

AN EXPERIMENTAL INVESTIGATION
OF CHLORINE'S ACTION ON PINENE
AND OPTIMIZATION FOR 2,6-DICHLOROCAMPHANE

A Thesis
Presented to
the Faculty of the Department of Chemistry
University of Houston

In Partial Fulfillment
of the Requirements for the Degree
Master of Science in Chemistry

by
Steven Robert Schmid
December 1977

To my wife, Diana

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Also, I wish to express my sincere thanks to Dr. G. Martin, for affording me the opportunity to use the Hewlett-Packard analytical gas chromatograph and digital processor, and to Ruth Inners, Steve Silber, and Paul Morrison for supplying the XL-100 nuclear magnetic resonance spectra.

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ABSTRACT

Optimization for 2,6-dichlorocamphane from continuous flow reactions of chlorine with α -pinene was accomplished using the simplex algorithm of Spendley, Hext, and Himsworth, as modified by Nelder and Mead. The yields (20-25%) obtained were 3.5 times greater than the best value previously reported in the literature. A central composite design study revealed that a second-order polynomial was not a good approximation for the response surface in carbon tetrachloride. The mole ratio of chlorine to α -pinene appeared to have some impact on determining the yield of 2,6-dichlorocamphane, especially when the ratio was less than or approximately equal to one.

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INTRODUCTION

History of Pinene and its Chlorination Products

"Pinene, the most important and widespread terpene hydrocarbon, is the major constituent of turpentine (from which the word terpene was derived), the volatile component of pine resins valued for centuries as a solvent."¹ Terpenes are those compounds which have carbon skeletons composed of two isoprene units and can be found in the essential oils, resins, and balsams of many plants. Literature concerning pinene is both diverse and voluminous. The topic for this thesis concerns the characterization and understanding of just a single reaction of pinene.

It is interesting to note that the structure (V) proposed for α -pinene in 1895 by Baeyer has withstood the test of time. Wallach, however, was the first to make systematic efforts to explain the reactions of pinene.² He reasoned that pinene contained only a single site of unsaturation, since upon treatment with hydrogen chloride, it gave predominantly monochloride product. The classical structure proof of Baeyer consisted, in part, of the oxidation of oil of turpentine with potassium permanganate to give monobasic acid product.³ Further oxidation with sodium hypobromite converted some of the product into a dibasic

acid (II) with evolution of an equivalent of bromoform. Baeyer concluded that a fraction of the original oxidation product (I) contained a $\text{CH}_3\text{CO}-$ group and that this product had been formed from structure (V), α -pinene. The other portion (III) of the product mixture could be converted into a ketone (IV) upon treatment with lead(IV)dioxide. It was later shown conclusively that structure (VI) corresponded to the other structural isomer of pinene.

This thesis will deal with the production of 2,6-dichloro-camphane from pinene. Deville⁴ and Naudin⁵ were among the earliest to investigate the chlorination of α -pinene. The product mixture proved to be too complex for characterization of each component. The primary product is thought to be pinene dichloride (VII), however, its instability even at low temperatures causes decomposition with liberation of hydrogen chloride. Aschan⁶ carried out the chlorination at -15°C , taking great care to exclude water, but still found a complex product mixture. He was able to isolate a solid bornyl dichloride (VIII), 2,6-dichlorocamphane, m.p.173-175C, along with a liquid dichloride and bornyl chloride (IX). The latter could be formed by the attack of hydrogen chloride, liberated from decomposing pinene dichloride, on α -pinene. Bornyl dichloride may be formed by direct rearrangement of pinene dichloride. Brus⁷ obtained similar results as well

as finding more highly halogenated compounds.

Bromination of α -pinene proceeds analogously, giving a mixture of bornyl bromide and bornyl dibromide, although there is a somewhat greater tendency for hydrogen bromide to be eliminated to form p-cymene (X). Kelly⁸ used the reaction of α -pinene with iodine to demonstrate the strain in the cyclobutane ring. Most olefins react sluggishly or not at all with iodine. However, when α -pinene is added rapidly to crystalline iodine, heat and a cloud of iodine vapor is evolved. Kelly postulated that the exothermicity is caused by the relief of strain in going from the bicyclo-[3.1.1]heptyl cation (XI) to the bicyclo [2.2.1]heptyl cation (XII). It is more likely that (XI) ring opens, since iodination of α -pinene gives p-cymene almost exclusively, although there is no direct experimental evidence. A practical application of this reaction is cited by James Herriot, an English veterinarian. He reported that, "... external wounds of large animals were packed with crystalline iodine and then doused with turpentine... The resulting eruption not only forced the vaporized iodine into the inaccessible extremes of the wound, but also left the farmer marveling at the wonders of veterinary science. Reactions of the patients remain unrecorded."⁹

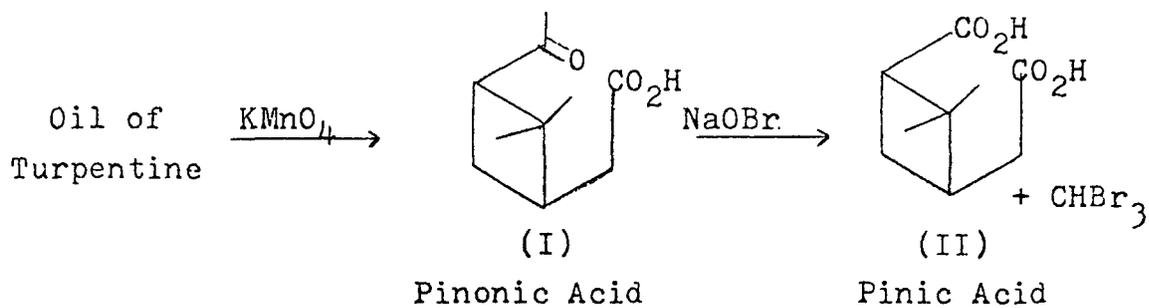
Kergomard,¹⁰ in 1953, found some halogenation (XIII),(XIV)

products of α -pinene with the pinane skeleton still intact. He also found a ring-opened dichloride (XV), along with 2,6-dichlorocamphane.

Six years later, Kwart and Null¹¹ produced 2,6-dichlorocamphane through a batch chlorination of α -pinene carried out at -10°C . Kwart and Null did not quote a percentage yield, but did report an actual yield of 80 grams 2,6-dichlorocamphane, having started with 1000 grams α -pinene.

Boriack,¹² in 1970, duplicated the reaction conditions of Kwart and Null and used the product as an intermediate in the synthesis of bornadiene (XVI). Bornadiene is a terpenoid with relatively little historical background, however, this compound is of interest for the thermal rearrangements it can undergo. Through nuclear magnetic resonance, one can monitor the course of rearrangement of deuterated bornadiene derivatives. A possible route to these derivatives of bornadiene involves conversion of deuterated pinene to the deuterated dichlorocamphane. Since the former is relatively expensive, higher yields than the six per cent achieved by Boriack would be desirable.

It is apparent that the reaction conditions chosen thus far have not been those that would produce optimum yield. It is a purpose of this thesis to first describe an effective means of achieving optimum response in a system and then to



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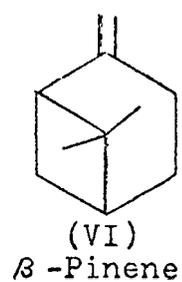
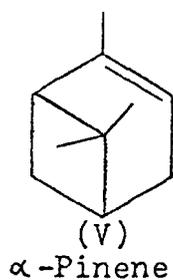
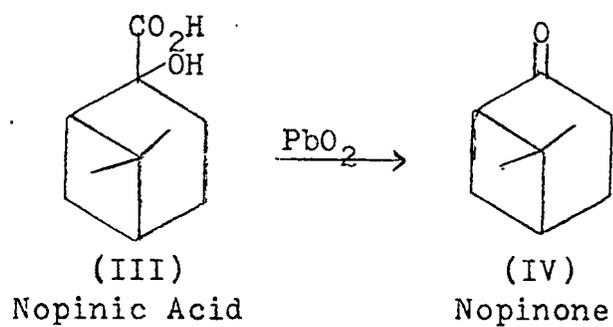
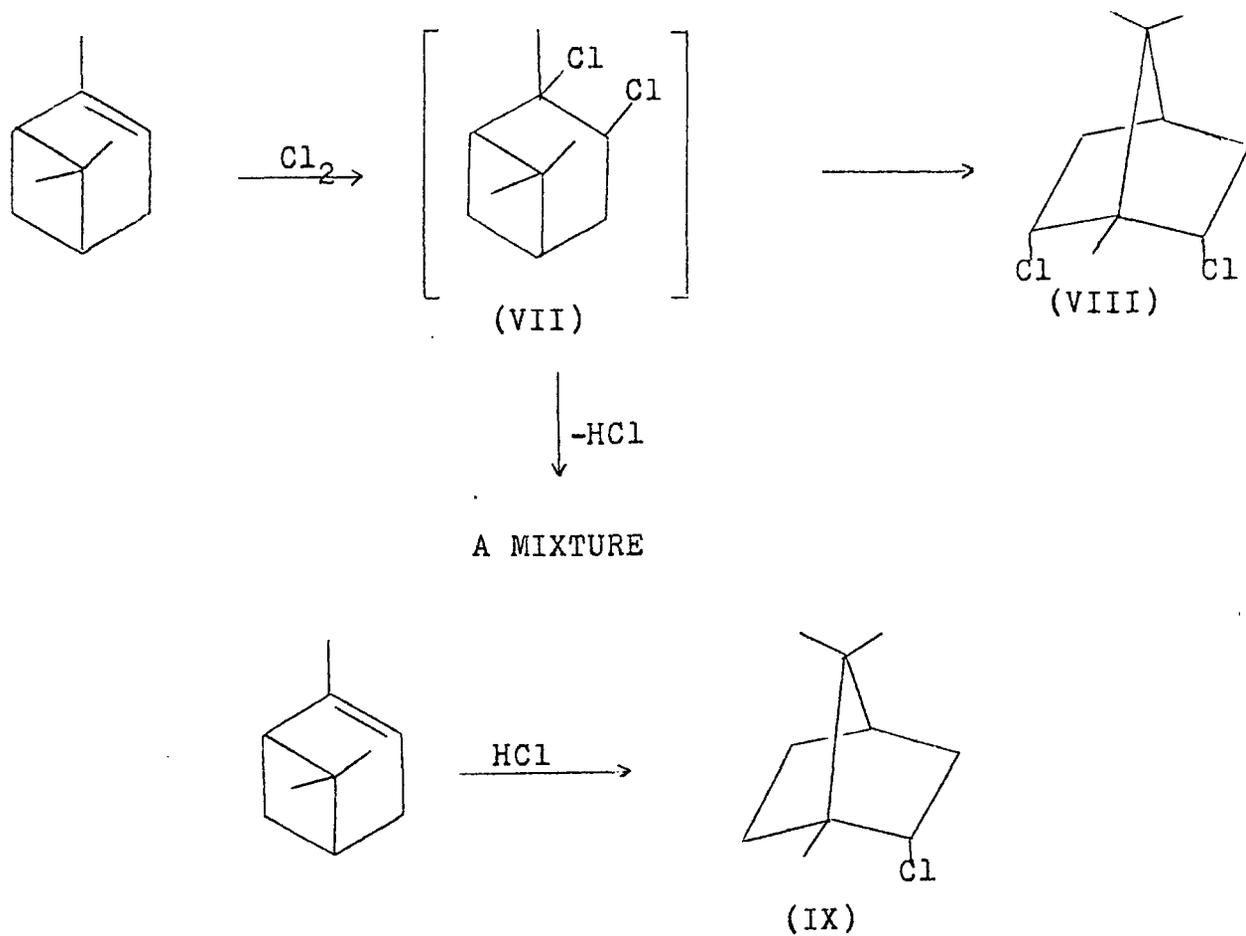


FIGURE 1: A Portion of Baeyer's Structure Proof for the Pinene Isomers and Nomenclature

FIGURE 2: Aschan's Scheme for α -Pinene Chlorination

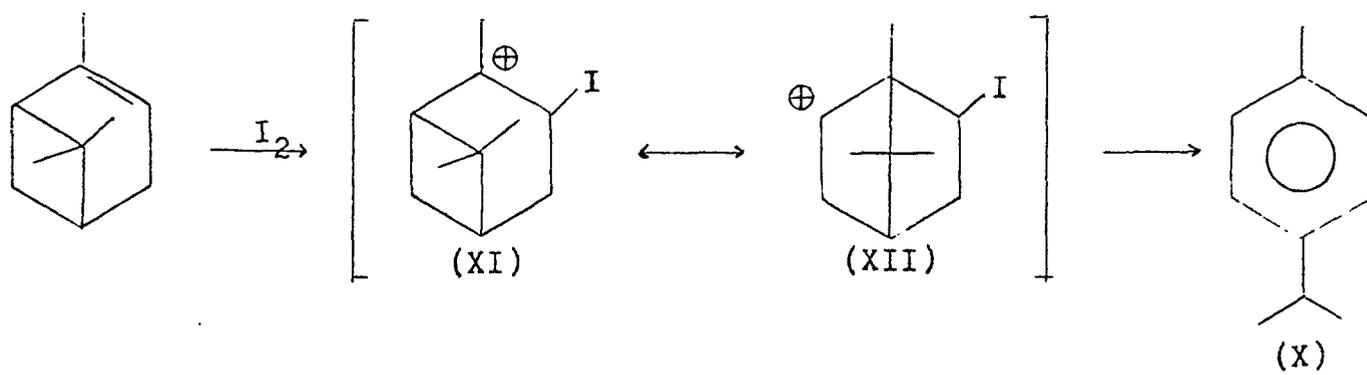


FIGURE 3: Kelly's Scheme for Iodination of α -Pinene

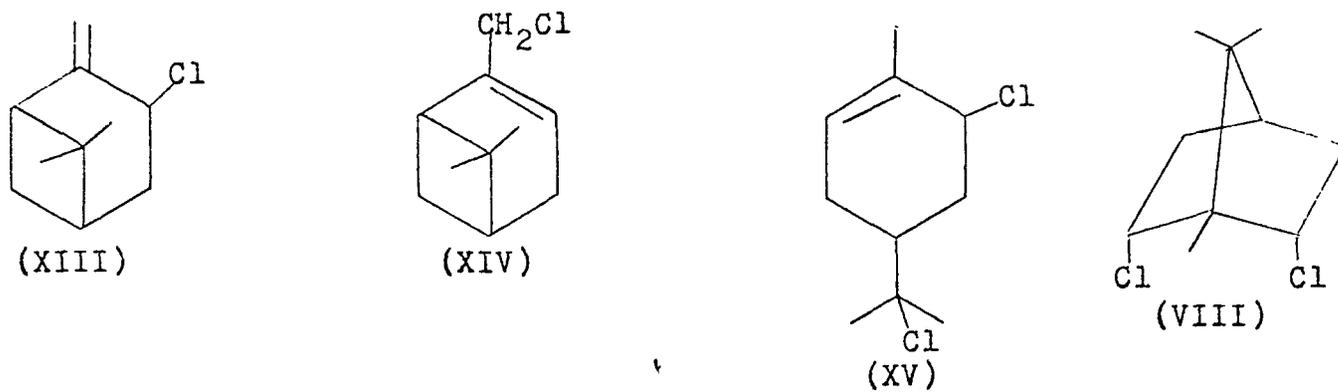


FIGURE 4: Pinene Chlorination Products
Identified by Kergomard

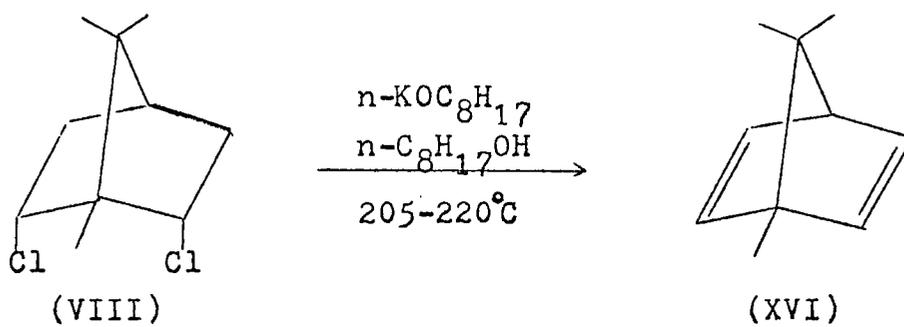


FIGURE 5: Boriack's Synthesis of Bornadiene

apply this method to the reaction of chlorine and pinene, using the yield of 2,6-dichlorocamphane as the response.

