

MECHANISM STUDIES OF THE
RETROPINACOL REACTION

By

LAMAR BISHOP PAYNE

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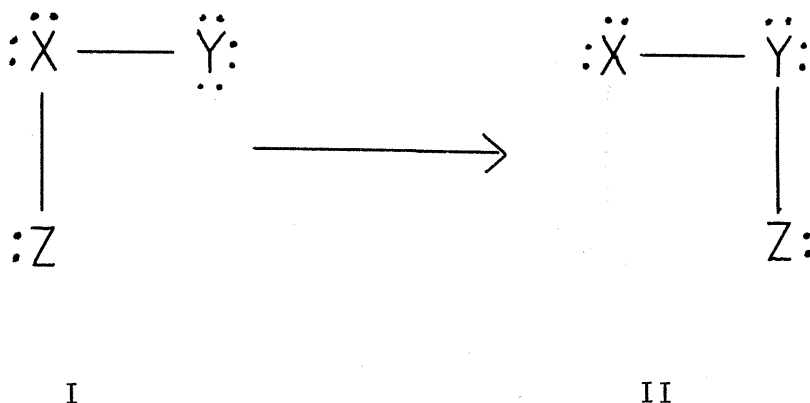
INTRODUCTION

The purpose of this study was to synthesize the p-toluene-sulfonates and methanesulfonates of cis- and trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol and to determine their behavior toward solvolytic and substitution reactions in regard to correlating possible rearrangements with a proposed mechanism for the retropinacol or Wagner-Meerwein rearrangements.

CHAPTER I

HISTORICAL

The retropinacol rearrangement belongs to a class of carbon skeletal rearrangements generally described as 1,2-shifts.¹ This class of reactions can be represented in a formal sense by a symbolized equation in which an atom or group Z, initially bonded to atom X, the migration origin, migrates to an adjacent atom Y, the migration terminus. The electron pairs shown in structures I and

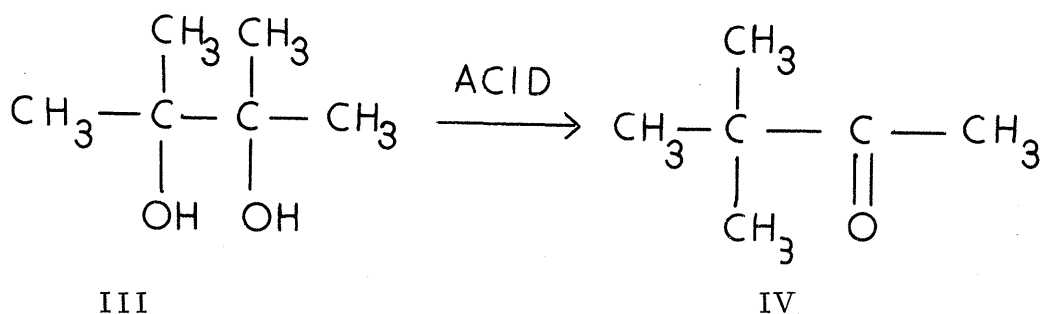


II are usually involved in covalent bonds to other atoms or groups. This schematic equation does not describe any mechanistic aspect

¹G. W. Wheland, "Advanced Organic Chemistry," 3rd Ed., John Wiley and Sons, Inc., New York, 1961, p. 537.

of such rearrangements, but indicates only the extent of structural or skeletal change.

