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Study of the Stereochemistry of a Carbanion Generated from an Azoacetate

Nguyen Thanh Buu

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STUDY OF THE STEREOCHEMISTRY OF A CARBANION
GENERATED FROM AN AZOACETATE

A Thesis
Presented to
The Faculty of the School of Graduate Studies
Western Michigan University

In partial fulfillment
of the requirement for
the degree of Master of Arts
in Chemistry

by
Nguyen Thanh Buu
Kalamazoo, Michigan
September 1965

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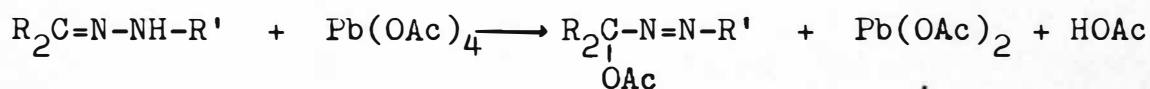
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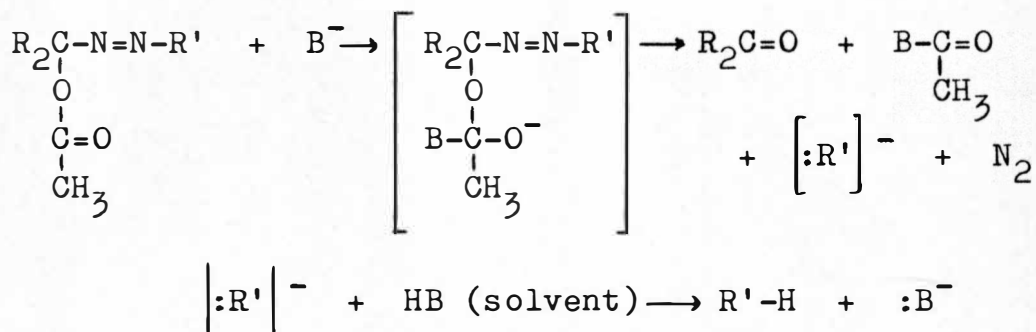
Acknowledgement is also hereby given to the National Science Foundation for financial assistance rendered for this project.

INTRODUCTION

The reaction of lead tetraacetate with ketohydrazone to form azoacetates has been reported recently by Iffland, Salisbury and Schafer (13) and may be represented by the following equation:



Of principal interest has been the base-catalyzed decomposition of an azoacetate in a protonic solvent to give a ketone, a hydrocarbon, nitrogen and an acetate salt. The following sequence of steps has been proposed to account for these products (11).



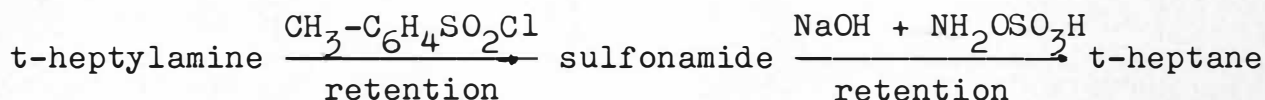
It is anticipated that if the nitrogen atom is bonded to the group R' at an asymmetric carbon atom, the stereochemistry of the carbanion may be examined. Furthermore, the asymmetric carbon atom may be developed from a

combination of simple alkyl groups; viz, methyl, ethyl, n-propyl, to afford an opportunity to study the stereochemical nature of this aliphatic carbanion. The carbanion suggested above may be properly designated as methylethyl-n-propyl-methyl carbanion. However, for convenience in the following discussion the term t-heptyl carbanion will be used.

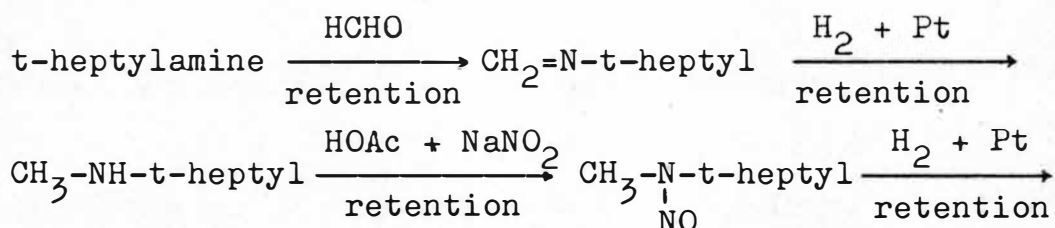
Finally, since this reaction has been achieved at low to moderate temperature (30-40°) thermal effects on the carbanion are reduced.

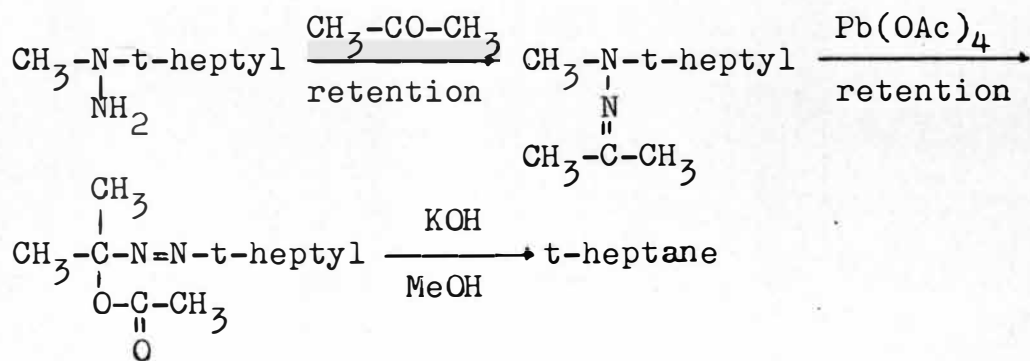
In order to examine the stereochemistry of the carbanion, if its reaction products are optically active, a configurational correlation between the azo compound and the related hydrocarbon must be known. The following synthetic sequences, starting from t-heptylamine were proposed to establish this relationship and form the methylhexane via the azoacetate:

Sequence A



Sequence B





Sequence A employs a reaction of a substituted sulfonamide with hydroxylamine-O-sulfonic acid recently described by Nickon (16). Retention of configuration was demonstrated in this reaction.