Methods Development

An optimization procedure should obtain the desired product in some yield, increase the yield, and then evaluate the effects of various experimental factors upon the yield. The classical approach to this problem would be to identify which factors are significant, uncover their functional relationship and then to find the best values for the significant factors. All too often, synthetic chemists halt their investigations into chemical reaction systems after having accomplished the first step.¹³ The importance of improving yields is most easily seen in a multistep synthesis, where the overall yield is a multiplicative function of the yields at each step. An understanding of the effects of various experimental factors on the yield enables one to specify individual tolerances necessary for reproducible results.

A quicker and more efficient approach requires the determination of the optimum yield for all factors, and then seeks to find the manner in which and to what extent they are significant. The key to this approach is an efficient optimization strategy. Attempts to optimize a system through

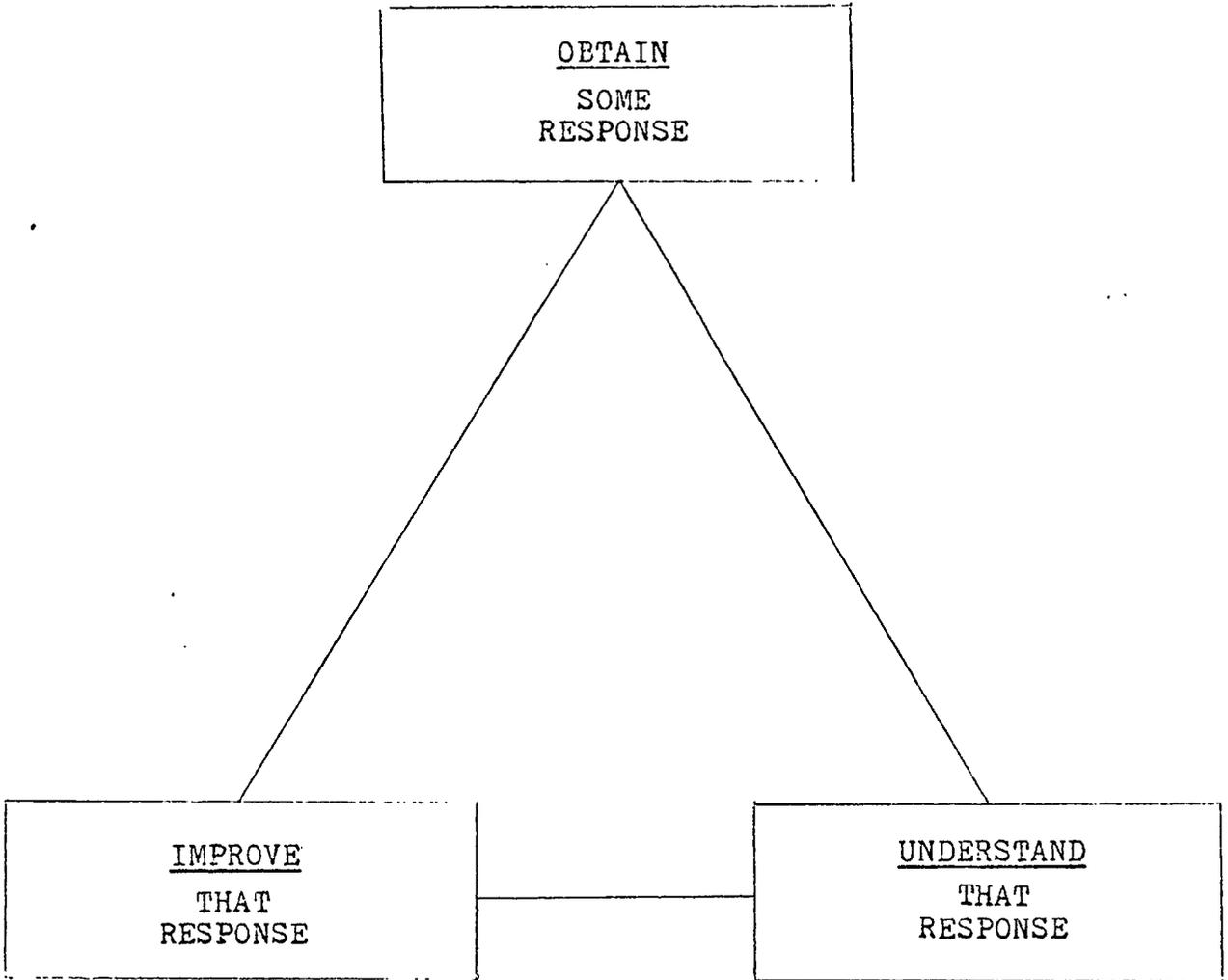


FIGURE 6: Scheme for Optimization Procedure

the customary one-factor-at-a-time method, where each factor is optimized in turn while the others are held constant, may be thwarted when applied to chemical systems having ridges in the response surface. A response surface is simply a graph of the output plotted against one or more system inputs. Ridges result from input interactions.

Experimental Designs

The sequential simplex algorithm of Spendley, Hext, and Himsworth,¹⁴ is a method which obviates this difficulty by varying more than one factor at a time. The algorithm takes a geometrical figure known as a simplex and moves it away from regions of poor response towards an optimum in the response surface.

The simplex is defined by $n+1$ points, where n stands for the number of input parameters. Thus, for a system with only one varying factor, a line segment would be employed to explore the response surface, while a triangle and tetrahedron would be used to explore the response surface for systems with two and three inputs, respectively. The variable-sized simplex of Nelder and Mead¹⁵ allows one to make expansions in favorable directions and contractions in unfavorable directions.

If k represents the number of moves the simplex makes

before it locates an optimum, then $k+n+1$ represents the total number of experiments required to be performed. The efficiency of the simplex algorithm can be seen directly from a comparison with a factorial grid search. The number of experiments required for such a search equals $k \cdot m^n$, where m represents the number of levels per factor and k and n retain their meanings from above. A system with three input parameters that requires five simplex moves to find an optimum response ($k=5, n=3$) would require $5+3+1=9$ experiments to be performed. A grid search for two factor levels would require $5 \cdot 2^3=40$ experiments, and for three factor levels would require $5 \cdot 3^3=135$ experiments! Thus, the absence of the factor level term in the simplex method eliminates many unnecessary experiments.

One may construct an initial simplex either arbitrarily or by utilizing one of the several algorithms available for this purpose. The principal concern is to avoid the placement of the $n+1$ points of the simplex in the same n -space. That is to say, the points composing a simplex for a two factor system should not be colinear, and those points composing a simplex for a three factor system should not be coplanar. Such a placement would result in a restricted movement through the factor space.

When attempting a simplex optimization in a chemical

reaction system where an unfortunate choice of factors can cause disaster, the size of the simplex should be kept relatively small. One might also consider simultaneously monitoring some warning outputs, e.g. pressure and temperature, along with the primary output.

If the simplex locates an optimum, there will usually exist some doubt as to whether the overall optimum has been located. Confidence in having found the overall optimum may be gained by starting the simplex in different regions of the factor space and always finding it converge to the same point. If different (local) optima are located, a choice can be made between them according to any number of criteria. Such criteria may include the absolute value of the desired response, the minimization of an undesired response, or the cost necessary to achieve an optimum.

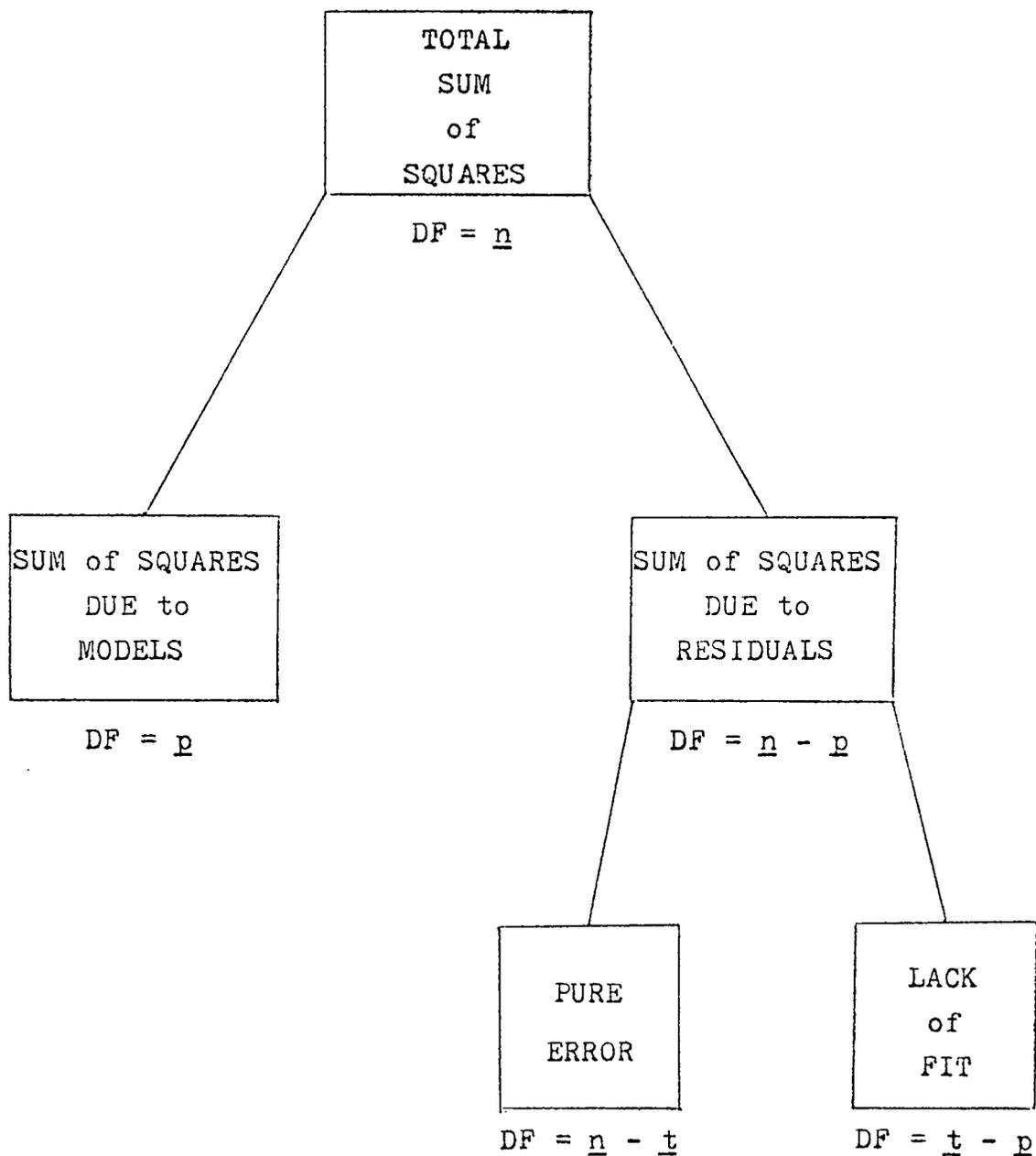
There is, however, no universal criterion which will guarantee convergence. One may set criteria based on the absolute value changes of the objective function or of the factors involved, such that the simplex is terminated when the changes are less than some predetermined limit. Alternative criteria for simplex termination include attainment of an adequate, although not optimum response, and completion of a predetermined number of function evaluations. It is possible, however, that premature termination could result

on a flat plateau or very steep slope if these criteria are strictly obeyed. This could be avoided by carrying out an experiment in a region far away from the one being investigated, or by starting the simplex in other areas of the factor space, as in the check against local optima.

That the simplex algorithm and its modifications have found applications in a wide variety of areas can be seen by reviewing the type of journals containing articles referencing its creators. Spendley, Hext, and Himsworth¹⁴ have been cited twenty-eight times in the Science Citation Index and Nelder and Mead¹⁵ ninety-three times over the past two years. One of the few studies relating simplex optimization to reaction yields was made by Dean, Heald, and Deming.¹³

It is often desirable to evaluate the behavior of the input parameters at the optimum. This can be accomplished by planning experiments to map the region of the factor space around the optimum. The experimental design might be a full factorial for two or three factors, or one of a variety of fractional factorials or composite designs for a greater number of factors. An empirical model, often a second-order polynomial, is chosen to fit the experimental data. A unique solution to the model is obtained only if the total number of treatment combinations is at least equal

to the number of parameters comprising the model. The polynomial, however, might only be a best fit through the experimental data established by the least squares method. For any experimental point along the model, one can calculate the difference between the observed response and the response that would fit the model exactly. This difference is referred to as a residual. Residuals are caused by pure experimental error and lack of fit of the model to the data. The contribution of pure error to residuals can be estimated if some experiments are replicated. As the number of replicate experiments increases, the estimation becomes better. Figures 7 and 8 detail the ways in which the total sum of squares of deviation from the model may be separated and the degrees of freedom necessary to compute them. The results of these calculations are commonly reported in an Analysis of Variance (ANOVA) table.



n = total number of experiments
 p = parameters of the model
 t = total number of experiments - number of replicates

FIGURE 7: Scheme Delineating the Degrees of Freedom
 Required for Regression and Analysis of Variance

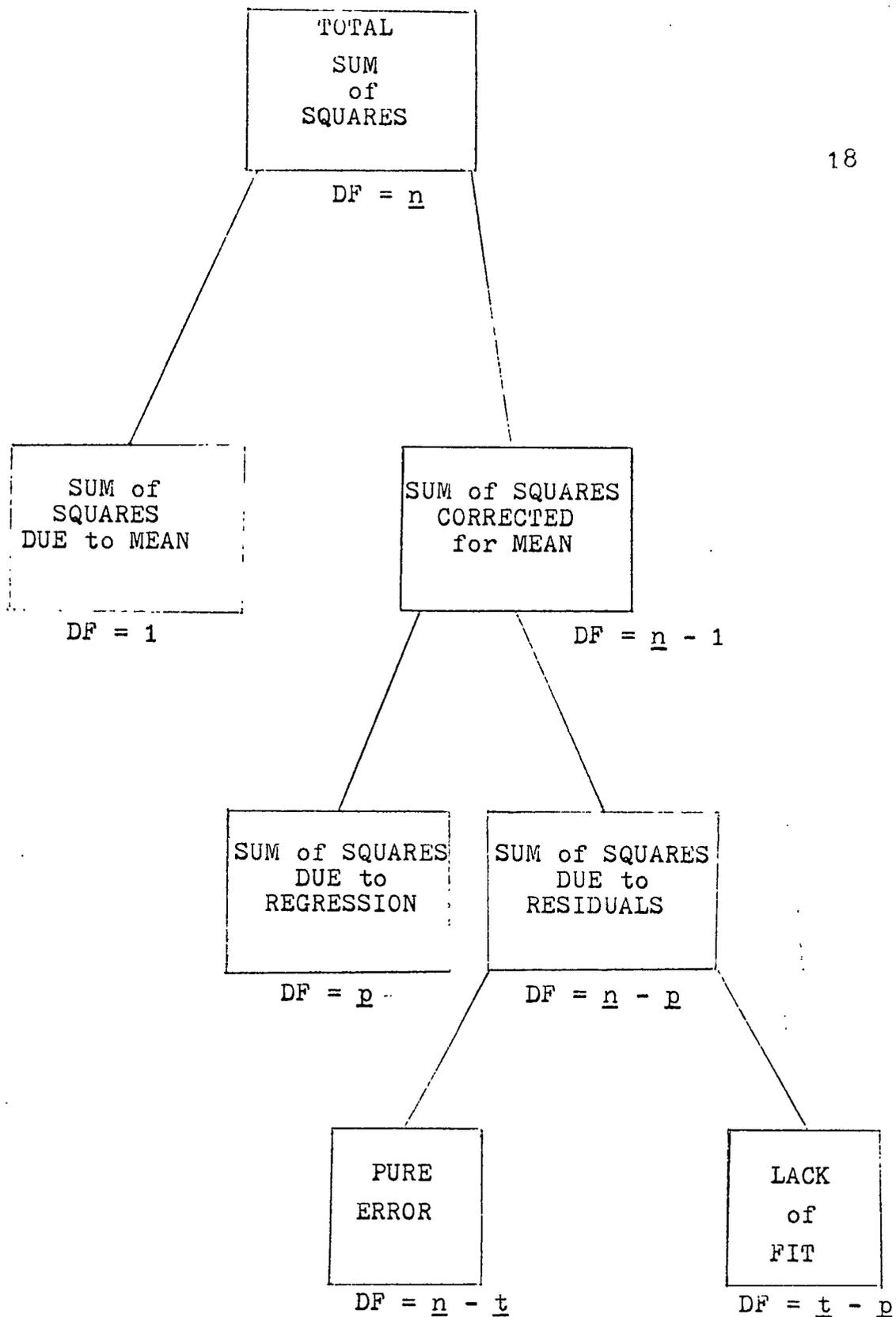


FIGURE 8: Scheme Delineating the Degrees of Freedom, Corrected for the Mean, Required for Regression and Analysis of Variance

STATEMENT of PURPOSE

It is a purpose of this thesis to describe the method of optimization applied to the continuous flow reaction of chlorine and α -pinene for production of 2,6-dichlorocamphane. It is also a purpose of this thesis to describe which factors employed in the optimization are most significant. Finally, this thesis will report some of the other products formed in the course of the reaction as determined by spectroscopic methods, and propose possible pathways leading to their formation.