One of the most familiar examples of this reaction type is the acid-catalyzed rearrangement of tetramethylethylene glycol (pinacol) (III) to give methyl tert-butyl ketone (pinacolone) (IV) as shown below. This reaction constitutes only the simplest

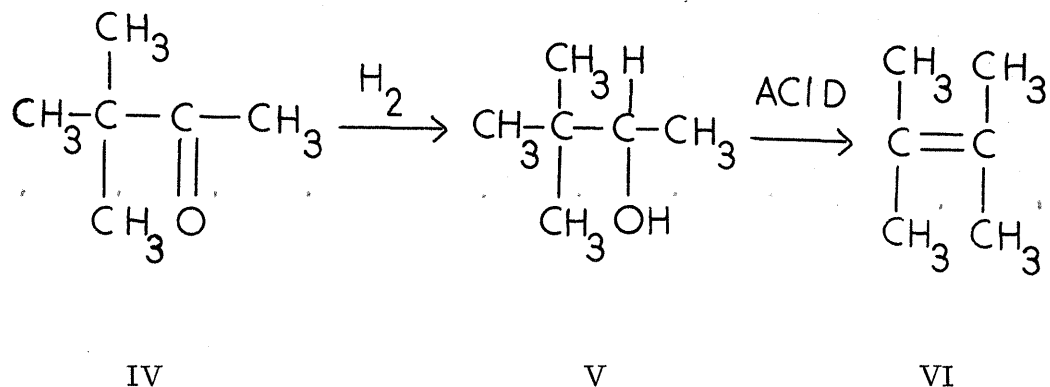


example of a large class of reactions described as the pinacol rearrangements.² Substitution of other groups for the methyl groups gives rise to innumerable possibilities for examples of this reaction type. In each case the rearrangement consists of a migration of a carbon-bonded group to an adjacent carbon.

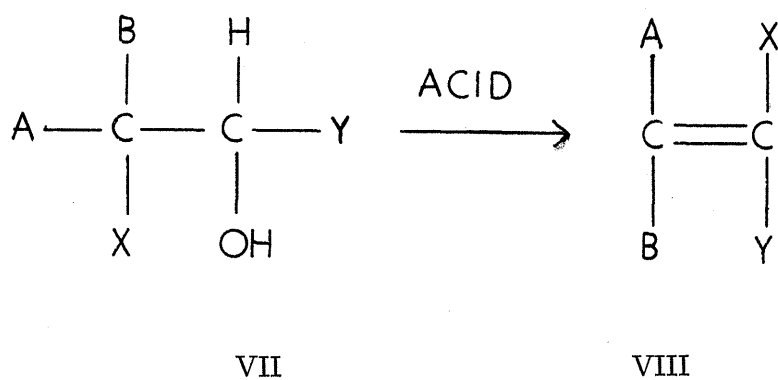
The reduction of the ketone IV gives methyl tert-butylcarbinol (pinacolyl alcohol) (V). In 1901 Zelinsky and Zelikow³ carried out an acid dehydration with this alcohol expecting to obtain tert-butyl-ethylene. The product, however, was found to be

² C. J. Collins, Quart. Rev. Chem. Soc., **4**, 357 (1960).

³ N. Zelinsky and J. Zelikow, Ber., **34**, 3249 (1901).



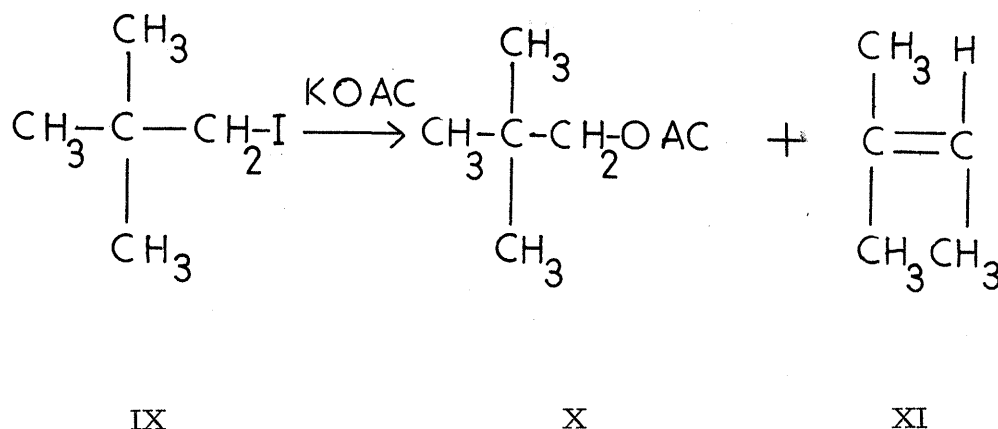
tetramethylethylene (VI), a product of rearrangement of the carbon skeleton. This can be viewed as a reverse pinacol or retropinacol rearrangement which can be schematically represented by the following equation. This, again, constitutes a 1,2-shift in the



carbon skeleton.

