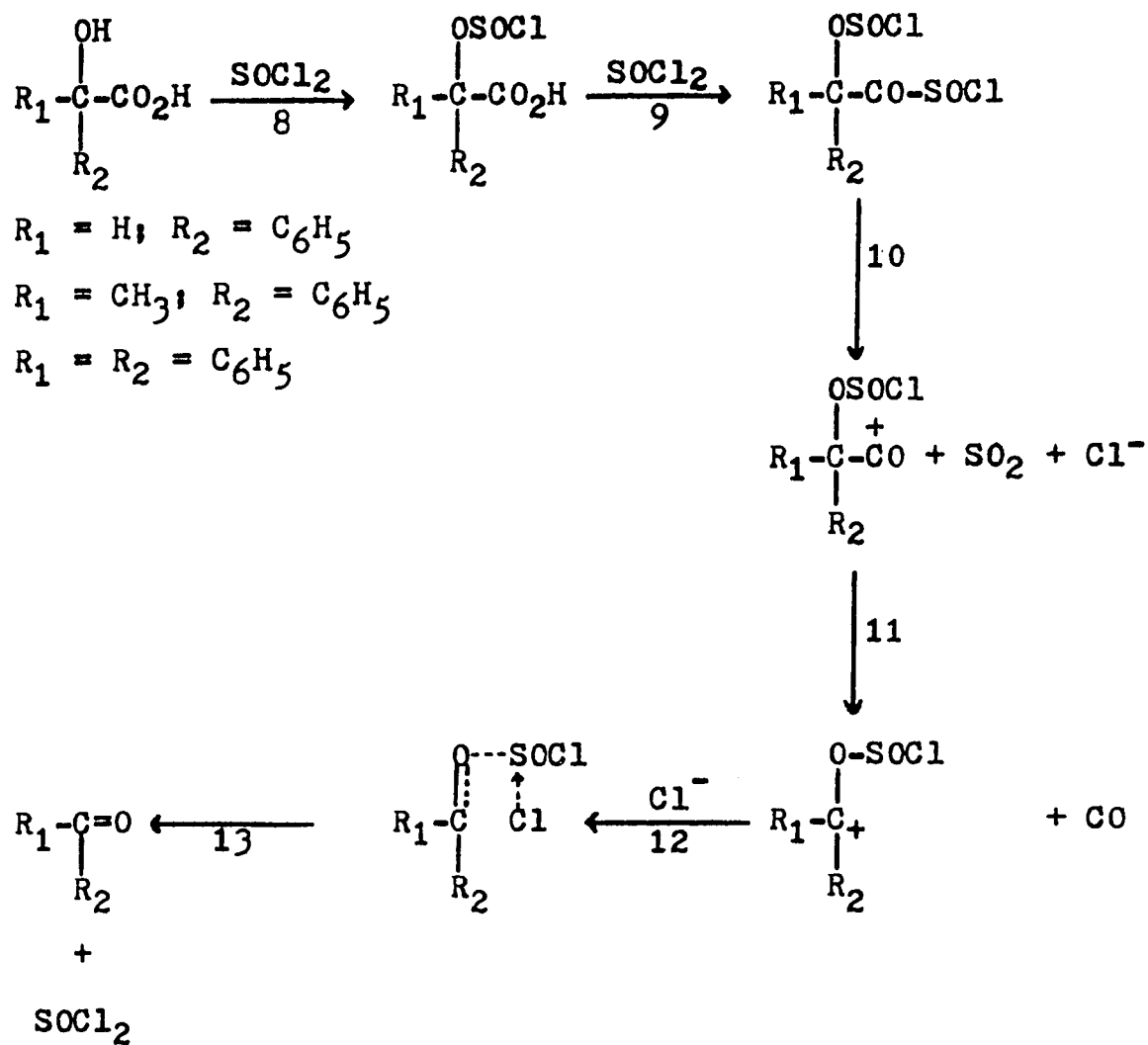


The formation of decarbonylation products from α -hydroxy substituted carboxylic acids may proceed as shown in Scheme VI. The competitive reaction experiment with benzhydrol and diphenylacetic acid requires formation of the alkyl chlorosulfite as the first step

(It can not be concluded from the competitive reaction experiment that the alkyl chloride function forms faster than the acid chloride). Reaction of this ester with excess thionyl chloride forms the mixed anhydride which may yield the acylium ion and hybrid carbonium ion (Scheme VI, steps 9, 10, 11) analogous to Scheme V. If correct, this decomposition sequence must have an over all rate comparable to the formation of the acid chloride (by either S_Ni or ion recombination at the acylium ion) and conversion of the alkyl chlorosulfite to the alkyl chloride. Finally, a chloride ion displacement at the sulfur atom will form to the observed carbonyl compounds (Scheme VI, step 13). It should be noted that ion combination with a chloride ion bonding to the carbonium ion carbon would reasonably lead to a gem-dichloro compound which was not detected. It is of interest that the structure (benzilic acid) permitting development of the most stable carbonium ion in step 11 develops the greatest observed yield of decarbonylation product.

With chlorophenylacetic acid, the required carbonium ion developed in decarbonylation would be less stable than that for the methoxy derivative. Consistently the yield of anomalous product (benzal chloride) is reduced and the trace amount formed is most likely hydrolyzed to benzaldehyde which was detected. Likewise, with those acids which failed to form detectable amounts of carbon monoxide

Scheme VI



(citric acid, chloroacetic acid, etc.) non-stabilized carbonium ions would be required. In these cases the principle reaction is the simple conversion of the carboxylic acid to the acid halide as shown in Scheme V (steps 1 through 3 or 1 through 5).