Sequence B includes the oxidative cleavage of a primary alkyl group by the action of lead tetraacetate on the N,N-disubstituted hydrazone. This indirect route to the azoacetate was necessary to circumvent failures in the preparation of the t-heptylhydrazine required for the more direct formation of acetone t-heptylhydrazone. All steps in this sequence, except the last one, do not modify the bond at the t-heptyl group. This permits the stereochemistry of the intermediate in the last step to be ascertained if optically active hydrocarbon is formed.

Ultimately the starting t-heptylamine was resolved and the synthetic sequences A and B were completed from racemic and optically active amine.

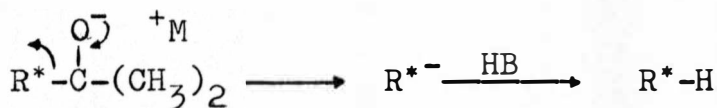
LITERATURE SURVEY

The stereochemical capabilities of carbanions, e.g., 2-phenyl-2-butyl anion, has been investigated by Cram and co-workers in recent years (4). The reactions studied involved carbon, oxygen, hydrogen and nitrogen as leaving group and proton and deuteron as electrophile. These reactions occur with as high as 99% retention, 60% inversion and 100% racemization, depending on the character of the solvent and the cations of the basic catalyst involved. Representative reactions are illustrated in the following chart:

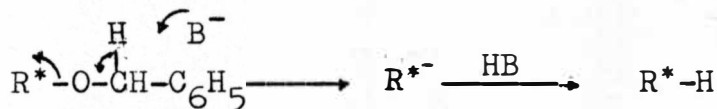
Chart I

Different leaving groups in E_1 reactions. $R^* = \text{C}_6\text{H}_5 - \overset{\text{CH}_3}{\underset{\text{C}_2\text{H}_5}{\text{C}^*}}$

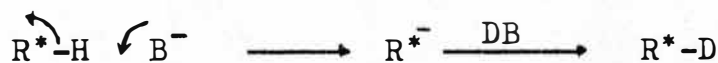
Carbon:



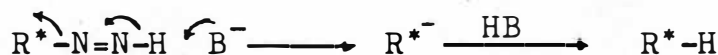
Oxygen:



Hydrogen:



Nitrogen:



In dimethyl sulfoxide, a non-protonic polar solvent in which ion development is favored, racemization is extensive. In solvents of low dielectric constants such as t-butyl alcohol, extensive retention was observed. In protonic solvents of high dielectric constants such as diethylene glycol, there is predominant inversion.

Cyclopropyl carbanions have been studied by Walborsky through decomposition of 1-methyl-2,2-diphenylcyclopropyl lithium with methanol (19). The reaction occurred with 80% retention of configuration.

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, the stereochemistry of the simple aliphatic carbanion generated from the corresponding azoacetate is of interest and its behavior will be compared with that observed by Cram and Walborsky.

EXPERIMENTAL PART

In the following experimental section all melting points and boiling points are uncorrected. All temperatures are expressed as degrees centigrade.

The ultraviolet spectra were measured with a Beckman Model DB spectrophotometer with the compounds dissolved in 95% ethanol.

The infrared spectra were obtained with a Berkin-Elmer Model 21 recording spectrophotometer and the assignment of bands was made according to Bellamy (2).

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

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

Specific rotations of compounds were measured with a Rudolph Model 62 polarimeter.

Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tennessee.

3-Methylhexane used for comparison work was purchased from Aldrich Chemical Co.

Preparation of t-Heptylamine.- A. Preparation of t-heptanol.-

This alcohol was prepared in 60-70% yield by reacting 2-pentanone with ethyl magnesium bromide, b.p. 138-142° at atmospheric pressure, n_D^{25} 1.4203. Literature values (18): b.p. 141°, n_D^{25} 1.4231.

B. Conversion of t-heptanol to t-heptylamine.- The method of Ritter and Kalish (17) was adapted for the preparation of this amine. A solution of 375 g. of sulfuric acid in 200 ml. of glacial acetic acid was added slowly, with stirring, to a solution of 172.5 g. (1.5 moles) of t-heptanol and 82.5 g. (1.5 g.f.wt.) of 90% sodium cyanide in 190 ml. of glacial acetic acid. The temperature of the reaction mixture was maintained between 40-60° by the use of an ice-water bath. The reaction mixture was allowed to stand for 2 days. A solution of 600 g. of sodium hydroxide in 800 ml. of water was then added slowly, with stirring and cooling, to the mixture. The reaction mixture was refluxed for 4 hours and then steam distilled. The distillate was made strongly alkaline with concentrated potassium hydroxide solution and the amine layer separated. The water layer was extracted 3 times with 50 ml. portions of pentane and the combined organic portions were dried over anhydrous potassium carbonate. After concentration distillation yielded 133 g. of colorless amine, b.p. 129.5-130.5°, n_D^{25} 1.4171.

Anal. Calcd. for $C_7H_{17}N$: C, 72.96; H, 14.88; N, 12.16. Found: C, 73.16; H, 14.88; N, 12.12. NMR spectra showed no tertiary hydrogen band (1.6 ppm. down field from TMS) thus indicating that this was a tertiary alkyl amine.

Resolution of t-Heptylamine.— Over a period of 1 hour, 460 g. (4.0 moles) of racemic t-heptylamine was added to a solution of 600 g. (5.2 moles) of (+)-tartaric acid in 2000 ml. of water. The mixture was heated over a steam bath for a period of 1 hour and allowed to cool to room temperature. The solution after being seeded and stored overnight in the refrigerator yielded 400 g. of white crystalline tartarate salt, m.p. 115-116°.

Anal. Calcd. for $C_{11}H_{23}O_6N$: C, 49.80; H, 8.74; N, 5.28. Found: C, 49.73; H, 8.65.

t-Heptylamine was extracted from the corresponding t-heptylamine-(+)-tartaric acid salt by the following typical procedure:

The tartarate salt (172 g., 0.65 mole) was dissolved in about 200 ml. of water. The solution was made alkaline with 56 g. of potassium hydroxide dissolved in 100 ml. of water. In order to avoid loss of t-heptylamine by evaporation, the potassium hydroxide solution was added slowly and the reaction flask was cooled in an ice-water bath. On standing the reaction mixture separated into

two layers. The water (lower) layer was extracted with three 20 ml. portions of pentane. The extracts were combined with the organic layer, dried over anhydrous potassium carbonate and distilled through a 31 cm. x 0.5 cm. tantalum wire spiral column. The distillation gave 72.2 g. (94% yield) of t-heptylamine.