The dehydrohalogenation of an alkyl halide, as in the case of the dehydration of an alcohol, is frequently accompanied by a skeletal rearrangement of the retropinacol type. For example,

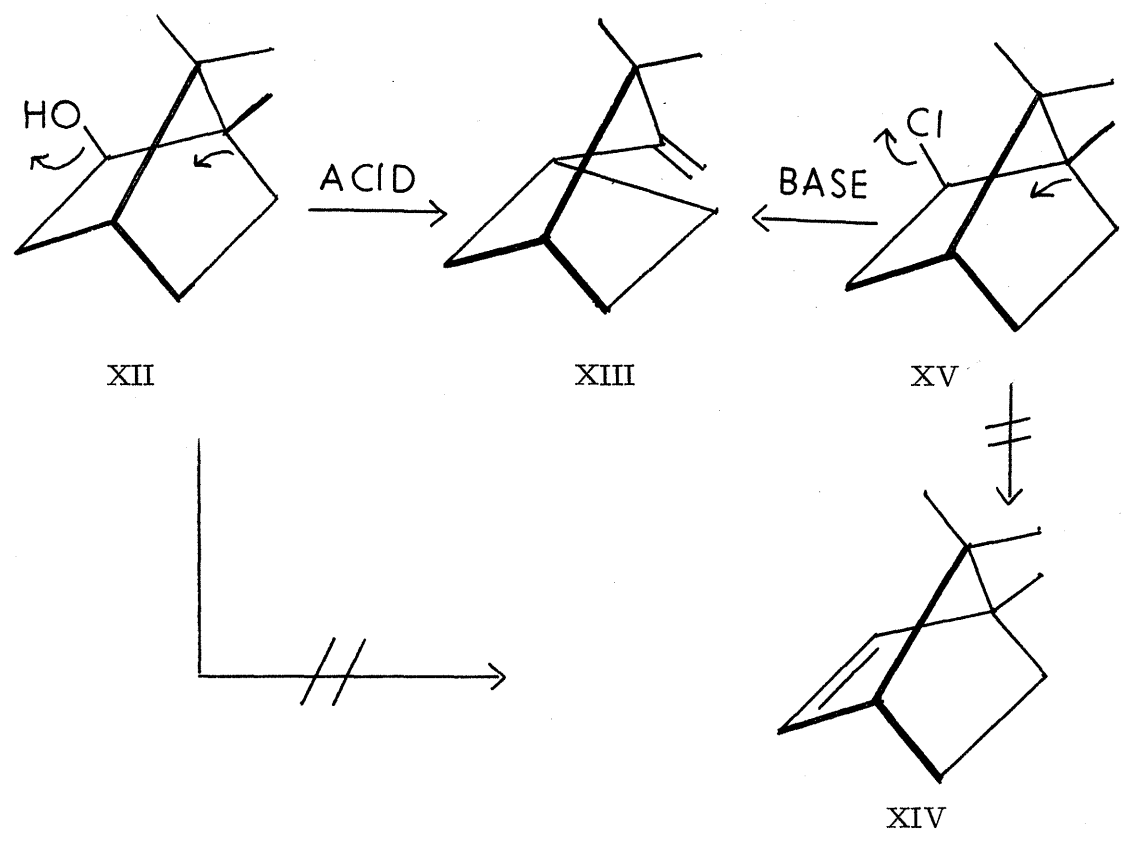
the bimolecular reaction of potassium acetate with neopentyl iodide (IX) in absolute ethanol gives not only the expected neopentyl acetate (X), but the rearranged product, trimethylethylene (XI) as well.⁴