EXPERIMENTAL RESULTS

Preliminary studies of the chlorination of α -pinene in cyclohexane revealed 10-chloropinene to be the principle product formed and 2,6-dichlorocamphane to be the compound produced in the second largest amount. It was also of interest to note that the stock solution of chlorine in cyclohexane contained a small amount of cyclohexyl chloride. A likely route to this product is free radical chlorination of the secondary carbon atom. Walling¹⁶ states that free radical chlorination of cyclohexane occurs even in the dark at cool temperatures. Free radical attack of chlorine at the C-10 position of pinene might be favorable due to the resonance stabilization of the allyl radical.

The desirability of a solvent more stable towards chlorination led to the use of benzene. This change of solvent decreased dramatically the amount of 10-chloropinene in the product mixture and 2,6-dichlorocamphane was found to be the principle product formed.

Keeping the flow rates of the reactants equal, the effect of temperature on the amount of 2,6-dichlorocamphane formed in the product mixture was investigated. The effect of different chlorine to pinene flow rates ratios was also investigated at these same temperatures. These studies

showed superficially that the ratio of flow rates and total flow rates were more important factors than was temperature in determining the percentage of 2,6-dichlorocamphane found in the product mixture. There was, however, some trend for increased amounts of 2,6-dichlorocamphane to be found in the product mixture as the temperature of reaction was lowered. A solvent change was necessitated in order to look at the effect of temperature below 0°C on the reaction. Chlorobenzene, m.p. -23°C , gave quite a different product distribution at -10°C . Exact experimental conditions and resultant product distributions for the studies discussed in this section can be found in Tables III-X in the Experimental section.

Using the ratio of flow rates and the total flow rates of the reactants as the factors of interest, an initial simplex was constructed in the heart of the factor space, as shown in Figure 9. More specifically, the ratio and sum of pump speed settings were used as variables, and these, in turn, varied the ratio and sum of the flow rates according to the calibration plot of Figure 10. The factor space boundaries were set by the mechanical limitations of the pumps. The simplex moved steadily towards regions of greater chlorine to pinene pump speed setting ratio, while the total pump speed setting remained nearly constant, as illustrated in Figures 11 and 12.

Termination of the simplex was made when it reached a plateau in the response surface and the change of response was less than one per cent between vertices (see Figure 13).

The concentration of one of the reactants was introduced as a third variable. Varying pinene concentration proved to be more convenient because of the time involved in making up and determining accurately the concentration of new stock solutions of chlorine. The change in the factor levels with increasing vertex number is shown in Figures 14, 15, and 16. Termination of the simplex was made after a plateau similar to that encountered above was reached (see Figure 17).

Further optimization for 2,6-dichlorocamphane would probably require investigating other variables of the reaction system. An obvious choice would be temperature. An investigation of the reaction at lower temperatures than 0°C would require a solvent of lower freezing point as previously mentioned. Carbon tetrachloride would be a likely candidate for such future studies as it affords good solubility for chlorine and is completely inert towards it chemically. To get an idea of the product distribution from reactions run in this solvent, a central composite design was employed to map the region of factor space previously searched by the simplex algorithm in benzene (see Figures 18 and 19). The design is analogous to that which would have been employed

to map the region of the optimum, had the simplex located one other than a plateau. Twenty-one experiments were carried out, including six replicates. The following full three-factor, second-order polynomial model was used to approximate the response of the reaction system.

$$\begin{aligned}
 Y = & B_0 + B_1 \text{ (Ratio of Pump Speed Settings)} \\
 & + B_{11} \text{ (Ratio of Pump Speed Settings)}^2 \\
 & + B_2 \text{ (Total Pump Speed Settings)} \\
 & + B_{22} \text{ (Total Pump Speed Settings)}^2 \\
 & + B_3 \text{ (Pinene Concentration)} \\
 & + B_{33} \text{ (Pinene Concentration)}^2 \\
 & + B_{12} \text{ (Ratio of Pump Speed Settings)} \\
 & \quad \quad \quad \text{(Total Pump Speed Settings)} \\
 & + B_{13} \text{ (Ratio of Pump Speed Settings)} \\
 & \quad \quad \quad \text{(Pinene Concentration)} \\
 & + B_{23} \text{ (Total Pump Speed Settings)} \\
 & \quad \quad \quad \text{(Pinene Concentration)}
 \end{aligned}$$

The estimates for parameters of this model obtained from regression analysis are listed here:

$$\begin{aligned}
 Y = & 21.11 + 1.57 \text{ (Ratio of Pump Speed Settings)} \\
 & - 1.26 \text{ (Ratio of Pump Speed Settings)}^2 \\
 & + 0.49 \text{ (Total Pump Speed Settings)} \\
 & - 0.25 \text{ (Total Pump Speed Settings)}^2 \\
 & - 0.89 \text{ (Pinene Concentration)}
 \end{aligned}$$

$$\begin{aligned} &+ 0.15 \text{ (Pinene Concentration)}^2 \\ &- 0.71 \text{ (Ratio of Pump Speed Settings)} \\ &\quad \text{(Total Pump Speed Settings)} \\ &+ 0.96 \text{ (Ratio of Pump Speed Settings)} \\ &\quad \text{(Pinene Concentration)} \\ &+ 0.34 \text{ (Total Pump Speed Settings)} \\ &\quad \text{(Pinene Concentration)} \end{aligned}$$

Table I, an analysis of variance (ANOVA) table, lists the significance of regression, the significance of lack of fit, and the coefficient of multiple determination. Table II gives the significance of the individual factors based on the variance of residuals.

Figures 20-22 are cell mean plots for the two factors and the one two-factor interaction with greater than 75% significance. Cell mean plots are a means of graphically illustrating dependence of the response on given factor levels.

Table I
Analysis of Variance

Source	Sum of Squares	d.f.	Variance
Due to Regression (Corrected for Mean)	113.45	9	12.61
Residual	47.40	11	4.31
Pure Error	3.06	6	0.51
Lack of Fit	44.34	5	8.87
<hr/>			
Total (Corrected for Mean)	160.85	20	---

Significance of Regression:

F = 2.93 95.2% d.f. = 9,11

Based on Variance of Residuals

Significance of Lack of Fit:

F = 17.39 99.8% d.f. = 5,6

Based on Pure Error Variance

Coefficient of Multiple Determination:

$R^2 = 0.71$

Table II
Hypothesis Testing
(Based on Variance of Residuals)

Parameter	Estimate	Std. Dev.	Rel. Std. Dev.	Calc. t	% Significance
B_0	21.11	1.354	0.06413	15.59	100.0
B_1	1.573	0.4725	0.3003	3.330	99.33
B_{11}	-1.263	0.5189	0.4110	2.433	96.68
B_2	0.4850	0.4641	0.9569	1.045	68.16
B_{22}	-0.2500	0.5189	2.075	0.4820	36.08
B_3	-0.8916	0.4425	0.4963	2.015	93.10
B_{33}	0.1476	0.4777	3.236	0.309	23.69
B_{12}	-0.7063	0.6356	0.9001	1.111	70.97
B_{13}	0.9593	0.6196	0.6460	1.548	85.01
B_{23}	0.3438	0.6356	1.848	0.5410	40.07

DISCUSSION

The factors selected as inputs to the reaction system in the preliminary simplex study were the ratio of reactant concentration and total reactant concentration. Had these factors been employed directly in the construction and translation of the initial simplex, much time would have been consumed in converting between the concentrations and the pump speed settings. Thus, a decision was made to substitute the mechanical factors, pump speed setting ratio and total pump speed setting, for the direct inputs to the system. The calibration curves, Figure 10, however, do permit conversion between the two classes of inputs whenever desirable. This method was also used in the three-factor simplex and central composite design studies.

As was previously mentioned in the experimental section, the central composite design was constructed in the same region of factor space that both simplexes had explored. From the experimental data accumulated in this region, it appeared that the response surface was fairly "soft". Tolerance levels for the inputs proved to be somewhat relaxed, as the responses were not widely divergent over the face of the design. Regression analysis on the second-order polynomial used to approximate the response surface,

however, yielded four parameters of greater than 75% significance. The largest and most significant of these was the pump speed setting ratio parameter of positive slope 1.57. A highly significant negative curvature parameter was also associated with the ratio input. The pinene concentration parameter was significant at the 85% confidence level. As was expected, there was a fairly significant interaction parameter for the pump speed setting ratio and the pinene concentration. This lends itself, at least in part, to the fact that pinene concentration is not only varied by changes in stock solutions, but also by changes in the ratio of reactant flow rates. Cell mean plots for the parameters described here can be found in Figures 20-22.

It was of interest to compute the actual mole ratios at each experimental point on the central composite design (see Figure 23). There seems to be some threshold value for this ratio prerequisite for the attainment of greater than or equal to twenty per cent yield of 2,6-dichlorocamphane. The three points in the designs that have associated yields significantly below twenty per cent also have chlorine to pinene ratios less than one. At low concentrations of chlorine, it is probable that any hydrochloric acid formed would react immediately with the great excess of pinene. These reactions could and do lead to a host of monochlorinated

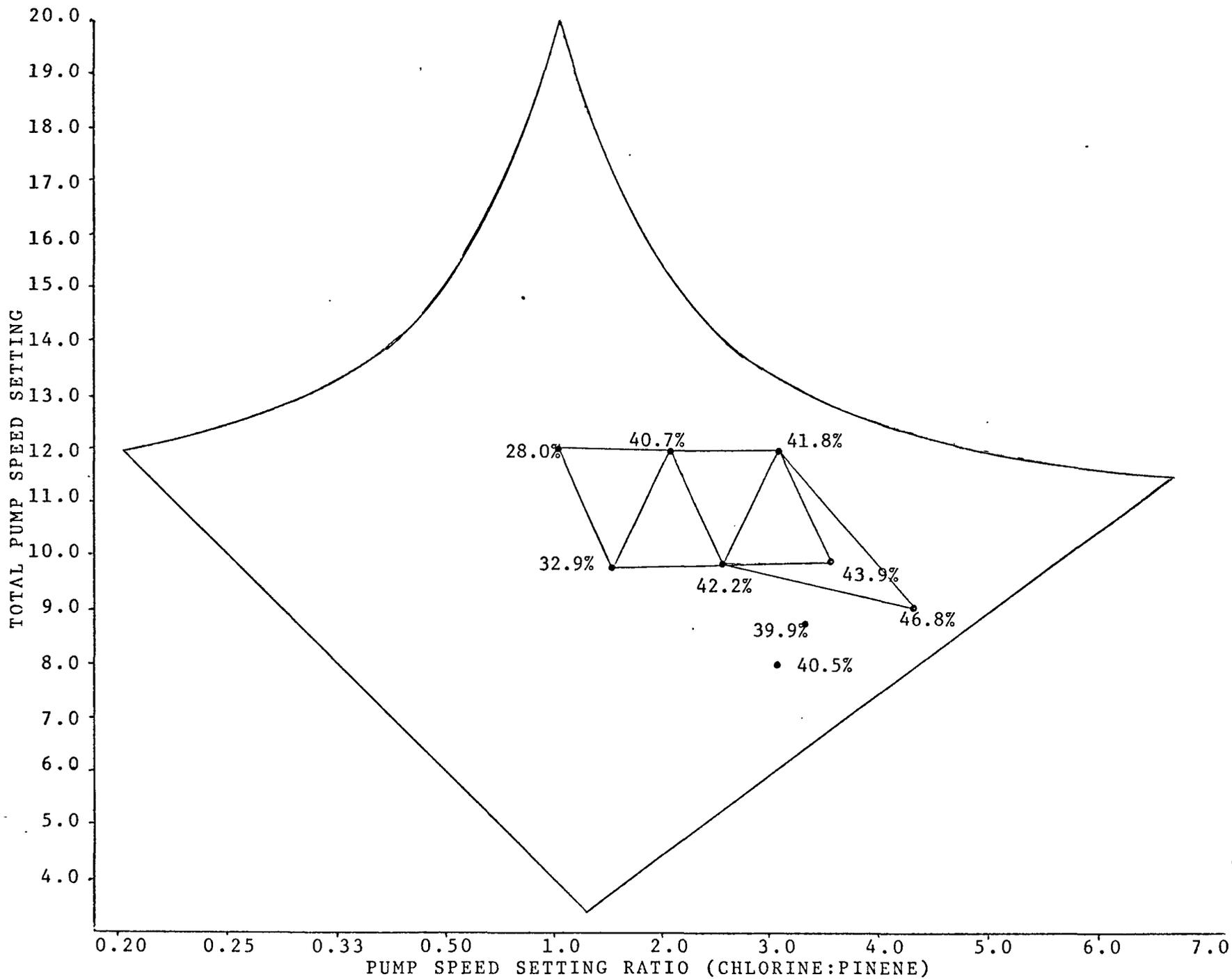
products in conjunction with ring-openings and skeletal rearrangements.^{17,18,19} After the chlorine to pinene mole ratio reaches a value somewhere between one and two, some of these side reactions seem to be suppressed and higher yields for the desired product are attained. Further increase in the mole ratio, however, has no significant effect in increasing the yield of 2,6-dichlorocamphane. Similar threshold values for mole ratio were also found in the simplex studies.

To determine the experimental precision in the central composite study, the standard deviation of a measurement due to experimental uncertainty was calculated from the variance due to pure error in Table I. This deviation (0.714) becomes fairly large when compared with the narrow range of responses found in Table IX. The poor degree of experimental precision can largely be ascribed to the uncertainty in estimating pump speed settings to the nearest tenth. Table I also shows that the regression was significant at the 95.2% confidence level based on variance of the residuals. Deviation of experimental points from the model was partially ascribed to the pure error of the system, but mostly to the lack of fit of the model, where the F-test based on pure variance was significant to the 99.8% confidence level. This suggests that a model other than the second-order

polynomial may provide a better fit to the experimental data.

Separation of 2,6-dichlorocamphane from the rest of the product mixture was achieved through gas-liquid chromatography. Analytical separation of the product mixture revealed the presence of some twenty-five to thirty constituents. Some of the major products were isolated and tentatively identified through nuclear magnetic resonance spectroscopy and to a lesser extent by mass spectroscopy. Spectral data can be found in the experimental section. Possible pathways leading to the formation of each product identified are illustrated in Figure 24. Once a bicyclo-[2.2.1] heptane has been formed from rearrangement of a pinane skeleton, it can also undergo various rearrangements, including a Wagner-Meerwein. These rearrangements have been reviewed by Berson.²⁰