Four successive recrystallizations of the salt were accomplished from water and the properties of the amine salt and the corresponding t-heptylamine at each stage are listed in the following table:

Table I

Properties of Active t-Heptylamine and
t-Heptylamine-(+)-tartaric Acid Salt

Crystallization Number		Weight of Salt	M.P. of Salt	Specific Rotation of Salt*	Specific Rotation of Amine**
I	Crop 1	400 g.	115-116	+15.1	-0.032
	Crop 2	250 g.	114-116	+14.5	-0.00
II	Crop 1	204 g.	123-125	+14.9	-0.041
	Crop 2	57 g.	124-126	+14.3	-0.057
III	Crop 1	104 g.	114-116	+14.2	-0.066
	Crop 2	34 g.	136-138	+15.8	-0.071
IV	Crop 1	60 g.	114-116	+14.8	-0.095
	Crop 2	5 g.	125-127		

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

** 1, 4 dm.; neat

The mother liquor from recrystallization number I (called mother liquor I) was made alkaline with potassium hydroxide-water solution. Extraction of the mixture by the usual method gave 86 g. (0.75 mole) of (+) t-heptylamine $[\alpha]_D^{25} = +0.024$ (1, 4 dm.; neat). The mother liquor II, III and IV were combined and yielded upon extraction about 20 g. of racemic t-heptylamine.

A 520 g. (4.4 moles) portion of racemic t-heptylamine was resolved following the above procedure. However, after two recrystallizations the salt yielded 144 g. of optically active t-heptylamine with the following properties: $[\alpha]_D^{25} = -0.032$, b.p. 129.5-131.5°.

Anal. Calcd. for $C_7H_{17}N$: C, 72.96; H, 14.88; N, 12.16. Found: C, 72.85; H, 14.69; N, 12.10.

This optically active amine was used as the starting material for the completion of sequence B.

Preparation of Racemic N-Methylene-t-heptylamine.— Over a period of 1 hour, 93 ml. (0.8 mole) of 40% formaldehyde solution was added with constant stirring and cooling to 92 g. (0.80 mole) of racemic t-heptylamine contained in a 1000 ml. round-bottomed flask equipped with an addition funnel, stirrer and reflux condenser. The mixture was stirred for 1 hour after the addition had been completed. On standing the reaction mixture separated into two layers. The water (lower) layer was made alkaline with potassium

hydroxide solution and extracted with three 20 ml. portions of pentane. The extracts were combined with the organic layer, dried over potassium hydroxide pellets and distilled through a tantalum wire spiral column. The distillation gave 80.4 g. (79% yield) of a clear lachrymatory liquid, b.p. 140-145°, n_D^{25} 1.4277.

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.27; H, 13.38; N, 10.88.

Preparation of (+) N-Methylene-t-heptylamine.- Optically active N-methylene-t-heptylamine was prepared according to the procedure outlined above, using 144 g. (1.25 moles) of optically active t-heptylamine, $[\alpha]_D^{25} = -0.032$ (1, 4 dm.; neat).

The reaction yielded 137.2 g. (86% yield) of the clear lachrymatory liquid, b.p. 141-145°, n_D^{25} 1.4318, $[\alpha]_D^{25} = +0.59$ (1, 2 dm.; neat).

Anal. Calcd. for $C_8H_{17}N$: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.33; H, 13.34; N, 11.10.

Preparation of Racemic N-Methyl-t-heptylamine.- Using a Parr low pressure hydrogenation apparatus, a solution of 76.5 g. (0.6 mole) of racemic N-methylene-t-heptylamine dissolved in 100 ml. of methanol was reduced with the

* The preparation of all active derivatives has been duplicated starting with the amine having $[\alpha] = -0.059$. For specific rotation of derivatives prepared from this amine see Table II.

aid of 0.05 g. of PtO_2 . After removing the solvent by distillation, 64.5 g. (84% yield) of secondary amine was collected as a clear liquid having the following properties: b.p. $140-155^\circ$, n_D^{25} 1.4243.

Preparation of (+) N-Methyl-t-heptylamine.- The above hydrogenation of N-methylene-t-heptylamine was duplicated starting with 137 g. (1.1 moles) of (+) N-methylene-t-heptylamine ($[\alpha]_D^{25} = +0.59$). There was obtained 127.5 g. (92% yield) of secondary amine, b.p. $142-155^\circ$, n_D^{25} 1.4218, $[\alpha]_D^{25} = +0.16$ (1, 2 dm.; d^{25} 0.924; neat).

Anal. Calcd. for $\text{C}_{18}\text{H}_{19}\text{N}$: C, 74.34; H, 14.82; N, 10.84. Found: C, 74.54; H, 15.00; N, 10.78.

Preparation of Racemic N-Nitrosomethyl-t-heptylamine.-

The method of Heath and Mattocks (10) was adapted for the preparation of N-nitrosomethyl-t-heptylamine from racemic N-methyl-t-heptylamine, sodium nitrite and acetic acid. The product formed from 61.9 g. (0.47 mole) of N-methyl-t-heptylamine was distilled under reduced pressure and six fractions of yellow oil were collected. Fractions 3-6 totalled 50 g. (65% yield) and gave the following range of properties: b.p. $132-140^\circ$ at 30 mm., n_D^{25} 1.4541-1.4578.

Anal. Calcd. for $\text{C}_8\text{H}_{18}\text{N}_2\text{O}$: C, 60.72; H, 11.46; N, 17.71. Found: C, 60.88; H, 11.57; N, 17.86.

Preparation of (+) N-Nitrosomethyl-t-heptylamine.-

Following the method indicated above active N-nitroso-methyl-t-heptylamine was prepared from 127 g. (1.0 mole) of active N-methyl-t-heptylamine ($[\alpha]_D^{25} = +0.16$). The active nitroso compound was obtained in 66% yield based on fractions 3-6 having the following range of properties: b.p. 128-135° at 28 mm., n_D^{25} 1.4538-1.4553; $[\alpha]_D^{25} = +1.43$ (1, 2 dm.; d^{25} 0.976; neat).