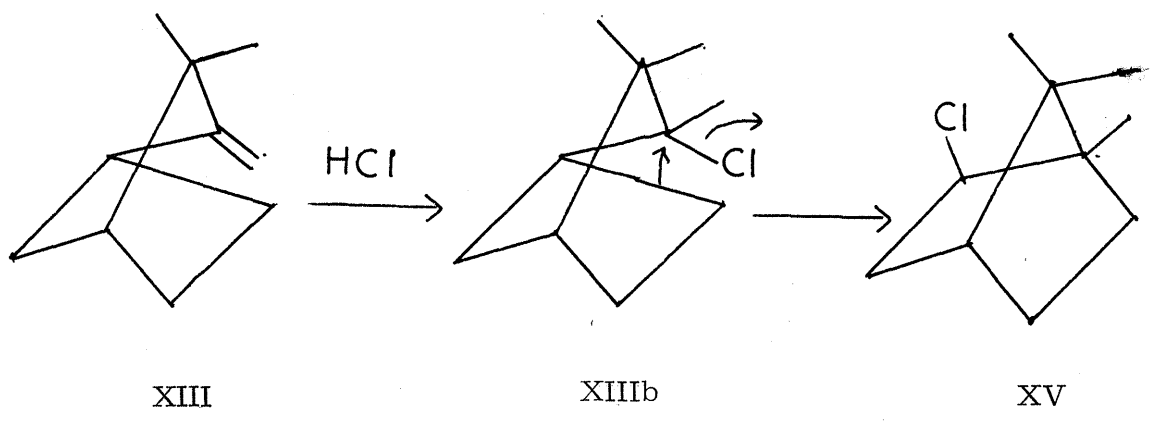
Such skeletal rearrangements occurring in terpenes are often referred to as Wagner or Wagner-Meerwein rearrangements.⁵ The dehydration of isoborneol (XII) by acidic reagents, sulfuric acid, zinc chloride and phosphoric acid, gives camphene (XIII) rather than the expected bornylene (XIV). In the same manner isobornyl

⁴ F. C. Whitmore, E. L. Wittle, and A. H. Popkin, J. Am. Chem. Soc., **61**, 1586 (1939).

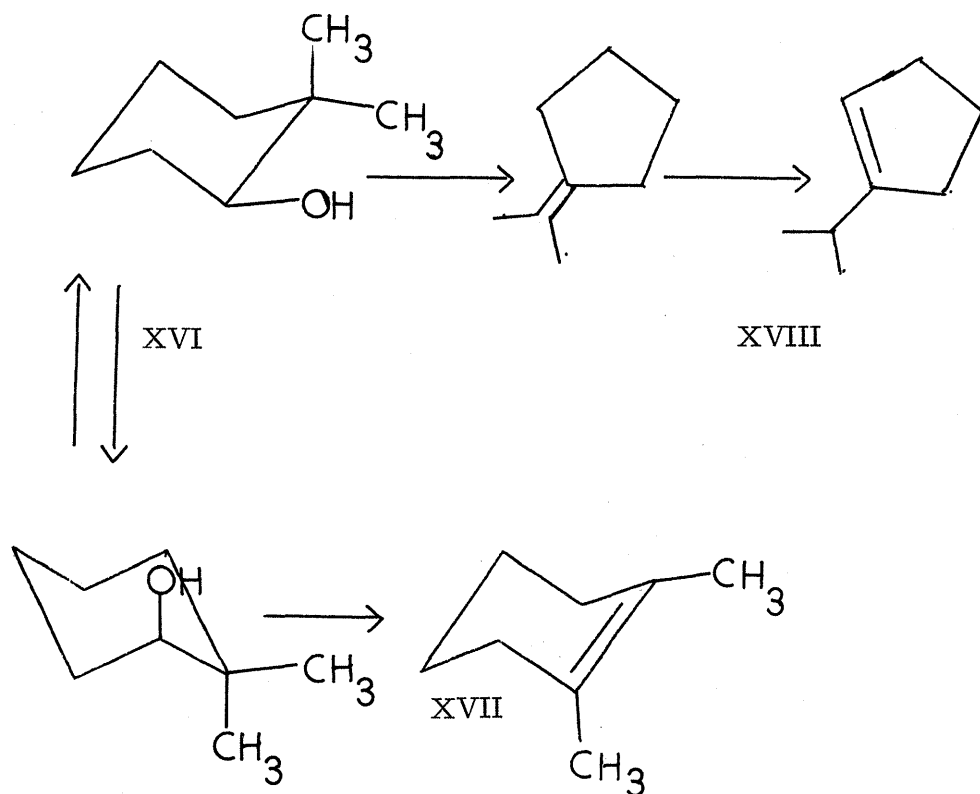
⁵ G. W. Wheland, "Advanced Organic Chemistry," 3rd Ed., John Wiley and Sons, Inc., New York, 1961, p. 540.