FIGURE 9
Progression of the 2-Factor Simplex
within the Factor Space



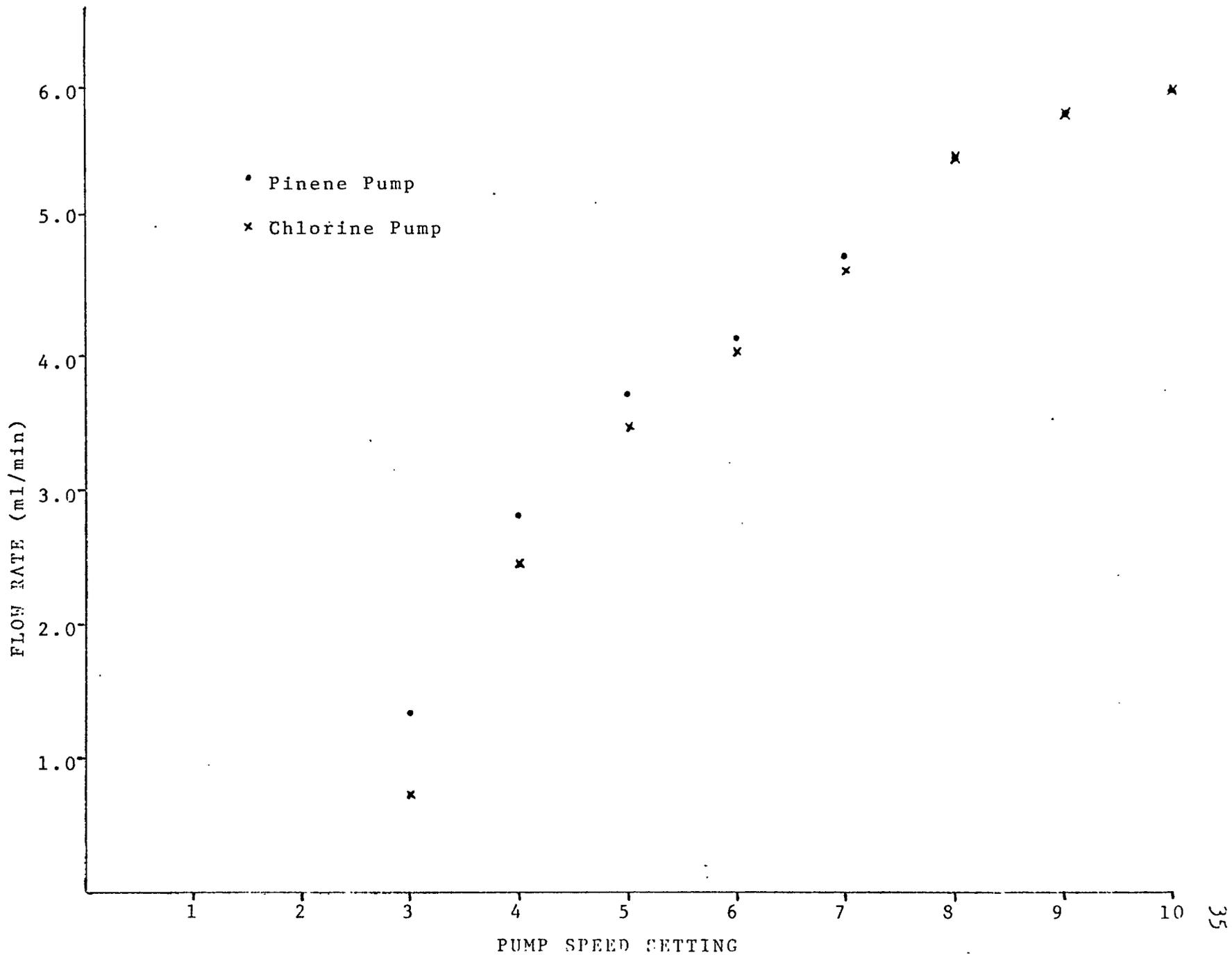
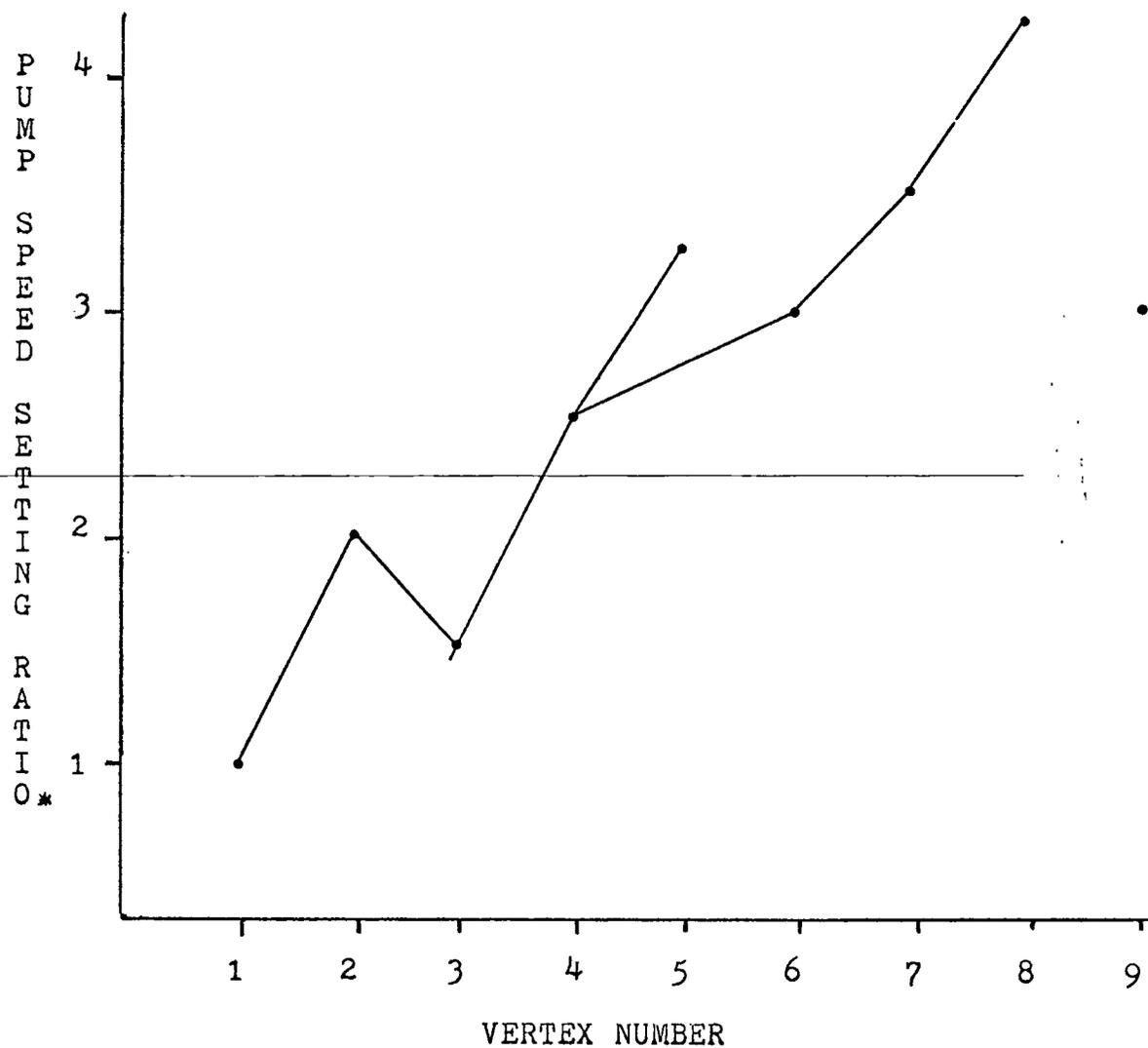


FIGURE 10: Calibration Plot for the Peristaltic Pumps



*Chlorine to Pinene

FIGURE 11: Variation of Pump Speed Setting Ratio with the 2-Factor Simplex Vertex Number

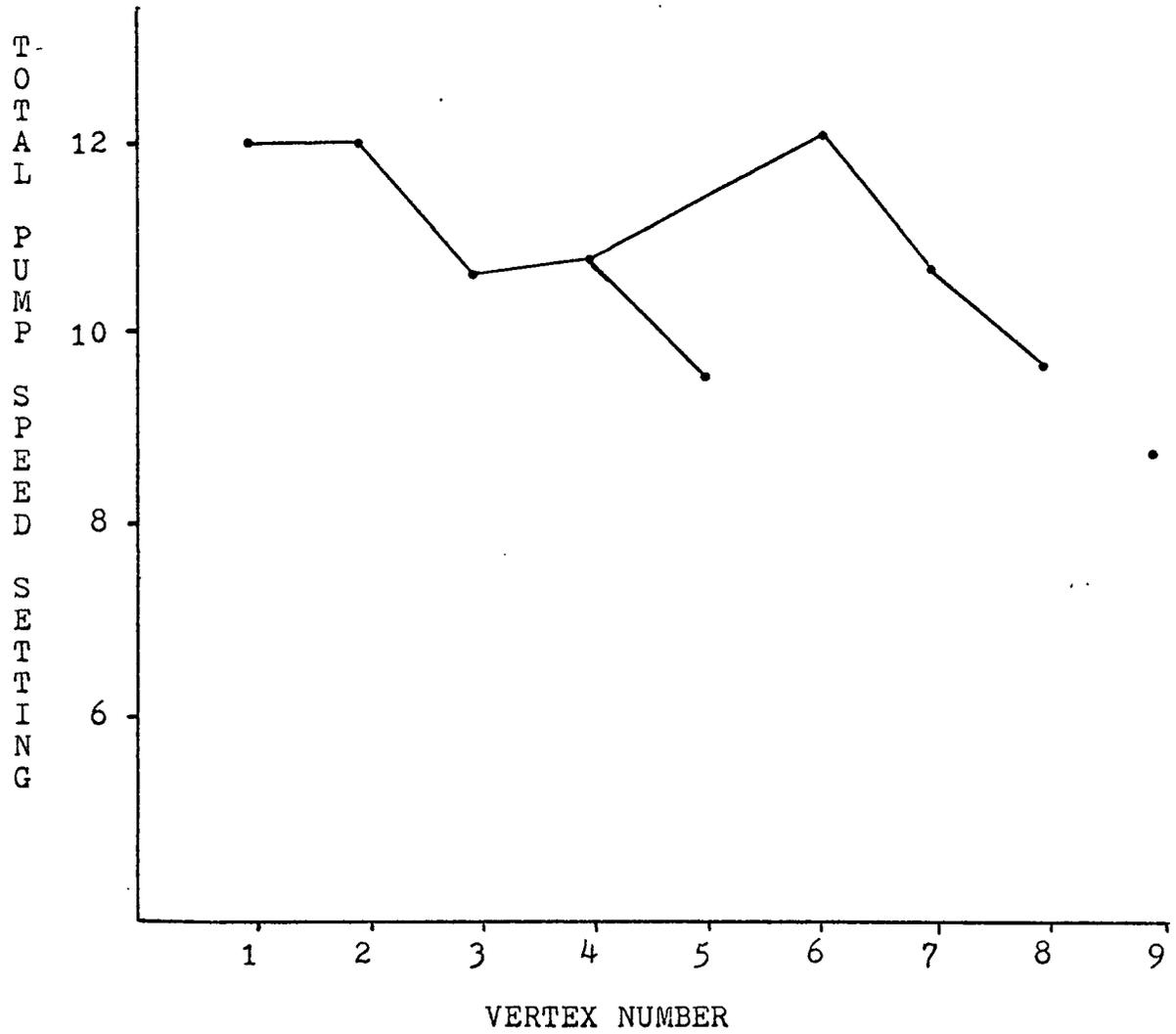


FIGURE 12: Variation of Total Pump Speed Setting with the Simplex Vertex Number

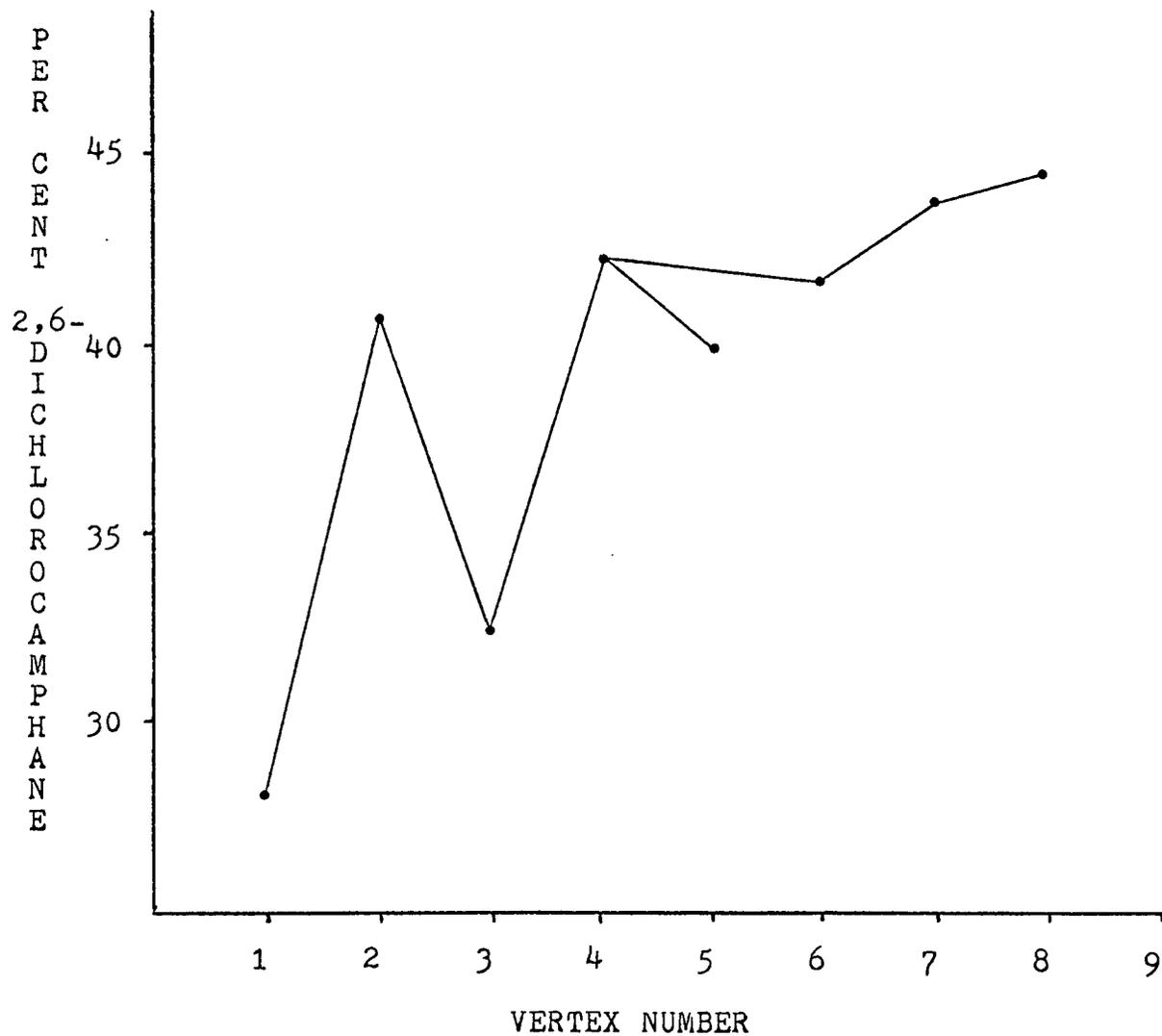


FIGURE 13: Variation of Per Cent 2,6-Dichlorocamphane in the Product Mixture with the 2-Factor Simplex Vertex Number

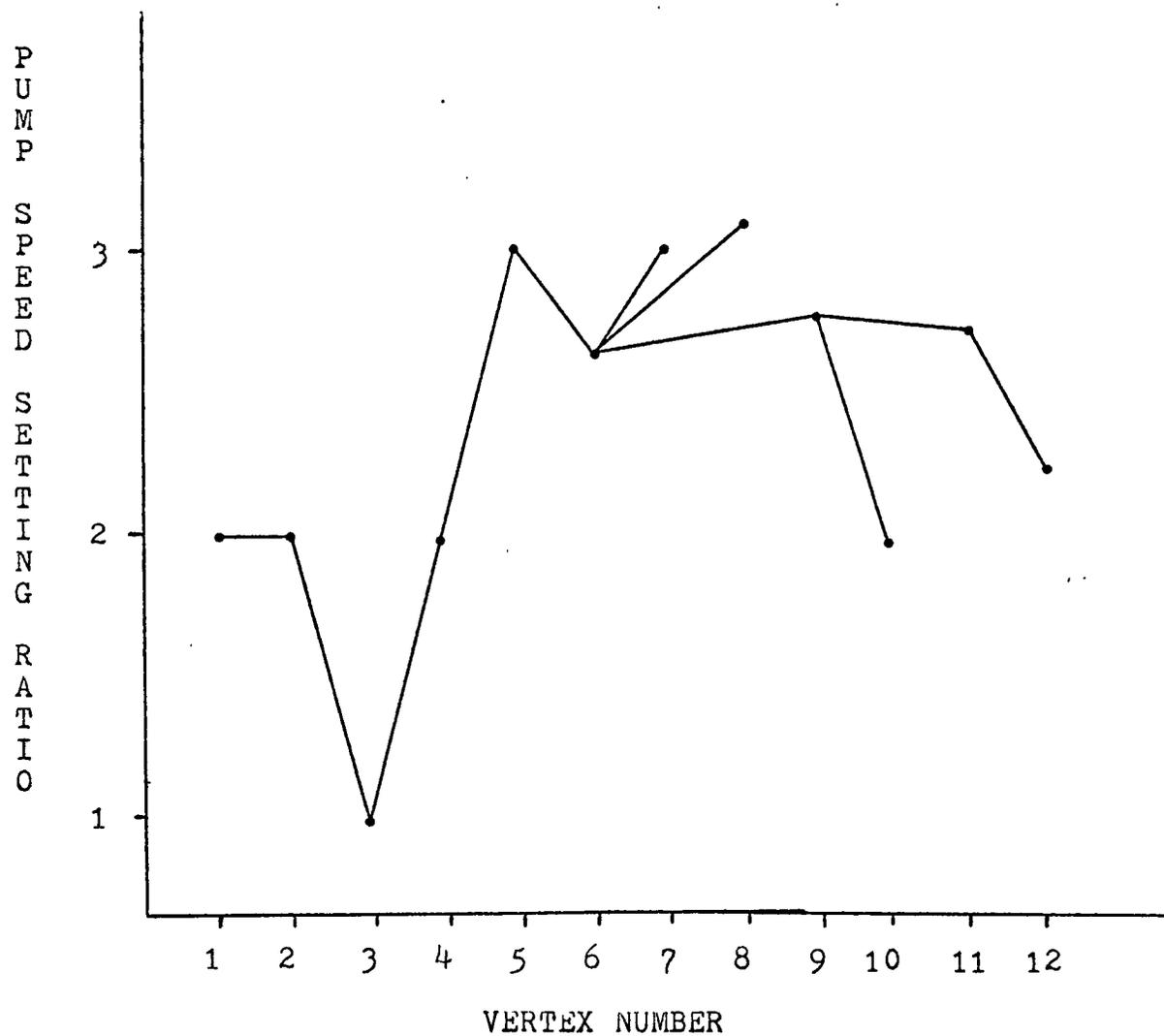


FIGURE 14: Variation of Pump Speed Setting Ratio with the 3-Factor Simplex Vertex Number