Anal. Calcd. for $C_8H_{18}N_2O$: C, 60.72; H, 11.46; N, 17.17. Found: C, 60.62; H, 11.46; N, 17.91.

Preparation of Racemic Methyl-t-heptylhydrazine.- A solution of 31.6 g. (0.20 mole) of N-nitrosomethyl-t-heptylamine in 192 ml. of glacial acetic acid was reacted with 52 g. (0.85 g.at.wt.) of zinc dust added slowly in small portions. The temperature was kept below 62° by cooling. The addition time was about 1 hour. The mixture was stirred for two hours. After 3 hours standing at room temperature the mixture was poured into a solution of 500 g. of sodium hydroxide in 200 ml. of water. The temperature of the solution was kept below 30° by cooling in an ice-water bath. The mixture was extracted twice with 100 ml. portions of pentane. After drying the pentane solution over anhydrous potassium carbonate, the pentane was removed by distillation and the residue was distilled under reduced pressure. Six portions of colorless

distillate were collected. Fractions 4-6 weighed 7.7 g. (26% yield) and gave the following range of properties: b.p. 41-52° at 6 mm., n_D^{25} 1.4412-1.4461.

Preparation of (+) Methyl-t-heptylhydrazine.- The procedure employed in the reduction of racemic N-nitrosomethyl-t-heptylamine was partly modified in the preparation of the corresponding optically active hydrazine starting from 107 g. (0.72 mole) of (+) N-nitrosomethyl-t-heptylamine ($[\alpha]_D^{25} = +1.43$). Dilute acetic acid (50:50) was used as solvent and the temperature of the solution was kept below 10° during the entire process of addition. The solution was stirred for a period of 18 hours. Since no phase separation was observed after the solution was made alkaline with concentrated sodium hydroxide solution, the mixture was extracted several times with large portions of pentane. The pentane portions were combined and dried over anhydrous potassium carbonate. Pentane was removed by distillation through the tantalum wire spiral column previously described and the crude hydrazine was distilled at reduced pressure. Six fractions of a clear liquid were collected in 53% yield (52.3 g.) based on fractions 5 and 6 having the following range of properties: b.p. 59-60° at 10 mm., n_D^{25} 1.4425-1.4458, $[\alpha]_D^{25} = +0.17$ (1, 2 dm.; d^{25} 0.944; neat).

Anal. Calcd. for $C_{11}H_{24}N_2$: C, 71.44; H, 13.12; N, 15.21. Found: C, 71.44; H, 13.19; N, 15.44.

Repetition of this reduction at a higher temperature range (20-40°) resulted in 35% yield of active N-methyl-t-heptylhydrazine.

Preparation of Racemic Acetone methyl-t-heptylhydrazone.-

A mixture of 14.5 g. (0.25 mole) of methyl-t-heptylhydrazine and 200 ml. (2.7 moles) of acetone were refluxed for one hour. The reaction mixture was cooled and separated into two layers after the addition of water. The organic layer was separated and the water layer was extracted three times with 10 ml. portions of pentane. The organic layer combined with the pentane extracts were dried over anhydrous potassium carbonate. Pentane was distilled through a 30 cm. Vigreux column and the residue distilled at reduced pressure. A 56% yield (10.30 g.) was collected, b.p. 90-98° at 20 mm., n_D^{25} 1.4477-1.4482.

Anal. Calcd. for $C_{11}H_{24}N_2$: C, 71.44; H, 13.12; N, 15.21.
Found: C, 71.44; H, 13.19; N, 15.44.

Preparation of (+) Acetone methyl-t-heptylhydrazone.-

Following the procedure described above 57.1 g. (0.31 mole) of optically active acetone methyl-t-heptylhydrazone was prepared from active methyl-t-heptylhydrazine ($[\alpha]_D^{25} = +0.17$). The yield was 83%; b.p. 79-91° at 14 mm., n_D^{25} 1.4432-1.4458; $[\alpha]_D^{25} = +0.24$ (1, 2 dm.; d^{25} 0.940; neat).

Anal. Calcd. for $C_{11}H_{24}N_2$: C, 71.67; H, 13.12; N, 15.21.

Found: C, 71.55; H, 13.12; N, 15.42.

Preparation of Racemic 2-Acetoxy-2-t-heptylazopropane.-

A solution of 9.2 g. (0.05 mole) of acetone N-methyl-t-heptylhydrazone dissolved in 50 ml. of methylene chloride was added dropwise to a stirred solution of 49 g. (0.11 mole) of lead tetraacetate dissolved in 150 ml. of methylene chloride. The temperature of the reaction mixture was maintained below 10° by immersing the reaction flask in an ice-water bath. After a few milliliters of the hydrazone had been added turbidity and a dark yellow color developed. The reaction mixture was stirred for an additional 30-40 minutes before 300 ml. of water was added. The methylene chloride solution was separated, washed successively with water, saturated sodium bicarbonate solutions and then dried over anhydrous sodium sulfate. The solvent was evaporated and the violet oil was distilled under reduced pressure. Distillation gave 2.8 g. of a yellow colored liquid, b.p. $60-80^{\circ}$ at 5 mm., n_D^{25} 1.4396. The ultraviolet spectra of this liquid showed absorption maxima at 358 m μ ($\log \epsilon$ 1.31) characteristic of alkyl azoacetates.

Preparation of (+) 2-Acetoxy-2-t-heptylazopropane.-

Optically active 2-acetoxy-2-t-heptylazopropane was prepared according to the procedure outlined above, starting with

9.2 g. (0.05 mole) of (+) acetone methyl-t-heptylhydrazone ($[\alpha]_D^{25} = +0.24$). The active azoacetate compound was obtained in 20% yield based on fractions 4 and 5 having the following range of properties: b.p. 75-100° at 4 mm., n_D^{25} 1.4413-1.4425; $[\alpha]_D^{25} = +0.19$ (1, 1 dm.; d^{25} 1.00; neat).