chloride (XV) heated, or by reaction with base, gives camphene rather than bornylene. In the reverse respect the addition of hydrogen chloride to camphene yields first the camphene hydrochloride (XIIIb) which subsequently rearranges to isobornyl chloride.



Wagner in 1899 considered rearrangements of the retropinacol type to be essential for the interpretation of the interconversions among bicyclic terpenes. After the work of Zelinsky and Zelikow had extended the rearrangement beyond the bicyclic field to the simple alicyclics, Meerwein⁶ demonstrated its application to a simple monocyclic case. The dehydration of 2,2-dimethylcyclohexanol (XVI) was effected with the acidic reagents, zinc chloride, potassium bisulfate, or oxalic acid. Two rearranged products were given, 1,2-dimethylcyclohexene (XVII) and 1-isopropylcyclopentene (XVIII).



⁶ H. Meerwein, Ann., **405**, 129-175 (1914).

This system can be recognized immediately as the cyclic analogue of pinacolyl alcohol. More than one mode of skeletal rearrangement gives rise to different rearranged products. Isopropylidenecyclopentane was not isolated as such, but was postulated as an intermediate in the formation of XVIII.

In certain of the early attempts toward a mechanistic interpretation of the retropinacol rearrangement, cyclic intermediates, cyclopropanes and epoxides, were postulated.^{7, 8} Since the chemical properties of these three-member rings were poorly understood at this time, it was hardly possible to demonstrate their presence as intermediates.

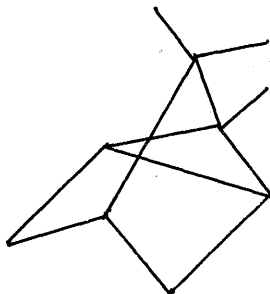
After the epoxy systems were more fully investigated, the epoxide theory was discarded. Few instances could be found in which the epoxide could be isolated and/or rearranged to the product.⁹ Possibly the greatest objection to the theory was that the formation of an intermediate ethylene oxide, even if correct, could not explain the 1,2-shift. Formation of the end product must still involve rearrangement of the epoxy intermediate.

⁷ E. Erlenmeyer, Ber., 14, 322 (1881).

⁸ A. Brecier and T. Zincke, Ann., 198, 141 (1879).

⁹ G. W. Wheland, op. cit., p. 540.

That a cyclopropane intermediate could not account for rearrangement in terpene systems has been shown by Meerwein and van Emster.¹⁰ In the conversion of isoborneol (XII) to