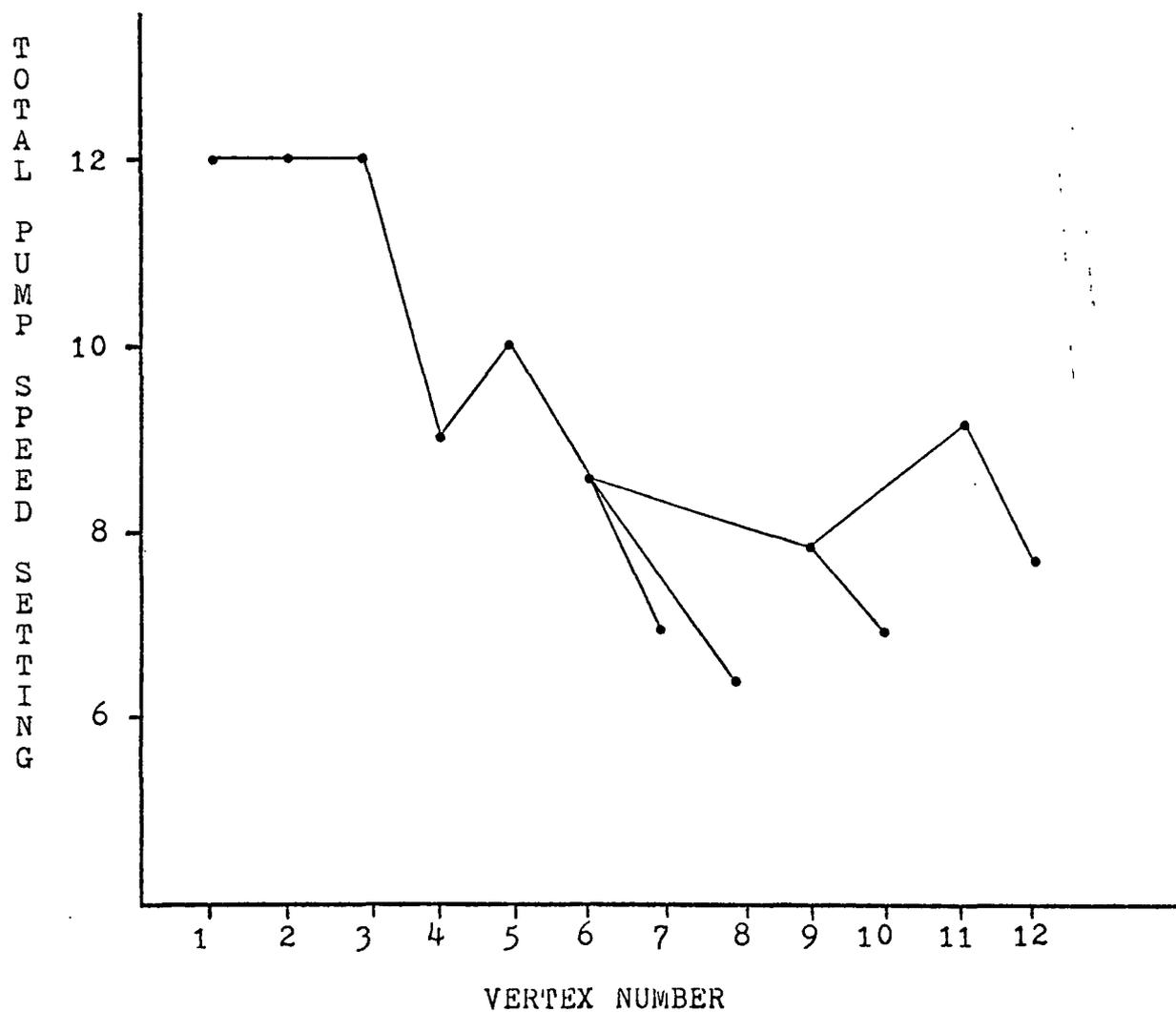


FIGURE 15: Variation of Total Pump Speed Setting with 3-Factor Simplex Vertex Number

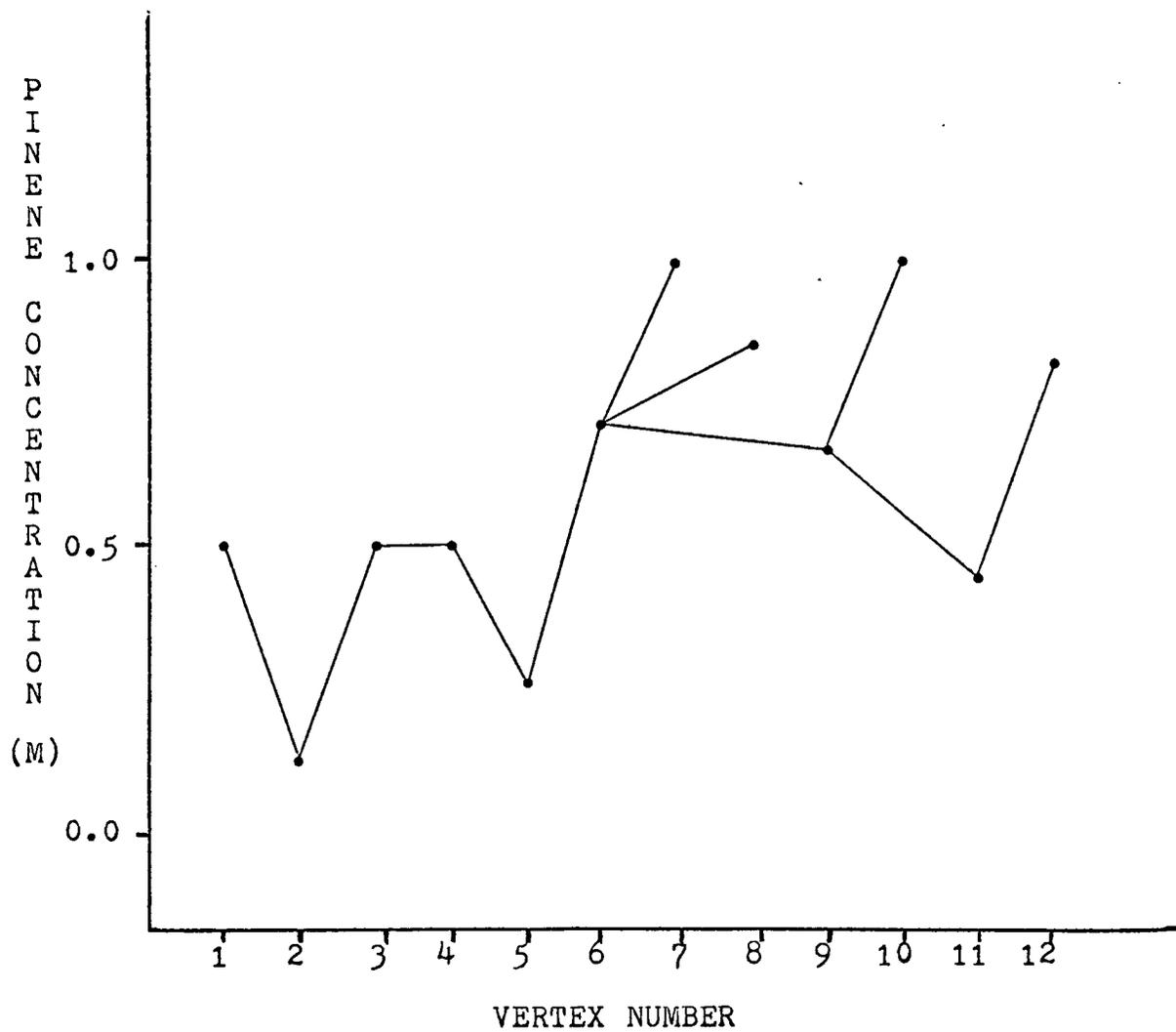


FIGURE 16: Variation of Pinene Concentration with the 3-Factor Simplex Vertex Number

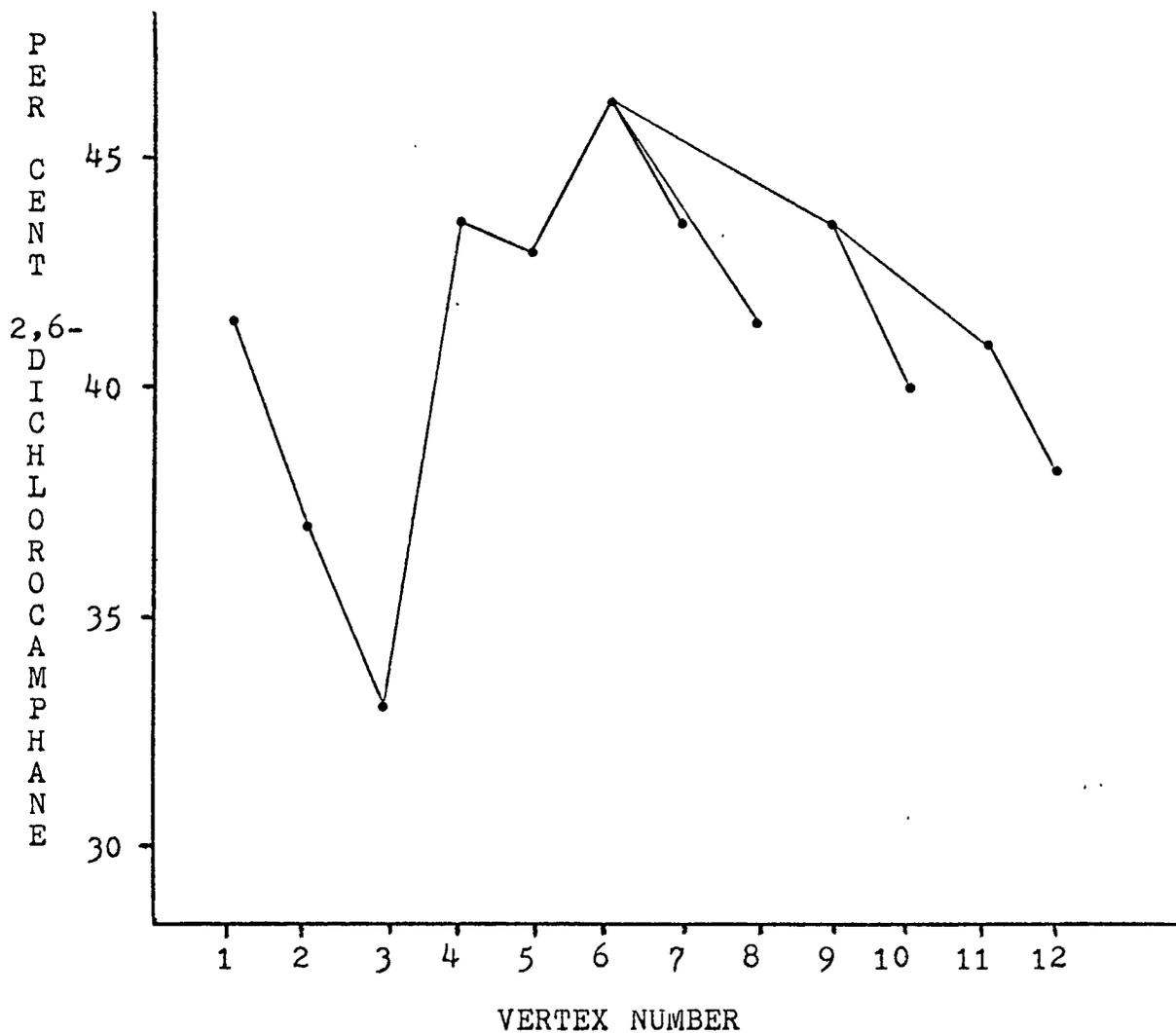
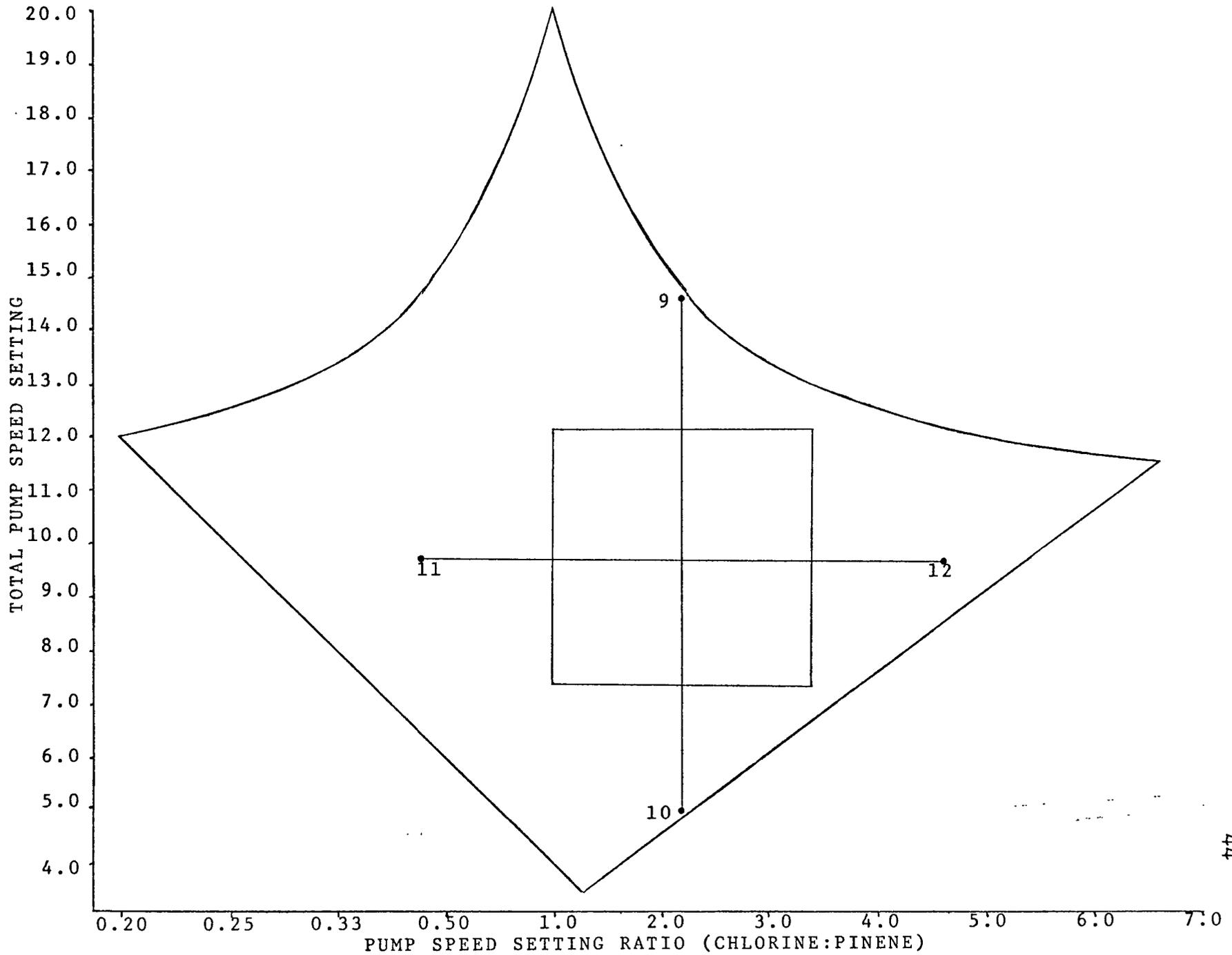


FIGURE 17: Variation of Per Cent 2,6-Dichlorocamphane in the Product Mixture with the 3-Factor Simplex Vertex Number