Anal. Calcd. for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.59; N, 12.27. Found: C, 62.97; H, 10.63; N, 12.43.

Formation of 3-Methylhexane from Racemic 2-Acetoxy-2-t-heptyl-azopropane.- The decomposition of this azoacetate was conducted in a solution prepared from 20 g. of potassium hydroxide dissolved in 20 ml. of water and diluted with 100 ml. of methanol. Thirty milliliters of this solution was placed in an Erlenmeyer flask equipped with a reflux condenser, a thermometer and a magnetic stirrer. Over a period of one-half hour 1.02 g. of the azoacetate was introduced dropwise. The reaction occurred slowly as indicated by the evolution of nitrogen gas. When the azoacetate addition was complete, the flask was warmed up to about 60° on a steam bath for one hour. Ten ml. of water was added and the mixture was steam distilled. The distillate was extracted three times with 10 ml. portions of pentane. The extracts were dried over anhydrous sodium sulfate and the pentane was separated by distillation through the tantalum wire column. The presence of 3-methylhexane in the residue was demonstrated by vapor

phase chromatography in a column containing silicone rubber liquid phase. The hydrocarbon was identified by comparison with authentic 3-methylhexane previously prepared by reduction of t-heptyl chloride via the Grignard reagent. The same retention time was observed for the hydrocarbon prepared from the two sources. No effort was made to isolate the 3-methylhexane.

Decomposition of (+) Azoacetate to Hydrocarbon. The decomposition of optically active azoacetate ($[\alpha]_D^{25} = +0.19$) to hydrocarbon followed the same procedure as above. However, the temperature of the reaction mixture was kept below 32° by cooling with a cold water bath throughout the entire process. Ten ml. of water were added and the mixture was extracted five times with 10 ml. portions of pentane. The 3-methylhexane was isolated by preparation scale vapor phase chromatography.

Optimum operating characteristics for resolution of the pentane-3-methylhexane mixture were determined empirically using a 20% solution of authentic 3-methylhexane (Aldrich Chem. Co.) in pentane. It was found that a silicone column (15-20% SE-30 on firebrick) gave satisfactory resolution. The 3-methylhexane fraction was delivered to the bottom of a 15 cm. x 1 cm. condensation tube cooled by trichloroethylene - dry ice mixture. The recovery

of 3-methylhexane was about 80% when known quantities of pentane-3-methylhexane solution were injected into the chromatograph.

The pentane extracts of the azoacetate decomposition reaction mixture totalled about 20 ml. and were dried over anhydrous sodium sulfate. The 3-methylhexane was isolated using the column and conditions outlined above. One ml. portions of the solution were injected using a 3 ml. syringe. The pentane solution yielded 0.20 g. of 3-methylhexane (yield 20%). This 3-methylhexane provided a retention time, IR spectrum identical with that of the authentic hydrocarbon (Aldrich Chem. Co. # M4980). The NMR spectrum, determined after addition of a trace of carbon tetrachloride-tetramethylsilane reference solution, was also identical with that of the authentic 3-methylhexane. Although the collection of bands at high field was complex, the principal absorption appeared at -0.90 and -1.26 ppm. relative to TMS. The hydrocarbon was examined for optical activity using a solution containing 0.20 g. of hydrocarbon dissolved in carbon tetrachloride (total volume: 0.6 ml.). The observed activity was essentially zero and less than the experimental error for the observation: $\alpha = 0.00 \pm 0.05$ (1, 1 dm.).

This base catalyzed decomposition of the azoacetate was repeated using the crude active azoacetate prepared from the reaction of 9.2 g. (0.05 mole) of (+) acetone

methyl-t-heptylhydrazone ($[\alpha]_D^{25} = +0.24$) and 49 g. (0.11 mole) of lead tetraacetate. Without purification this crude azoacetate was treated with potassium hydroxide-methanol-water mixture as previously described for the purified azoacetate. The 3-methylhexane (0.2 to 0.3 g.) isolated chromatographically was somewhat colored (brown) evidently from a colored impurity having the same retention time. This impure 3-methylhexane was purified by washing with three 0.5 ml. portions of cold concentrated sulfuric acid. This purified 3-methylhexane provided an NMR spectrum identical to that of the authentic hydrocarbon. A solution containing 0.20 g. dissolved in 0.60 ml. carbon tetrachloride exhibited no optical activity ($a = 0.00 \pm 0.05$; $l, 1 \text{ dm.}$).

Preparation of Racemic t-Heptyltoluenesulfonamide.- This sulfonamide was prepared by reaction of 11.5 g. (0.1 mole) of racemic t-heptylamine with 19.1 g. (0.1 mole) p-toluenesulfonyl chloride in 100 ml. of dry pyridine. The mixture was heated over a steam bath for one hour, cooled and was acidified with concentrated hydrochloric acid. The sulfonamide was extracted with three 50 ml. portions of ether. The ether was evaporated and the residue, after recrystallization from ethanol, gave 13.5 g. (50% yield) of white crystalline sulfonamide, m.p. $83-85^\circ$.

Anal. Calcd. for $C_{14}H_{23}NO_2S$: C, 62.41; H, 8.60;

N, 5.20. Found: C, 62.47; H, 8.76; N, 5.05.

Preparation of the (-) t-Heptyltoluenesulfonamide.- Active t-heptyltoluenesulfonamide was prepared using 80.5 g. (0.7 mole) of (+) t-heptylamine ($[\alpha]_D^{25} = +0.024$) and 134 g. (0.7 mole) of p-toluenesulfonyl chloride in the manner specified above. The product after two recrystallizations in ethanol gave m.p. 85.0-86.5°, $[\alpha]_D^{25} = -1.55$ (1, 2 dm.; c, 10; ethanol).

Anal. Calcd. for $C_{14}H_{23}NO_2S$: C, 62.41; H, 8.60; N, 5.20. Found: C, 62.53; H, 8.74; N, 5.41.