The simplicity of this explanation for the formation of the anomalous decarbonylation products via acylium and carbonium ion intermediates lends support to the postulate that the reaction of all carboxylic acids with thionyl chloride may produce acid chlorides via an acylium ion intermediate. Thus, this simple reaction deserves re-examination to evaluate this proposal.

SUMMARY

Anomalous reactions of thionyl chloride with certain α -substituted carboxylic acids are demonstrated. The decarbonylation reactions of O-methylmandelic acid, atrolatic acid, methoxyacetic acid, mandelic acid, benzilic acid and α -chlorophenylacetic acid with excess thionyl chloride were completed in a closed system and the products, including gaseous, examined. In all of these reactions carbon monoxide was shown to be present and depending upon the acid's structure an aldehyde, ketone or chloroether was identified as reaction product. The greatest decarbonylation was observed with benzilic acid which formed benzophenone in 73% yield.

The formation of these unexpected products may be simply explained by an ionic mechanism involving an acylium ion which decomposes to form a resonance stabilized carbonium ion.

BIBLIOGRAPHY

1. D. C. Iffland, L. Salisbury and W. R. Schafer, J. Amer. Chem. Soc., 83, 747 (1961).
2. N. T. Buu, "M. A. Thesis", Western Michigan University, 1965.
3. A. Streitwieser, Jr., J. I. Brauman, J. H. Hammons and A. H. Pudjaatmaka, J. Amer. Chem. Soc., 87, 384 (1965).
4. H. E. Zimmerman and B. S. Thyagarajan, ibid., 82, 2505 (1960).
5. R. L. Letsinger, ibid., 72, 4842 (1950).
6. H. M. Walborsky and A. E. Young, ibid., 83, 2595 (1961).
7. A. N. Nesmeyanov, O. A. Reutov and S. S. Poddubaya, Doklady Akad. Nauk, U. S. S. R., 88, 479 (1953).
8. D. J. Cram, J. Allinger and A. Langemann, Chemistry & Industry, 919 (1955).
9. S. Winstein, T. G. Traylor and C. S. Garner, J. Amer. Chem. Soc., 77, 3741 (1955).
10. G. Wittig and U. Schoellkopf, Tetrahedron, 3, 91 (1958).
11. S. Winstein and T. G. Traylor, J. Amer. Chem. Soc., 78, 2597 (1956).
12. D. J. Cram, J. L. Mateos, F. Hauck and K. Langemann, ibid., 81, 5774 (1959).

13. D. J. Cram and W. D. Nielsen, ibid., 83, 2174 (1961).
14. D. J. Cram, C. A. Kingsbury and A. Langemann, ibid., 81, 5785 (1959).
15. D. J. Cram, C. A. Kingsbury and B. Rickborn, ibid., 83, 3688 (1961).
16. D. J. Cram and J. S. Bradshaw, ibid., 85, 1108 (1963).
17. L. J. Bellamy, "The Infrared Spectra of Complex Molecules", 2nd Ed., John Wiley and Sons, Inc., New York, 1959.
18. C. L. Butler and L. H. Cretcher, J. Amer. Chem. Soc., 55, 2605 (1933).
19. C. Losse, Ber., 87, 1279 (1954).
20. D. F. Heath and A. R. Mattocks, J. Chem. Soc., 4226 (1961).
21. G. S. Gordon, R. L. Burwell, J. Amer. Chem. Soc., 71, 2355 (1949).
22. R. A. Evans, "M. A. Thesis", Western Michigan University, 1962.
23. D. C. Iffland and E. Cerda, J. Org. Chem., 28, 2769 (1963).
24. E. L. Eliel, "Stereochemistry of Carbon Compounds", p. 101, McGraw-Hill Book Company, Inc., New York, 1962.
25. J. J. Ritter and T. Kalisch, J. Amer. Chem. Soc., 70, 4048 (1948).

26. L. F. Fieser and M. Fieser, "Advanced Organic Chemistry", p. 717, Reinhold Publishing Corporation, New York, 1961.
27. J. S. McFadyen and T. J. Stevens, J. Chem. Soc., 584 (1936).
28. R. Escales, Ber., 18, 893 (1885).
29. L. Kalb and O. Gross, ibid., 59, 727 (1926).
30. H. Meyer, Monatsh. f. Chem., 22, 792 (1901).
31. M. S. Simon, J. B. Rogers, W. Saenger and J. Z. Gougoutas, J. Amer. Chem. Soc., 89, 5838 (1967).
32. W. Reeve and I. Christoffel, ibid., 72, 1480 (1950).
33. T. Langvad, Acta Chem. Scand., 8, 336 (1954).
34. von F. Straus and H. Heinze, Ann. Chem., 493, 191 (1932).
35. J. Jacobus, M. Raban and K. Mislow, J. Org. Chem., 33, 1142 (1968).
36. J. Jacobus, M. Raban, J. Chem. Ed., 46, 351 (1969).
37. A. J. Krubsack and T. Higa, Tetrahedr. L., 49, 5149 (1968).
38. R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds", 5th Ed., John Wiley and Sons, Inc., New York, 1965.
39. P. D. Bartlett and H. F. Herbrandson, J. Amer. Chem. Soc., 74, 5971 (1952).

40. (a) E. S. Lewis and C. E. Boozer, J. Amer. Chem. Soc., 74, 308 (1952).
(b) E. S. Lewis and C. E. Boozer, ibid., 75, 3182 (1953).

VITA

The author was born in Sen-Yu, Fukien, Republic of China, on October 10th, 1935, the son of late Mr. and Mrs. Bin-chow Lin. He was married to Hui-chun Pong in April 1965. He received the Bachelor of Science degree from National Taiwan Normal University in June 1959 and earned the Master of Science degree from The University of Washington at Seattle in June 1965. He entered the Graduate School of Western Michigan University in August of 1967.