FIGURE 18

Cross-section of the Central Composite Design
in the Factor Space



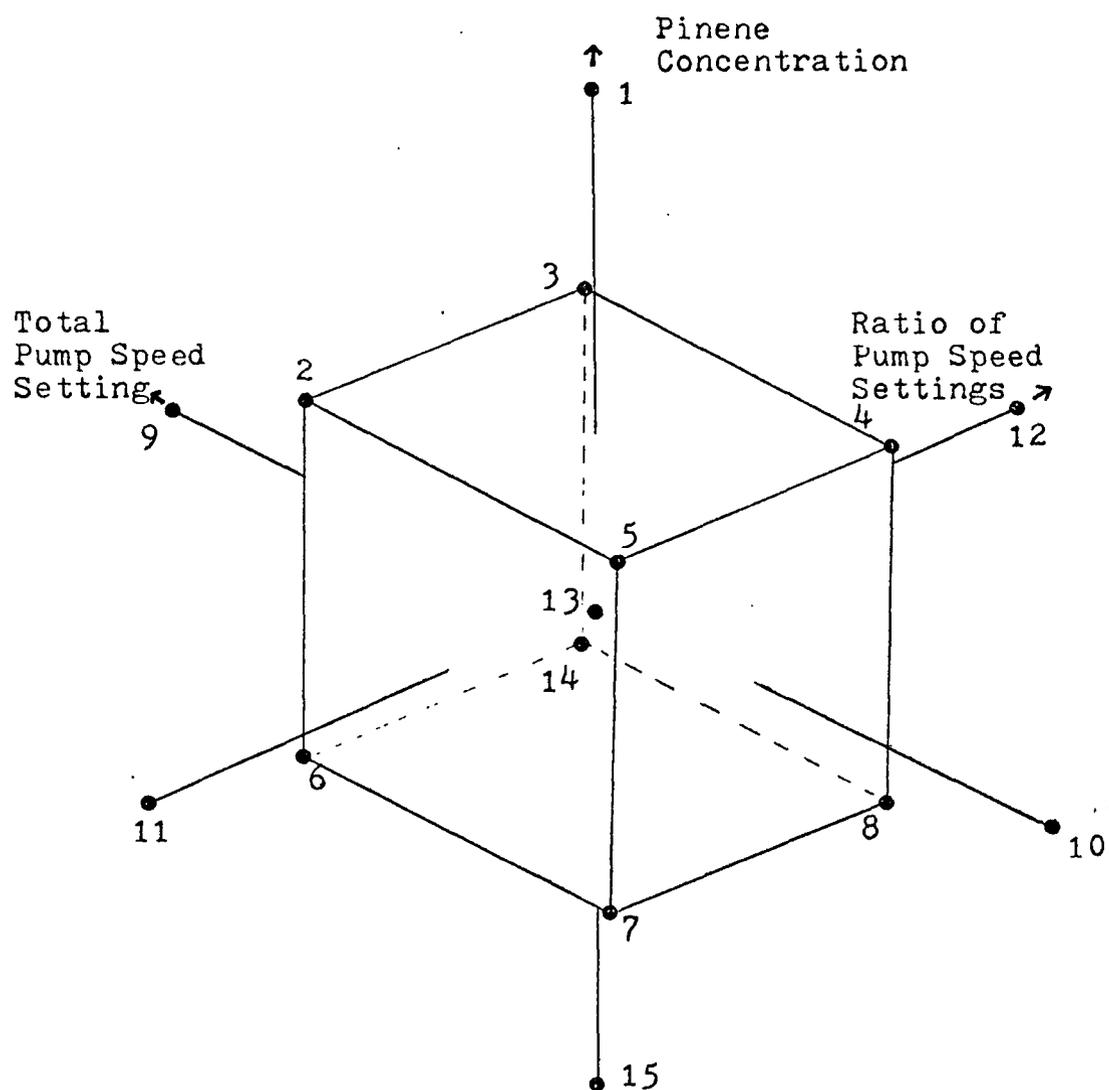
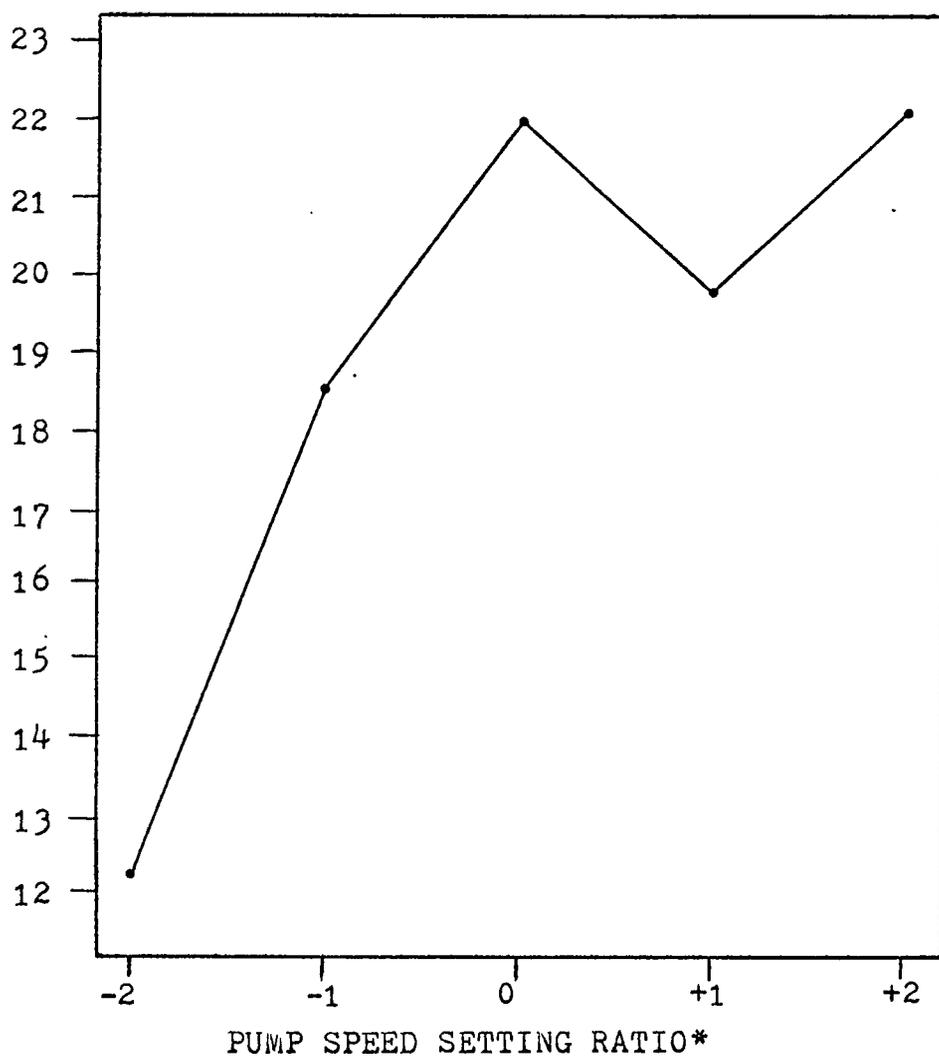


FIGURE 19: Central Composite Design



* Chlorine to Pinene

FIGURE 20: Cell Mean Plot for Main Effect of Pump Speed Setting Ratio

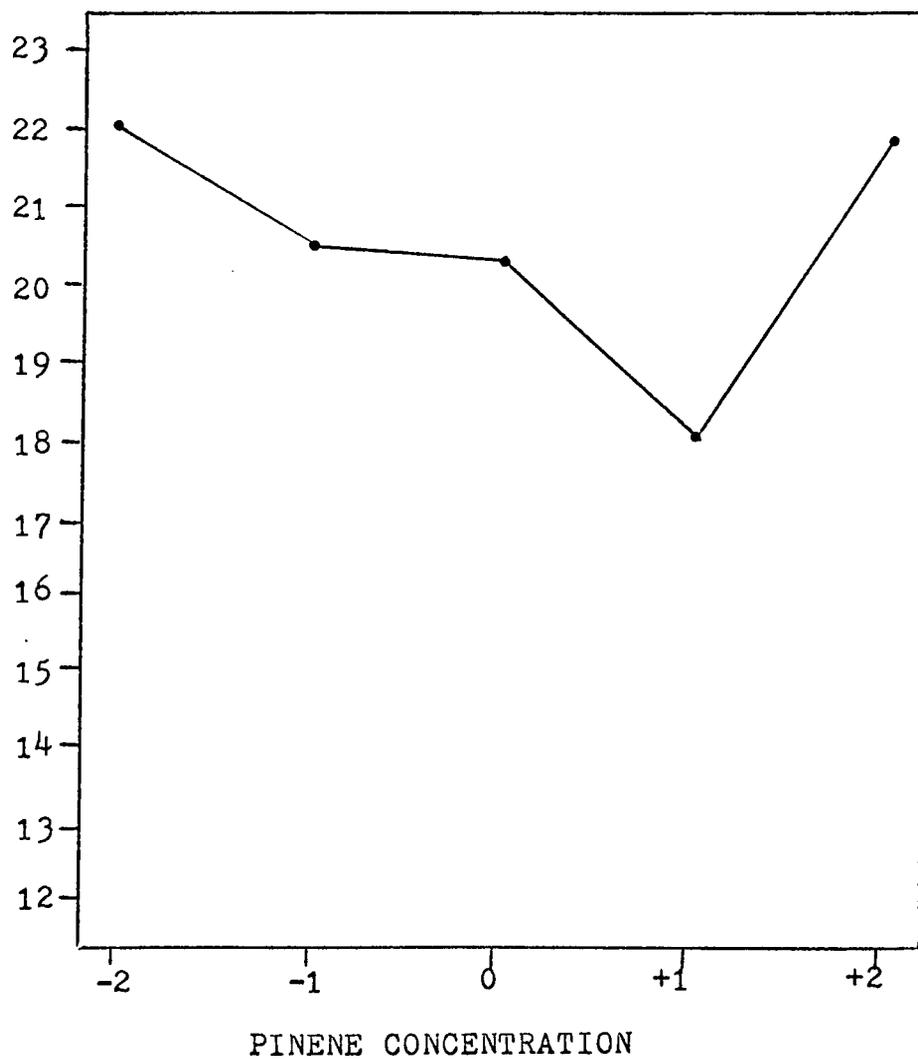


FIGURE 21: Cell Mean Plot for Main Effect of Pinene Concentration

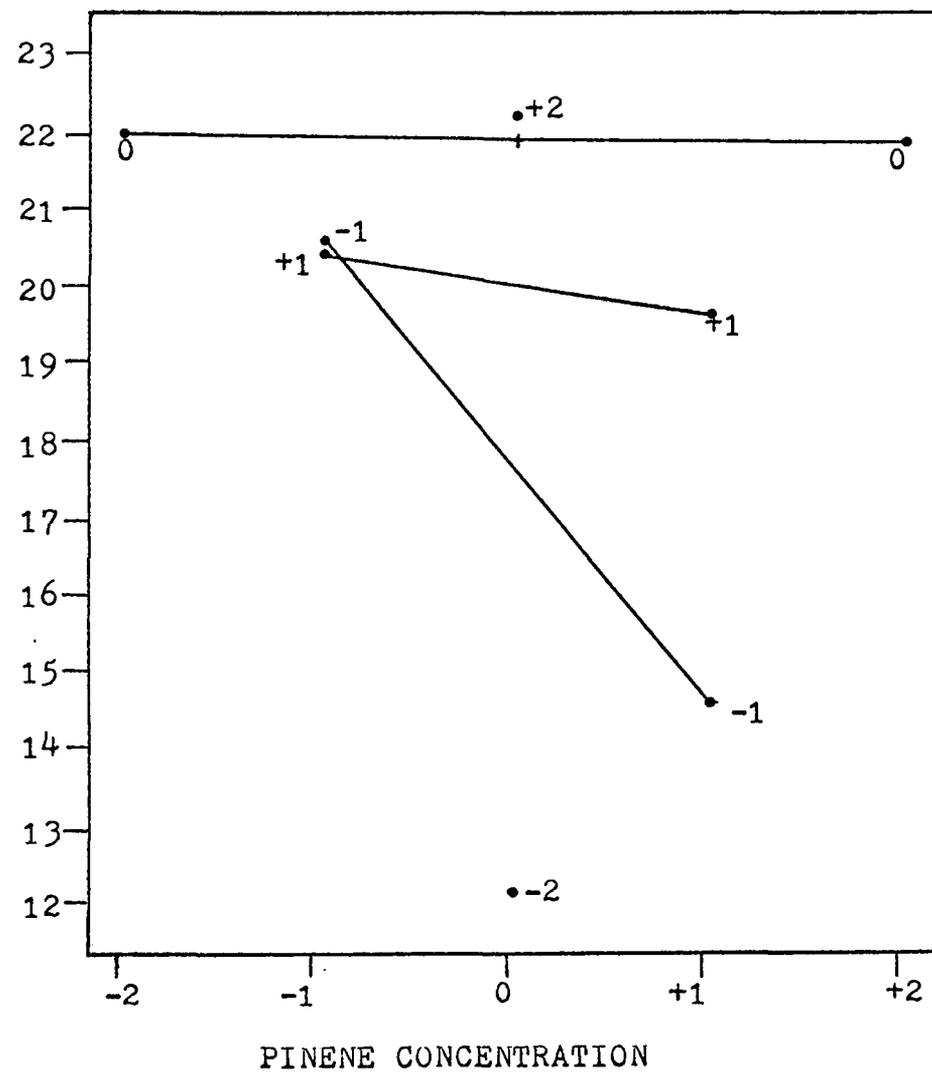


FIGURE 22: Cell Mean Plot for Interaction Between Pump Speed Setting Ratio and Pinene Concentration