Reaction of Racemic Toluenesulfonamide with Hydroxylamine-O-Sulfonic Acid.- A 1-liter three-necked flask equipped with a magnetic stirrer, a heating mantle, reflux condenser and a take-off condenser was used. Methylene chloride was placed in a distillation receiver cooled in an ice-water bath. A solution containing 10.76 g. (0.06 mole) of the sulfonamide dissolved in hot aqueous sodium hydroxide (6 g. in 80 ml. of water) was placed in the flask. About 50 ml. of ethanol was added to make the system homogeneous. The mixture was heated until the temperature reached 80-90°. Hydroxylamine-O-sulfonic acid was added in small portions through the reflux condenser which was kept stoppered except during the addition of the acid. This addition of 50 g. (0.45 mole) of hydroxylamine-O-sulfonic acid required

about 3 hours. Distillation of the reaction mixture continued for approximately 1 hour. The contents of the receiver were transferred quantitatively to a separatory funnel and were acidified with dilute hydrochloric acid. The methylene chloride layer was washed two times with water and dried over anhydrous sodium sulfate. Analysis of the methylene chloride solution by means of gas liquid chromatography using a column containing silicone rubber liquid phase indicated a component having the same retention time as that for 3-methylhexane prepared by reduction of t-heptyl chloride via the Grignard reagent. The 3-methylhexane was not isolated.

Reaction of (-) t-Heptyltoluenesulfonamide with Hydroxylamine-O-Sulfonic Acid.- Following the general procedure outlined for the racemic sulfonamide 8.1 g. (0.03 mole) of (-) t-heptyltoluenesulfonamide ($[\alpha]_D^{25} = -1.55$) was treated with 80 g. (0.71 mole) of hydroxylamine-O-sulfonic acid. The temperature of the reaction mixture was maintained at 80-90°. In this instance the distillation receiver contained p-xylene. The resulting 3-methylhexane-p-xylene solution was introduced in portions of approximately 1.2 ml. into the gas chromatograph using the silicone column (16-20% SE-30 on firebrick). There was collected by the usual procedure less than 0.10 g. of a liquid having a retention time corresponding to that of 3-methylhexane. The product

was diluted to 1.0 ml. with carbon tetrachloride for observation of optical activity. No rotation greater than experimental error could be observed (1, 1 dm.).

The reaction was repeated on three times the scale described above. The hydrocarbon product was collected in 10 ml. of pentane. Isolation of the 3-methylhexane chromatographically by the usual procedure gave 0.32 g. of product having the retention time of 3-methylhexane. The IR spectrum was largely similar with that of 3-methylhexane. However, the NMR spectrum of the liquid was very much different from that of 3-methylhexane. No proton band above -0.5 ppm. was observed. The liquid decolorized dilute potassium permanganate solution and, after quickly washing with cold concentrated sulfuric acid, yielded about 0.10 g. of a clear liquid. NMR spectrum of the purified liquid was identical with that of 3-methylhexane. Polarimeter examination as described above gave no observation of activity greater than experimental error ($\alpha = 0.00 \pm 0.05^\circ$). This reaction was repeated an additional two times with no changes in either the quality of the crude 3-methylhexane or the observation of optical activity.

DISCUSSION OF RESULTS

Synthetic sequences A and B (cf. p. 6) were developed to provide two routes from t-heptylamine to 3-methylhexane. It was anticipated that sequence A would be accomplished with stereochemical retention at each stage as indicated by the recent research of Nickon (16). This sequence, if successful, would establish the rotation signs for t-heptylamine and 3-methylhexane having the same relative configuration. Knowledge of this relationship would be necessary in order to properly interpret the stereochemical course of the last step in sequence B - if optically active 3-methylhexane would be obtained in this sequence.

Sequence B was designed to enable the indirect preparation of an optically active t-alkyl azoacetate; viz, active 2-acetoxy-2-t-heptyl azopropane. This indirect route via the unsymmetrical disubstituted hydrazine was necessary as a consequence of earlier failures to prepare t-heptylhydrazine (7). The feasibility of the sequence involving the oxidative removal of the methyl substituent was demonstrated by Cerda (12). In sequence B all reactions, except the last, do not modify the C-N bond at the t-heptyl group and retention may be concluded with assurance. Thus, completion of sequences A and B will enable an interpretation of the stereochemistry of the decomposition of the azoacetate and its reaction intermediates.

Since there was reasonable likelihood that t-heptyl amine might be resolved by means of diastereoisomeric salts formed from available optically active acids this compound provided a convenient juncture for these two synthetic routes.

The accomplishment of synthetic sequences A and B are discussed in the first part of this section. In the later sections the resolution of t-heptylamine, the stereospecificity of the reactions employed in sequences A and B and conclusions regarding the stereochemistry of the t-heptyl carbanion produced via base catalyzed decomposition of an azoacetate will be reviewed.

Preparation of 3-Methylhexane from t-Heptylamine.

The published procedures for the preparation of compounds leading to the azoacetate were adapted with little or no modification.

The t-heptyl group was developed in the usual Grignard preparation of tertiary alcohols starting from ethyl bromide and 2-pentanone. Conversion of the tertiary alcohol to the tert-carbinyl amine was accomplished in concentrated sulfuric acid with sodium cyanide according to the general synthetic procedure described by Ritter and Kalish (17). Development of the secondary amine proceeded smoothly by the formation of N-methylene-t-heptylamine followed by its catalytic hydrogenation.

Nitrosation of methyl-t-alkyl secondary amines has been described by Heath and Mattocks (10).

The methyl-t-heptylhydrazine was prepared by reduction 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. Two kinds of solvents were tried: glacial acetic acid and dilute aqueous acetic acid (50:50) acid at three temperature ranges, 40-60°, 20-40° and 5-20°. It was noted that the reduction in dilute acetic acid and at temperature below 20° gave the highest yield. It was believed that under more extreme conditions, the N-N bond may be broken to form N-methyl-t-heptylamine. Such a variation has been reported in the literature (8).