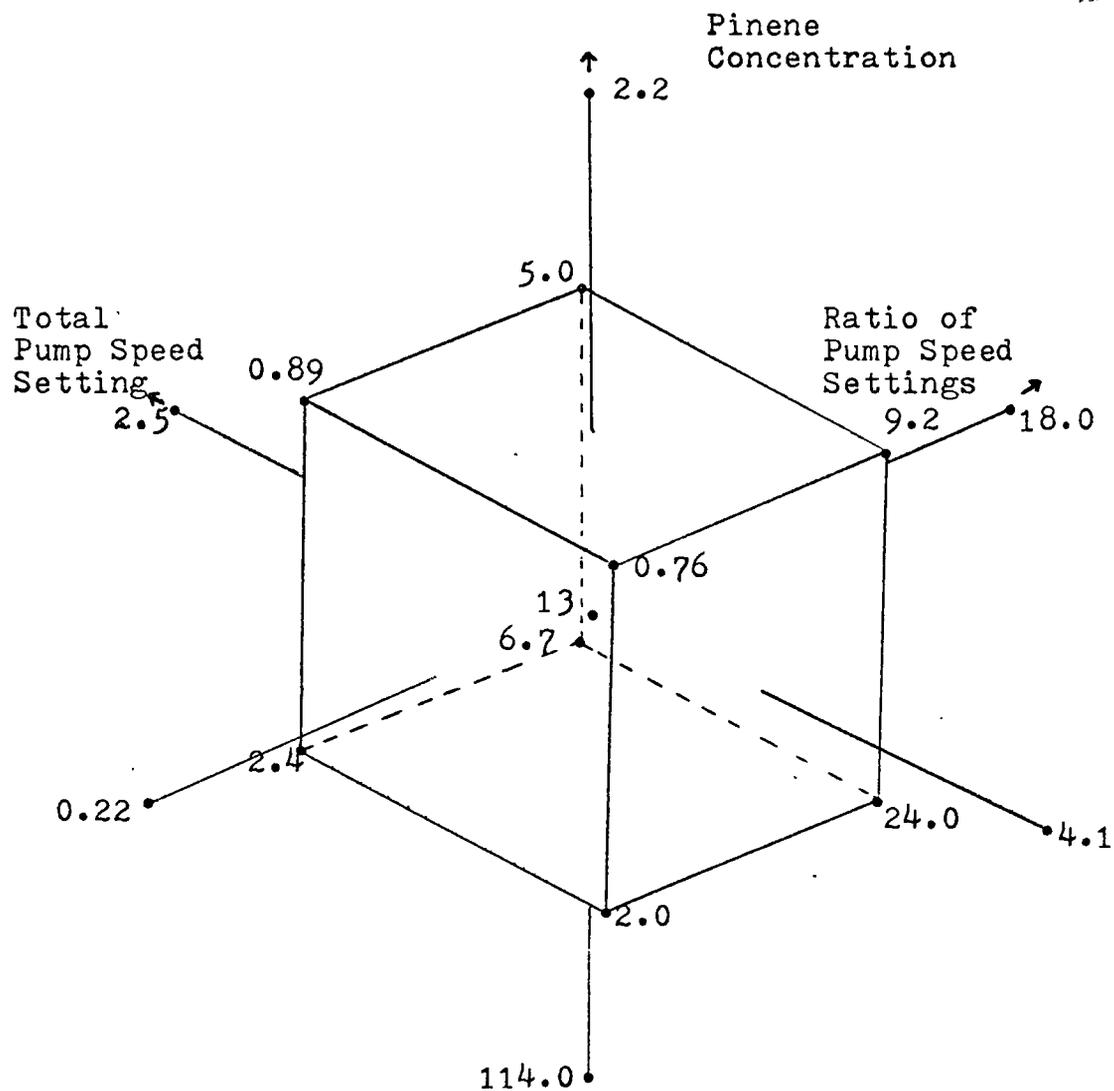


FIGURE 23: Mole Ratios* at Points on the Central Composite Design

* Chlorine to Pinene

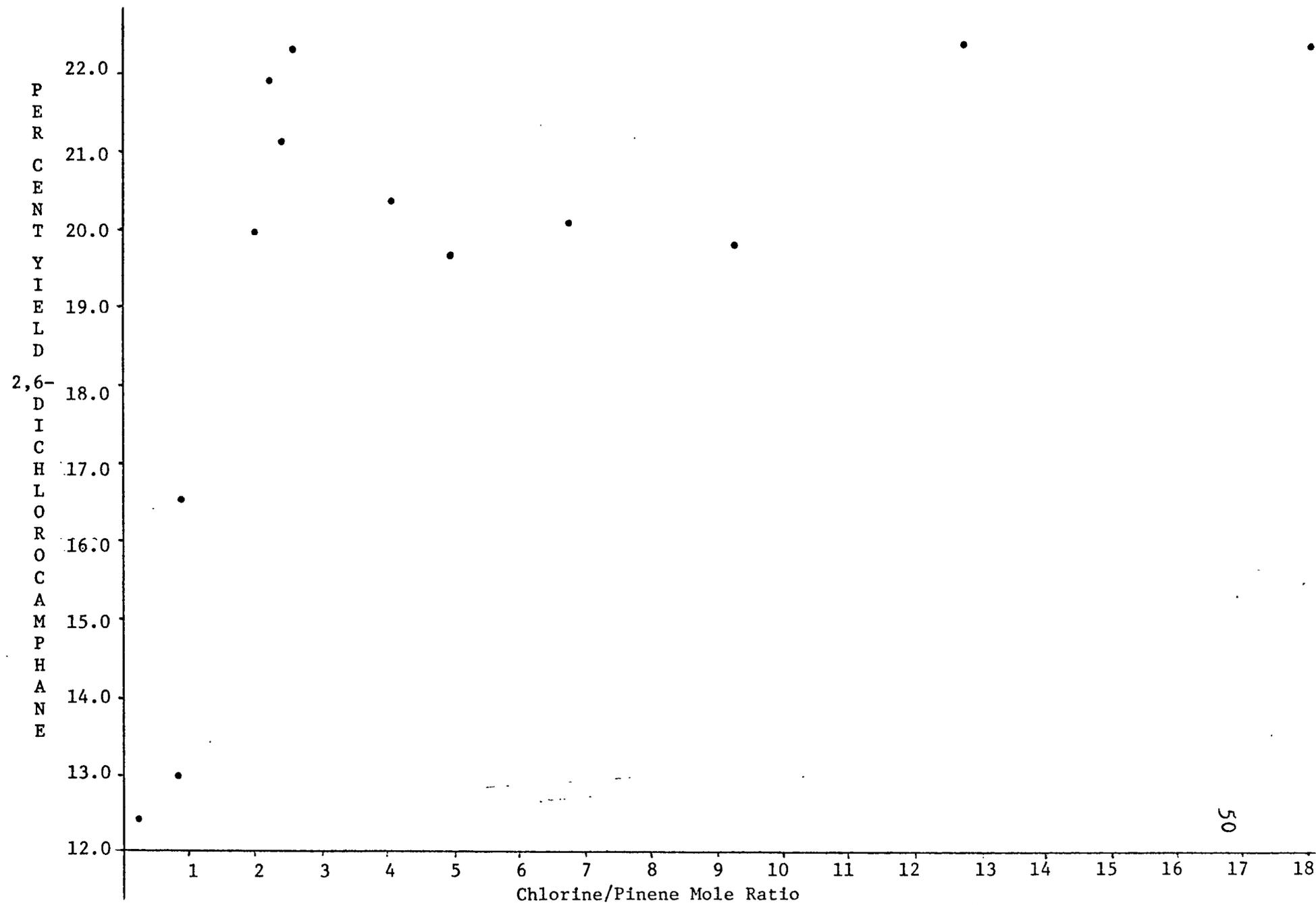


FIGURE 23a. Variation of Per Cent Yield 2,6-Dichlorocamphane with Chlorine/Pinene Mole Ratio

CONCLUSION

Reaction of chlorine with α -pinene yields a complex product mixture. However, through use of the simplex algorithm, it became possible to increase the relative percentage of 2,6-dichlorocamphane in the mixture. Yields for 2,6-dichlorocamphane in carbon tetrachloride solution were 3.5 times greater than the best value previously reported in the literature. A central composite design study revealed that a second-order polynomial was not a good approximation for the response surface in this solvent. Although the experimental uncertainty in this study was shown to be somewhat high, the narrow range of responses seemed to minimize its importance. The mole ratio of chlorine to α -pinene appeared to have some impact on determining the yield of 2,6-dichlorocamphane, especially when the ratio was less than or approximately equal to one.

EXPERIMENTAL

Analytical separation of product mixtures was achieved by using a Hewlett-Packard 5730A temperature programmable gas chromatograph equipped with a flame ionization detector. This unit was under the control of a Hewlett-Packard 3385A digital processor which also performed automatic integration. Mass spectra were obtained from a Hewlett-Packard 5930A mass spectrometer interfaced with a Hewlett-Packard 5710A gas chromatograph. Electron impact ionization was used. Preparative gas-liquid chromatography was performed on a Varian A-90P3 Autoprep Instrument equipped with a thermal conductivity detector. Continuous-wave nuclear magnetic resonance (nmr) spectra were obtained from a Varian T-60 spectrometer operated at 60MHz. Samples were run in carbon tetrachloride and chemical shifts were recorded in parts per million downfield from tetramethyl silane (TMS). ^1H nmr spectra were obtained at 100 MHz by means of the Fourier-transform method on a Varian XL-100 spectrometer with a Nicolet data system, internally locked to the deuterium frequency of 15.24 MHz. Samples were run in 99.8 atom %D deuteriochloroform and chemical shifts were referenced to 7.26 ppm, the chemical shift of the residual hydrogen in the chloroform. ^{13}C nmr fully ^1H decoupled spectra were obtained at 25.16 MHz also

by means of the Fourier-transform method. Nuclear magnetic resonance data are presented in the order (chemical shift): multiplicity, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broadened; integration; assignment.

Determination of Chlorine Concentration

High purity (99.5%) chlorine gas was obtained from Matheson Gas Products. Solvents used for chlorine gas were cyclohexane, benzene, and carbon tetrachloride. Addition was made by bubbling the gas into the solvent. The concentration of chlorine in solution was determined according to the titrimetric procedure of Meites.²¹ Stock solutions were made up in the range of 0.5M-1.0M and the error was determined to 0.001M.

Preliminary Small-sized Batch Chlorination of α -Pinene

A 25 ml aliquot of 0.5M Cl₂/cyclohexane solution was added with stirring to 2.5g α -pinene in 25 ml cyclohexane. A portion of the solvent was evaporated and the product mixture analyzed. Since the purpose of the reaction was to calibrate the gas chromatographic column and identify some of the products, no yields are reported.

Continuous Flow Reactions

In a typical experiment, streams of reactants in solution (benzene for simplex studies and carbon tetrachloride for

central composite design studies) were pumped through VITON tubing (.315"x.1625" I.D.xO.D.), via Masterflex Model 7545-10 variable speed (5-100 RPM) peristaltic pumps. This system provided flow rates of 0.75-6.0 ml/min. The tubing was fitted snugly with rubber O-rings into a polyvinylchloride SWAGELOK "T" (3/16" I.D. inlet and 1/8" I.D. mixing chamber). This fitting was attached to a coiled glass tube (4 mm I.D.) reactor. Temperature control (+0.2°C) was afforded by a Haake Model E12 constant temperature circulator immersed in a 15 l water reservoir. Figure 25 diagrams the experimental setup. Solutions were allowed to mix for four minutes, or about the equivalent of eight retention times, before 5 ml of product was collected. Product compositions are listed in Tables III-X. The supply lines and reactor were pumped dry after each run. Reactant solutions were pumped out of 25 ml Erlenmeyer flasks capped with rubber septums. Under these conditions, the concentration of Cl₂ remained constant at 0.750M during the reaction time. Varying the dial settings on the pump control units produced changes in the ratio of flow rates and the total flow rates of the reactants. Stock solutions of pinene were prepared as required.

The following products appeared when reactions were run in benzene and carbon tetrachloride. The initial letters refer to the product distribution tables.

"C" C₁₀H₁₄ p-Cymene (X)

1.20 (s,3H, methyl), 1.27 (s,3H, methyl), 2.32 (s,3H, methyl), 2.88 (quintet,1H, methine), 7.12 (s,4H, aromatic)
m/e 91, 117, 119(Base Peak), 134(Molecular Ion)

"E" C₁₀H₁₇Cl Bornyl Chloride (IX)

0.87 (s,6H, gem-dimethyl), 0.93 (s,3H, methyl),
1.33 (m,3H, aliphatic), 1.70 (m,2H, aliphatic), 2.05 (m,1H, aliphatic), 2.44 (m,1H, aliphatic), 4.17 (dq,1H, CHCl)
m/e 93, 95(Base Peak), 136, 157, 159, 172(Molecular Ion),
174(M+2)

"I" C₁₀H₁₄Cl₂ 3,10-Dichloropinene (XVII)

0.86 (s,3H, methyl), 1.31 (s,3H, methyl), 2.38 (d,6H, aliphatic), 4.20 (d,2H, -CH₂Cl)
m/e 91, 107(Base Peak), 141, 169, 171, 139, 191,
204(Molecular Ion), 206(M+2), 208(M+4)

"J" C₁₀H₁₆Cl₂ 2,6-Dichlorocamphane (VIII)

0.94 (s,6H, gem-dimethyl), 1.06 (s,3H, methyl), 1.73 (m,3H, aliphatic), 2.60 (m,2H, aliphatic), 4.30 (bq,2H, CHCl)

^{13}C nmr referenced to CDCl_3 absorption at 76.90 ppm
 11.69(C-10), 20.32(C-8 and C-9), 39.98(C-3 and C-5),
 43.03(C-4), 49.40(C-7), 52.84(C-1), 63.95(C-2 and C-6)

m/e 91, 93(Base Peak), 129, 131, 135, 170, 171, 172,
 206(Molecular Ion), 208(M+2)

"L" $\text{C}_{10}\text{H}_{16}\text{Cl}_2$ 2,10-Dichlorocamphane (XVIII)

0.99(s,3H, methyl), 1.11(s,3H, methyl),
 1.58-1.98(unresolved absorption,5H, aliphatic), 2.62(dd,1H,
 aliphatic), 2.75(dd,1H, aliphatic), 3.68(d,1H, $-\text{CH}_2\text{Cl}$, $J=12\text{Hz}$),
 4.02(d,1H, $-\text{CH}_2\text{Cl}$, $J=12\text{Hz}$), 4.39(m,1H, CHCl)

m/e 77, 91,(Base Peak), 169, 171, 205(Molecular Ion),
 207(M+2), 209(M+4)

"M" $\text{C}_{10}\text{H}_{13}\text{Cl}_3$ (XIX)

1.58(s,6H, gem-dimethyl), 1.72-2.36(unresolved absorptions,
 4H, aliphatic), 4.20(m,2H, $-\text{CH}_2\text{Cl}$), 6.25(s,1H, olefinic)

m/e 77, 91, 177(Base Peak), 179, 181, 212, 214, 216,
 239(Molecular Ion), 241(M+2)

The following product appeared when the reaction was run
 in cyclohexane:

$\text{C}_{10}\text{H}_{15}\text{Cl}$ 10-Chloropinene (XIV)

0.82(s,3H, methyl), 1.32(s,3H, methyl), 2.30(b,6H,
 aliphatic), 3.92(bd,2H, $-\text{CH}_2\text{Cl}$), 5.57(bs,1H, olefinic)

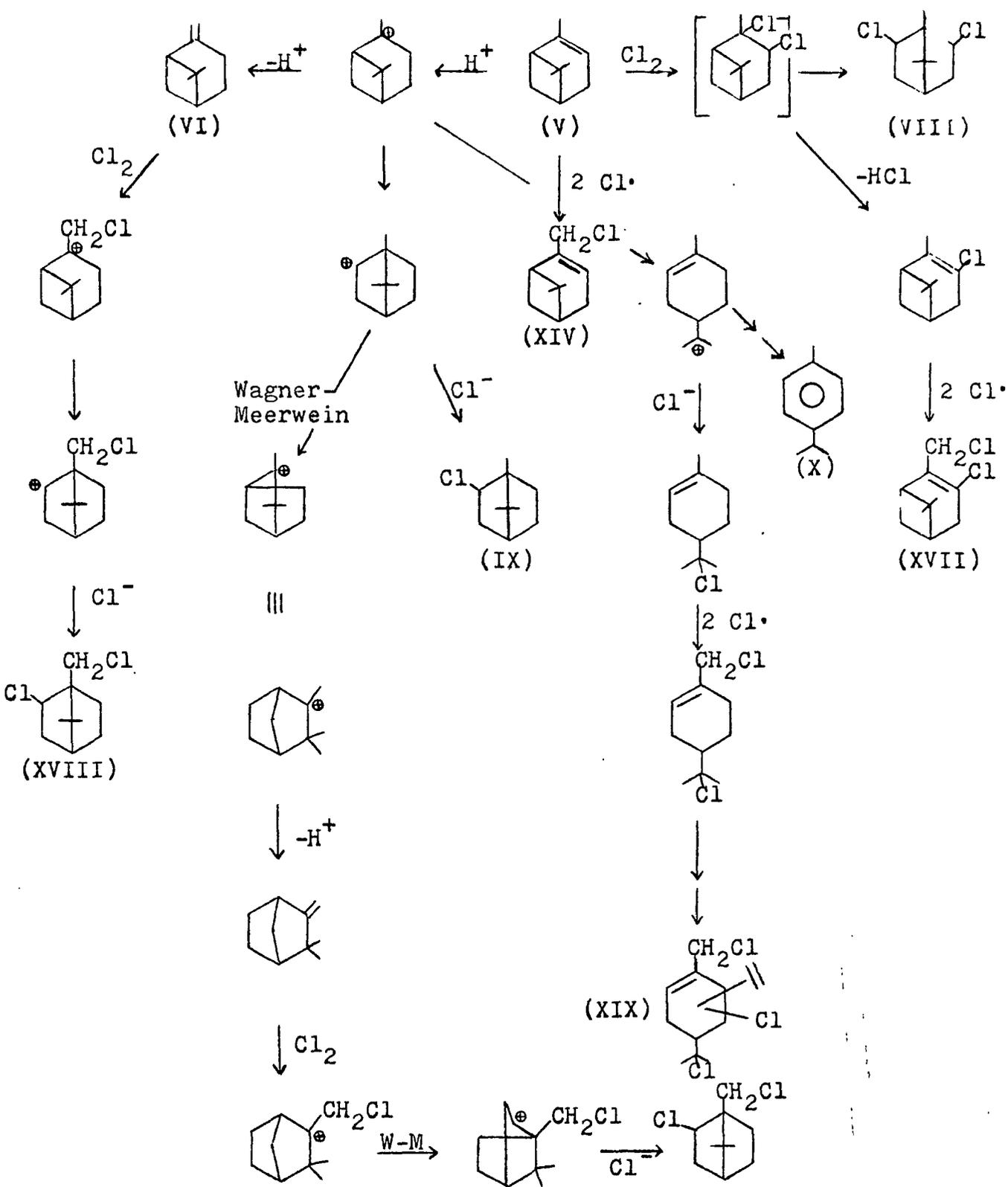


FIGURE 24: Possible Pathways Leading to the Formation of Products Identified in the Experimental Section

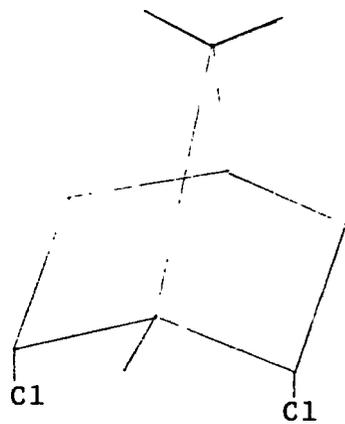
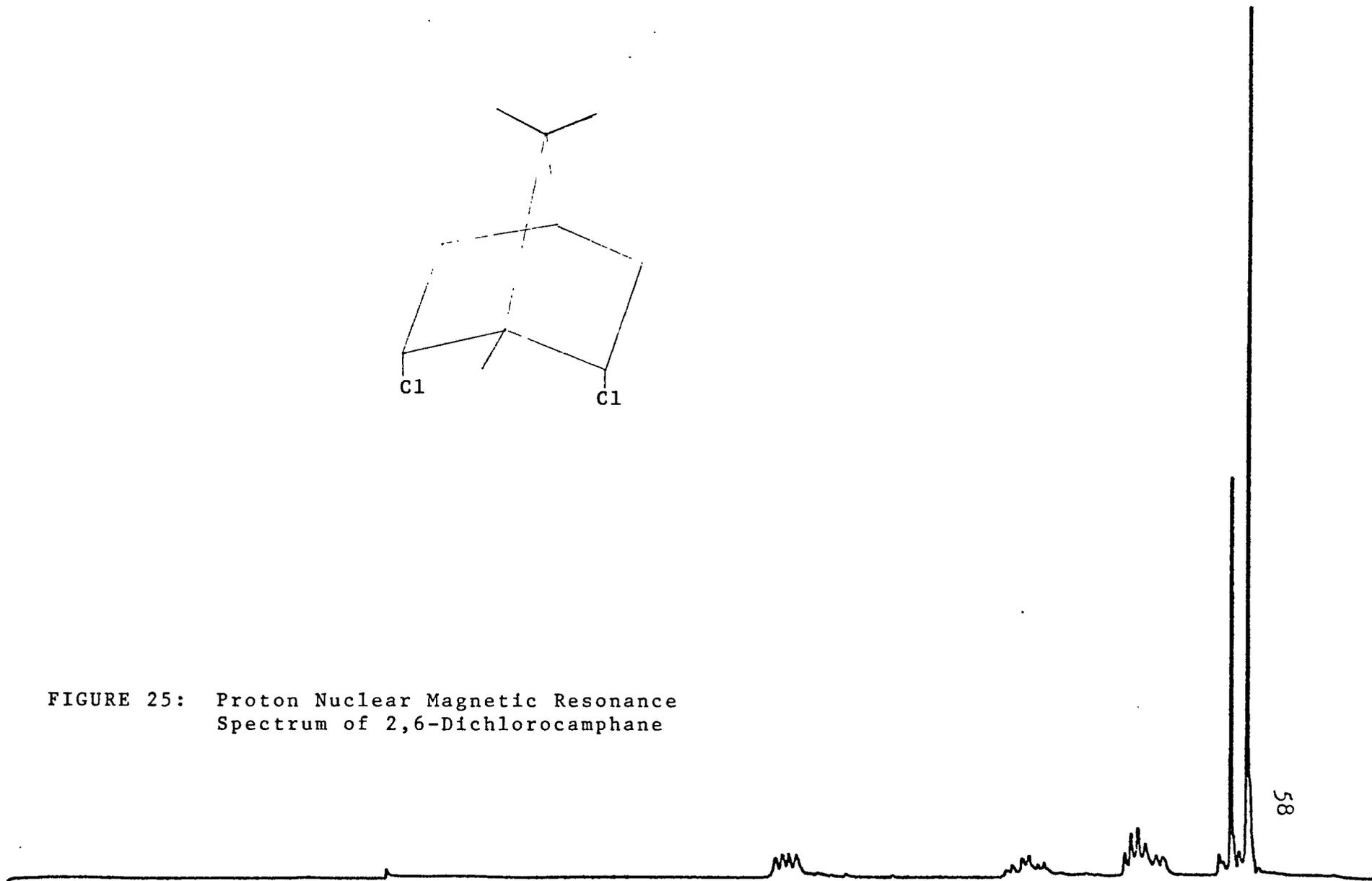


FIGURE 25: Proton Nuclear Magnetic Resonance Spectrum of 2,6-Dichlorocamphane



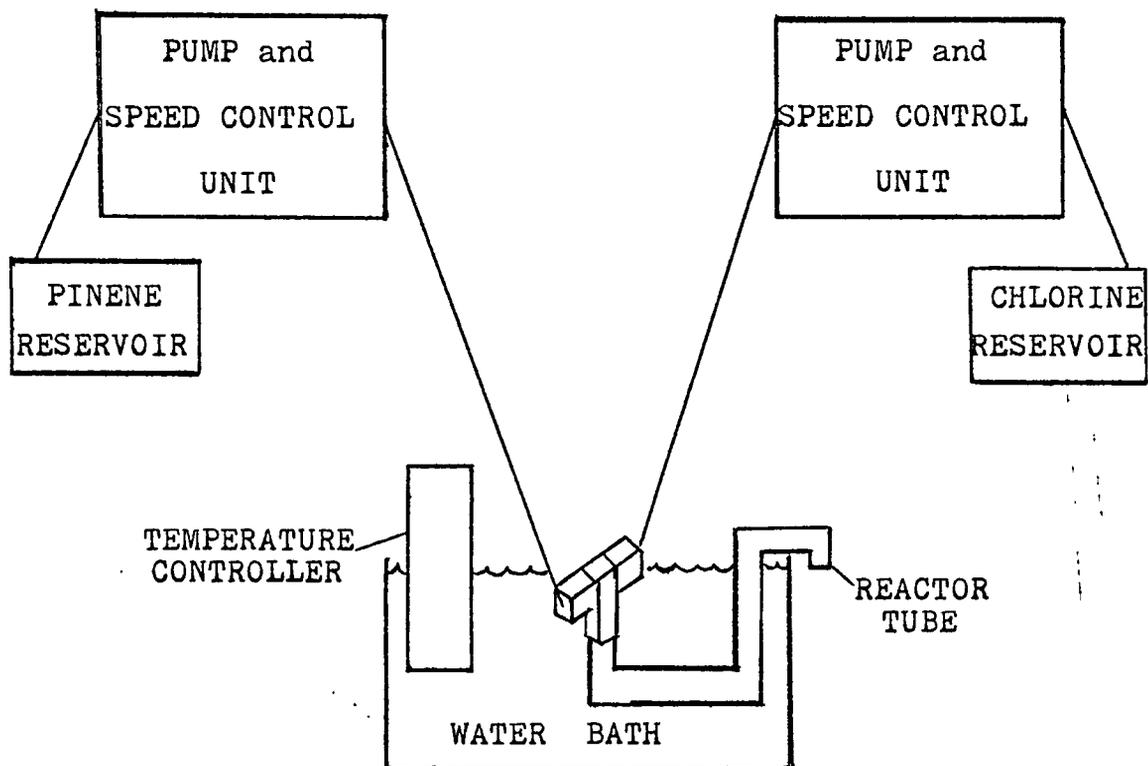


FIGURE 26: Block Diagram of Equipment Setup

TABLE III. EFFECT of FLOW RATE RATIOS and
TEMPERATURES on PRODUCT DISTRIBUTION

RATIO of PUMP SPEED SETTINGS	TEMPER- ATURE	PRODUCT DISTRIBUTION (%)*															
		A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	
1.00	0C	7.7	7.3	7.5	6.7	36.7	-	-	2.6	3.2	22.9	4.1	1.3	-	-	-	
1.00	20C	7.2	7.2	9.4	8.9	36.0	-	-	2.5	3.0	22.4	3.3	-	-	-	-	
4.00	0C	0.7	-	2.2	8.3		2.2	-	10.5	8.0	43.2	14.1	5.4	5.4	-	-	
4.00	20C	1.0	-	7.2	6.6		1.7	-	8.7	6.6	43.1	14.5	5.3	5.3	-	-	
4.00	40C	5.0	-	3.9	5.2		0.8	-	6.3	4.4	33.1	9.9	12.5	4.7	3.9	10.2	
4.00	60C	5.2	-	4.3	5.7		0.6	-	6.3	5.2	32.4	10.3	12.0	6.0	9.7	2.3	
1.00	-10C	5.8	5.6	3.2	4.1	62.6	-	-	0.2	0.4	18.0	-	-	-	-	-	

Flow rates are related to pump speed settings as shown in Figure

*The experiment at -10C was run in chlorobenzene; all others were run in benzene.
Product distributions were determined on an Autoprep gas chromatograph.

TABLE IV. TWO-FACTOR VARIABLE SIZED SIMPLEX
INFORMATION AND RESULTS

<u>VERTEX</u>	<u>RATIO of PUMP SPEED SETTINGS</u>	<u>TOTAL PUMP SPEED SETTINGS</u>	<u>PINENE CONCENTRATION</u>	<u>PER CENT 2,6-DICHLOROCAMPHANE</u>
1	1.00	12.00	0.750M	28.0
2	2.00	12.00	0.750M	40.7
3	1.50	10.30	0.750M	32.3
4	2.50	10.35	0.750M	42.2
5	3.25	9.50	0.750M	39.9
6	3.00	12.05	0.750M	41.8
7	3.50	10.40	0.750M	43.9
8	4.25	9.60	0.750M	44.5
9	3.00	8.60	0.750M	44.2

Chlorine Pump Speed Setting/Pinene Pump Speed Setting
All experiments were run in benzene.
Per cent composition of product mixture as determined on
Autoprep gas chromatograph

TABLE V . . PRODUCT DISTRIBUTION from EXPERIMENTS*
of the TWO FACTOR SIMPLEX.

<u>VERTEX NUMBER</u>	A	B	C	D	E	F	G	H	I	J	K	L
1	6.7	9.3	6.7	6.7	32.4	-	-	2.7	2.7	28.0	4.9	-
2	3.1	1.6	8.4	5.6	10.7	-	-	4.9	5.6	40.7	11.6	7.7
3	4.6	3.8	9.0	5.3	25.7	-	-	3.6	3.6	32.3	8.0	3.9
4	2.2	-	6.3	6.7	1.5	-	-	5.6	6.0	42.2	14.5	14.9
5	2.5	-	5.9	7.0	0.8	-	-	6.2	5.8	39.9	15.3	15.4
6	3.0	-	7.0	9.0	1.0	-	-	5.5	5.2	41.8	14.4	12.9
7	2.8	-	6.2	6.5	0.9	-	-	6.2	5.6	43.9	14.3	13.6
8	2.8	-	4.7	6.3	0.8	-	-	6.3	5.4	44.5	15.6	13.6
9	3.0	-	5.3	6.7	0.9	-	-	6.2	5.5	44.2	15.2	13.0

* See Table IV for experimental conditions.

TABLE VI. THREE-FACTOR VARIABLE SIZED SIMPLEX
INFORMATION AND RESULTS

<u>VERTEX</u>	<u>RATIO of PUMP SPEED SETTINGS</u>	<u>TOTAL PUMP SPEED SETTINGS</u>	<u>PINENE CONCENTRATION</u>	<u>PER CENT 2,6-DICHLOROCAMPHANE</u>
1	2.00	12.00	0.500M	41.3
2	2.00	12.00	0.125M	36.7
3	1.00	12.00	0.500M	33.0
4	2.00	9.00	0.500M	43.6
5	3.00	10.00	0.250M	43.0
6	2.66	8.66	0.709M	46.2
7	2.99	6.99	1.001M	43.4
8	3.10	6.44	0.847M	41.5
9	2.83	7.83	0.667M	43.3
10	2.00	7.00	1.000M	39.1
11	2.75	9.25	0.437M	41.2
12	2.25	7.75	0.813M	37.9

Chlorine Pump Speed Setting/Pinene Pump Speed Setting
All experiments were run in benzene
Per cent composition of product mixture as determined on
Autoprep gas chromatograph

TABLE VII. PRODUCT DISTRIBUTION from EXPERIMENTS*
of the THREE FACTOR SIMPLEX

<u>VERTEX NUMBER</u>	A	B	C	D	E	F	G	H	I	J	K	L
1	3.2		5.5	5.7		1.7	-	7.5	6.0	41.3	15.2	13.8
2	2.5		4.3	10.8		0.8	0.3	5.9	6.5	36.7	14.7	17.5
3	6.3		6.6	29.5		-	-	4.5	5.8	33.0	9.9	4.5
4	2.2		4.1	6.7		0.2	-	8.0	6.1	43.6	13.7	15.6
5	2.6		5.3	6.3		0.5	-	6.8	5.0	43.0	14.3	16.6
6	1.9		3.8	6.5		1.9	-	5.3	3.8	46.2	16.0	14.5
7	2.4		5.1	5.8		1.7	-	6.5	5.4	43.4	15.8	13.8
8	2.7		5.4	18.2		0.4	-	5.4	7.8	41.5	12.0	6.6
9	2.3		4.8	8.4		1.3	-	6.3	7.6	43.3	15.4	11.6
10	2.5		5.1	6.9		1.4	-	6.9	6.9	39.1	15.2	15.9
11	3.4		7.3	7.6		1.2	-	7.3	5.8	41.2	16.1	10.1
12	2.4		5.4	5.4		1.4	-	6.5	4.8	37.9	17.1	19.1

* See Table VI for experimental conditions.

TABLE VIII. CODING of FACTORS in the
CENTRAL COMPOSITE DESIGN

<u>CODED LEVEL</u>	<u>RATIO of PUMP SPEED SETTINGS</u>	<u>TOTAL PUMP SPEED SETTINGS</u>	<u>PINENE CONCENTRATION</u>
-2	0.45	4.90	0.050M
-1	1.00	7.30	0.300M
0	2.20	9.70	0.550M
+1	3.40	12.10	0.800M
+2	4.60	14.50	1.050M

Chlorine Pump Speed Setting/Pinene Pump Speed Setting
Concentration of Pinene in Carbon Tetrachloride
Results of Central Composite Design listed in Tables IX. and X.

TABLE IX. CENTRAL COMPOSITE DESIGN
INFORMATION AND RESULTS

<u>PERFORMANCE ORDER</u>	<u>POINT on CENTRAL COMPOSITE DESIGN</u>	<u>RATIO of PUMP SPEED SETTING</u>	<u>TOTAL PUMP SPEED SETTINGS</u>	<u>PINENE CONCENTRATION</u>	<u>PER CENT YIELD of 2,6-DICHLOROCAMPHANE</u>
11	7	-1	-1	-1	20.2
19	7	-1	-1	-1	19.5
6	5	-1	-1	+1	12.9
5	6	-1	+1	-1	21.9
13	6	-1	+1	-1	20.6
10	8	+1	-1	-1	20.8
15	4	+1	-1	+1	19.3
16	4	+1	-1	+1	20.1
12	14	+1	+1	-1	20.2
4	3	+1	+1	+1	19.4

TABLE IX. (CONTINUED)

21	3	+1	+1	+1	19.9
20	2	-1	+1	+1	16.5
18	15	0	0	-2	22.0
9	10	0	-2	0	20.3
7	11	-2	0	0	12.3
2	1	0	0	+2	21.0
14	1	0	0	+2	22.7
1	9	0	+2	0	22.3
8	12	+2	0	0	22.2
3	13	0	0	0	22.1
17	13	0	0	0	22.5

TABLE X. PRODUCT DISTRIBUTION from EXPERIMENTS
of the CENTRAL COMPOSITE DESIGN

<u>EXPT ORDER</u>	A&B	C	D&E	F	G	H	I	I'	J	K	L
11	7.4	6.9	39.5	0.4	-	5.4	2.2	-	34.4	3.7	-
19	7.1	5.2	42.3	-	-	5.3	1.4	-	34.3	4.3	-
6	57.1	5.0	18.7	-	-	1.8	1.0	-	14.7	1.7	-
5	2.0	3.8	8.6	1.3	-	17.6	4.2	0.7	38.5	14.2	9.2
13	1.9	3.5	8.9	1.2	-	16.5	3.7	1.0	37.4	14.7	11.1
10	1.5	2.2	4.3	2.1	-	17.4	3.7	0.6	38.8	15.8	13.6
15	2.1	2.8	4.2	1.9	-	16.5	4.3	-	40.0	15.7	12.5
16	2.0	3.0	4.8	1.8	-	16.9	3.9	0.8	38.8	15.8	12.1
12	1.5	2.5	3.8	2.2	-	18.1	3.6	0.6	40.2	13.3	14.1
4	2.2	1.9	3.6	1.4	0.2	17.0	4.9	1.0	42.3	15.8	9.6

TABLE X. (CONTINUED)

21	2.1	2.5	5.0	2.1	-	16.1	4.1	-	40.4	14.5	13.2
20	17.9	6.8	43.2	-	-	2.1	1.6	-	26.8	1.6	-
18	0.9	1.3	6.7	2.2	1.3	22.2	4.0	-	40.0	12.0	9.3
9	0.3	2.0	5.0	2.2	-	18.6	5.0	0.6	40.1	15.6	10.5
7	76.7	1.9	13.1	-	-	0.6	0.3	-	6.8	0.5	-
2	2.3	4.0	9.1	1.6	-	16.7	4.7	0.8	39.3	13.3	8.1
14	2.6	4.5	11.8	1.4	-	14.8	3.9	0.6	37.0	13.8	9.6
1	2.0	2.4	5.2	1.6	0.5	15.6	4.5	0.9	39.3	15.9	12.0
8	1.8	2.5	4.0	2.4	-	17.4	4.6	0.6	41.2	13.4	12.0
3	1.8	2.0	4.3	1.5	-	16.7	5.3	-	38.9	15.7	13.8
17	1.4	3.1	4.5	1.5	-	15.7	3.6	0.6	41.9	15.1	12.1

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