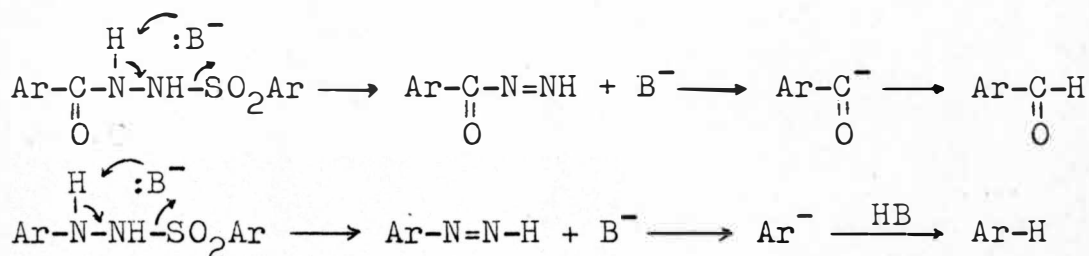
The sequence leading to azoacetate would certainly be shorter if a direct way of preparing the corresponding hydrazine could be found. Survey of the literature showed that two methods have been proposed: 1) reaction of primary amine with chloroamine reported by Audrieth (1), 2) reaction of primary amine with hydroxylamine-O-sulfonic acid described by Gever and Hayes (9). However, adaptation of the above methods to the preparation of the N-methyl-t-heptylhydrazine by Evans and Salisbury have failed to give any usable amount of hydrazine (7).

The oxidation of N,N-disubstituted ketohydrazone

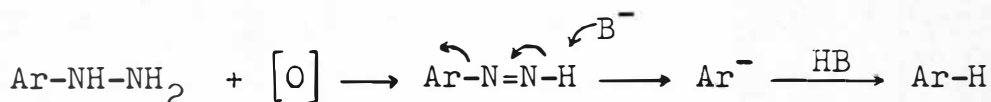
with lead tetraacetate has been analyzed in detail in a previous paper (12). The yield of the azoacetate from the corresponding acetone methyl-t-heptylhydrazone was low as compared with other yields reported particularly for the benzophenone derivative. Nevertheless, the acetone derivative was prepared in order to minimize solubility difficulties in the base catalyzed decomposition step. Since it appeared that the impure azoacetate product decomposed with evolution of nitrogen at room temperature, it was initially believed that the low yield in this reaction could be attributed to the partial decomposition of the crude azoacetate during the distillation at the relatively high temperature. However, this idea was discarded after observing that an equal amount of hydrazone, when oxidized to the corresponding azoacetate and decomposed directly to the hydrocarbon yielded approximately the same amount of hydrocarbon as when the distillation of the crude azoacetate was carried out before its decomposition. The stability of this azoacetate was finally demonstrated by the lack of decomposition of the carefully prepared sample for elemental analysis. Neither evolution of gas nor change of color was observed in a sample exposed to air 1 week at room temperature.

The decomposition of the azoacetate to hydrocarbon was believed to proceed with the loss of nitrogen from the RN_2^- to give a carbanion which subsequently captures

a proton from the solvent. This step seems to be feasible as suggested by the latter stage of the Wolff-Kishner reaction (20). The possibility of breaking into the late stage of Wolff-Kishner reduction from a starting material other than hydrazones was suggested by two analogies. In the McFadyen-Stevens reaction (15), an arenesulfonhydrazide was treated with base to give ultimately an aldehyde, nitrogen serving as a leaving group. Treatment of sulfonamides of arylhydrazine with base has in some cases provided the aromatic hydrocarbon:



Another approach was suggested by the fact that arylhydrazine can be readily oxidized to give aromatic hydrocarbon (14).



Experimentally the azoacetate was found to undergo cleavage in base to give 3-methylhexane although in low yield. The identity of the product was established by comparison of the retention time, IR and NMR spectra with that of the authentic hydrocarbon.

Sequence A involves the reductive deamination of t-heptylamine. The mechanism of this reaction, reported by Nickon, involves two steps. In the first step an aliphatic primary amine is converted to an N-alkyl substituted aromatic sulfonamide. In the second step, the sulfonamide is treated in hot alkaline solution with hydroxylamine-O-sulfonic acid acting as an aminating agent. The pathway proposed for this reaction involves the N-amination of the sulfonamide by hydroxylamine-O-sulfonic acid followed by formation of monosubstituted diimide which readily converts to hydrocarbon by loss of nitrogen. The reported yields of this process vary from a maximum of 80% to a minimum of 2%.

Adaptation of Nickon's method to the reduction of t-heptylamine to 3-methylhexane produced, however, some unexpected results. The product collected was not pure alkane in spite of the fact that the collected product had the same retention time as 3-methylhexane. The product appeared to contain olefin and hydrocarbon, as suggested by reaction with dilute potassium permanganate, by partial solution in cold concentrated sulfuric acid and principal absorption at -1.5 ppm. relative to TMS in the NMR spectrum. Following purification by treatment with cold sulfuric acid the identity of the hydrocarbon was established by comparison of the NMR and IR spectra with that of an

authentic hydrocarbon.

Resolution of t-Heptylamine.

Study of the stereochemistry of carbanion requires the completion of the synthetic sequences with optically active compounds. Accordingly the starting material, t-heptylamine, was resolved via formation of diastereoisomer salt with optically active (+)-tartaric acid. The resolution although straightforward, brought to light some interesting characteristics:

The t-heptylamine after four recrystallizations of the (+) tartrate salt showed a low specific rotation: $[\alpha]_D^{25} = -0.096$. Although it is possible that this amine was not fully resolved further crystallizations were not obtained because of the small amount of starting material remaining at this point. Nevertheless, there is reason to believe that tertiary aliphatic amines in general possess a low specific rotation. Search in the literature reveals no prior resolution of a tertiary aliphatic amine. A comparison of the specific rotations of the isoelectronic secondary carbinols and secondary alkyl amines shows that the amines have about one-half the specific rotation of the corresponding alcohol; viz, 2-butanol, $[\alpha]_D^{20} = +13.9$; 2-butylamine, $[\alpha]_D^{25} = -5.0$ (18). Davies et al (6) has reported a resolution of 3-methyl-3-hexanol with a resulting specific rotation of 0.19. If the rotational

relationship between secondary alcohols and secondary amines noted above holds in this tertiary alkyl series, it may be concluded that the t-heptylamine will have a low specific rotation and the specific rotation of the optically pure amine may be about 0.095. If this assumption is correct the optical purity of the resolved amine will approach 100%.

The melting point of t-heptylamine-(+)-tartarate salt at different stages of the resolution do not reflect the optical purity of the t-heptylamine. It was initially thought that the melting point would vary with the degree of purity. Results showed that no correlation between the melting point and the degree of purity is evident (cf. Table I, p. 13).

The specific rotation of the tartarate salts obtained in the successive recrystallizations do not indicate the optical purity of the t-heptylamine. Again, as in the case of melting point, no correlation could be drawn between the optical activity of the salt and that of the amine.

Resolution of t-heptylamine was attempted with other acids including (+)-malic, (+)-benzoyltartaric, (+)-camphor-sulfonic and (+)-camphoric acids together with a series of solvents such as water, ethanol, methanol, ethyl acetate, dioxane and chloroform. Some combinations such as (+)-camphoric acid-ethyl acetate, dibenzoyl tartaric acid-methanol gave

recrystallizable salts. However, the amine isolated in each case was inactive within experimental error. Thus, (+)-tartaric acid and water seem to be the best resolving combination for the t-heptylamine.

It was found that specific rotations of the amine derivatives increased as the hydrogen attached to the nitrogen was replaced by more polar substituents. This was illustrated by the table below:

Table II

Compounds	Specific Rotation Series 1	Specific Rotation Series 2	Ratio: <u>Series 1</u> <u>Series 2</u>
R^*-NH_2	-0.059	-0.032	1.84
$R^*-N=CH_2$	+1.08	+0.59	1.83
R^*-N-CH_3 H	+0.26	+0.16	1.63
R^*-N-CH_3 NO	+2.36	+1.43	1.65
R^*-N-CH_3 NH ₂	+0.35	+0.17	2.06
$R^*-N=N-C-CH_3$ CH ₃ CH ₃	+0.54	+0.24	2.24
$R^*-N=N-C-CH_3$ OAc CH ₃		+0.19	

The table above serves also to show that the stereo-specificity of the reactions is essentially maintained in each reaction. The ratio of the specific rotations of the products resulting from two different optically active t-heptylamines is approximately the same as that of the amines.

Configuration Correlation.

It was expected at the start of this study that a correlation of configuration could be established between t-heptylamine and 3-methylhexane through synthetic sequence A as described in the introduction. However, the reaction of sulfonamide with hydroxylamine-O-sulfonic acid did not proceed as cleanly as reported by Nickon. The very low yield of the hydrocarbon made it tedious and time-consuming to obtain sufficient product to give polarimeter readings above experimental error when 1 dm. sample tube was used. From the observations obtained, it must be concluded that the hydrocarbon is optically inactive and the configurational correlation attempted has been unsuccessful. The possibility that the hydrocarbon might be of low optical purity (i.e., largely racemic) could be clarified if a larger volume of material was available to allow the use of longer (i.e., 4 dm.) polarimeter sample tube. If the activity equalled the experimental error ($\pm 0.05^\circ$) the calculated maximum specific rotation would be $\pm 0.15^\circ$.

Since the specific rotation for the 3-methylhexane has been reported (18) as large as 9.5° the optical purity of the hydrocarbon produced in this reaction can not exceed 1.5%. Nickon reported retention of configuration with optical purity in the order of 20%. The purification of this hydrocarbon included a cold concentrated sulfuric acid wash not employed by Nickon. (Actually the hydrocarbons were not isolated by Nickon. Their identity was established from IR spectra of the reaction product dissolved in carbon tetrachloride.) Although there was concern that racemization might be caused by this sulfuric acid treatment it is believed to be insignificant. Burnwell and Gordon (3) have studied the racemization of (+) 3-methylheptane when stirred with 98% sulfuric acid. They found no racemization after 1 hour at 25° . However, racemization did slowly occur after 72 hours at 50° and the loss in rotation was about 5.0%.

Stereochemistry of t-Heptyl Carbanion.

The failure to observe optical activity in the 3-methylhexane produced from (+) 2-acetoxy-2-t-heptylazo-propane requires the conclusion that complete racemization occurred in this reaction and that the reaction intermediate (t-heptyl carbanion) at some point in the progress of the reaction became planar.

This formation of racemic hydrocarbon is at variance

with the results anticipated from the decomposition of $R^*-NH-NH-SO_2Ar$ and $R^*-NH-NH_2$ in aqueous-organic solvent combinations containing dissolved potassium hydroxide as reported by Cram (5) and coworkers. In the formation of 2-phenylbutane from the above optically active hydrazine derivatives the percent inversion or retention increased with decreasing concentration of water in the reaction mixture. Thus, with $R^*-NH-NH-SO_2Ar$ the percent inversion increased from 1% to 7% as the solvent was changed from 100% water to 95% water-5% methanol. Further, with the same substrate the percent retention increased regularly from 5% to 44% as the solvent was changed from 90% water-10% dimethylsulfoxide to 100% dimethylsulfoxide. The reaction solvent in the azoacetate decomposition was 20% water-80% methanol. 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 types of ions. In view of these observations, it was anticipated that the inversion or retention would be significant. If the optical purity of the azoacetate used in the decomposition was comparable to that of the starting material, t-heptylamine (about 30%), total retention or inversion would yield hydrocarbon having rotation

of 2.95° . A 6% retention or inversion would have provided an observation greater than polarimetric experimental error.

It should be noted that the reaction intermediate leading to the active hydrocarbon obtained by Cram is $R^*-N_2^-$, the same as believed to be involved in the azo-acetate decomposition process.

SUMMARY

A reaction sequence was designed and completed which enabled the preparation of 3-methylhexane from optically active methylethyl-n-propylcarbinyllamine via an azoacetate. 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. Optically inactive hydrocarbon was obtained indicating that the carbanion failed to maintain non-planar geometry.

From the optically active amine a second reaction sequence leading to the hydrocarbon via a sulfonamide intermediate was examined with the intent to provide an independent correlation of configuration between the amine and the hydrocarbon. Although retention of configuration had been claimed for each step in the sequence when applied to other optically active series, in this instance impure and optically inactive 3-methylhexane was formed.

The optically active methylethyl-n-propylcarbinyllamine necessary for this study was obtained by resolution of the racemic amine via the (+)-tartarate salt. This is the first resolution of a tertiary alkyl primary amine.

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VITA

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APPROVAL OF EXAMINING COMMITTEE

(Chairman)

Date