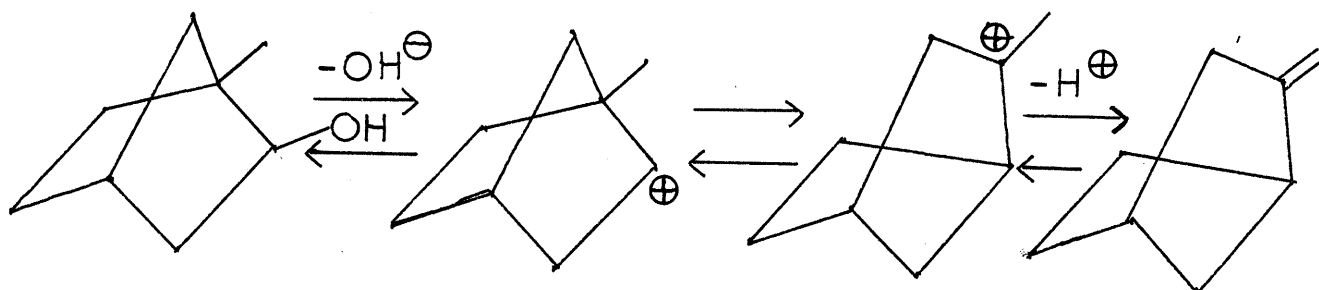
XIX

camphene, the known tricyclene, 1-methyltricyclo-[2.2.1.0]-heptane (XIX) was considered an intermediate. Isoborneol is converted to camphene readily in 33% aqueous sulfuric acid. However, under these conditions, the tricyclene does not undergo such a reaction. Hence, it cannot be an intermediate. Though the same intermediate could be postulated for the conversion of camphene to isobornyl chloride, both these compounds can be optically active, since neither contains a plane nor center of symmetry. The tricyclene is inactive since it is symmetrical. If this intermediate

¹⁰ H. Meerwein and K. van Emster, Ber., 53, 1815 (1920).

intervened in the conversion, the result would be a complete racemization of the product. It is found experimentally, however, that (+)-isobornyl chloride can be converted to (-)-camphene.

The retropinacol rearrangement was first described as an equilibrium of ionic intermediates by Meerwein and van Emster in 1922.¹¹ This work as well as that of Stieglitz¹² and others provided



the underlying concepts for Whitmore's well known theory, a comprehensive explanation of the 1,2-shift.¹³

Whitmore's formulation of a generalized mechanism for simple 1,2-shifts involves three essential stages:^{14, 15}

¹¹ H. Meerwein and K. van Emster, Ber., 55, 2500 (1922).

¹² J. Stieglitz and B. Stagner, J. Am. Chem. Soc., 38, 2047 (1916).

¹³ F. C. Whitmore, J. Am. Chem. Soc., 54, 3274 (1932).

¹⁴ G. W. Wheland, op. cit., p. 540.

¹⁵ F. E. Condon and H. Meislich, "Introduction to Organic Chemistry," Holt, Rinehart, and Winston, Inc., New York, 1960, p. 795.

1. Formation of an unstable intermediate involving an electron deficient carbon with only six electrons by means of:
 - a. Spontaneous loss of an atom or group.
 - b. Loss of a group due to an attack by another reagent.
2. Migration of a group from an adjacent atom to fill the valence shell of the original electron deficient carbon atom giving a more stable structure, but retaining a different electron deficient center.
3. Neutralization of the electron deficiency by reaction to form the product.

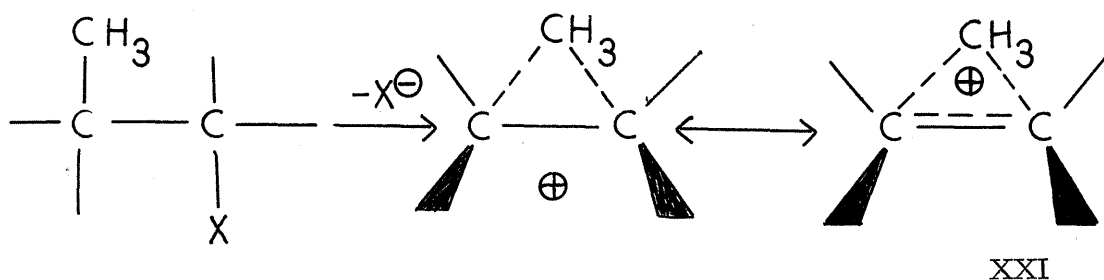
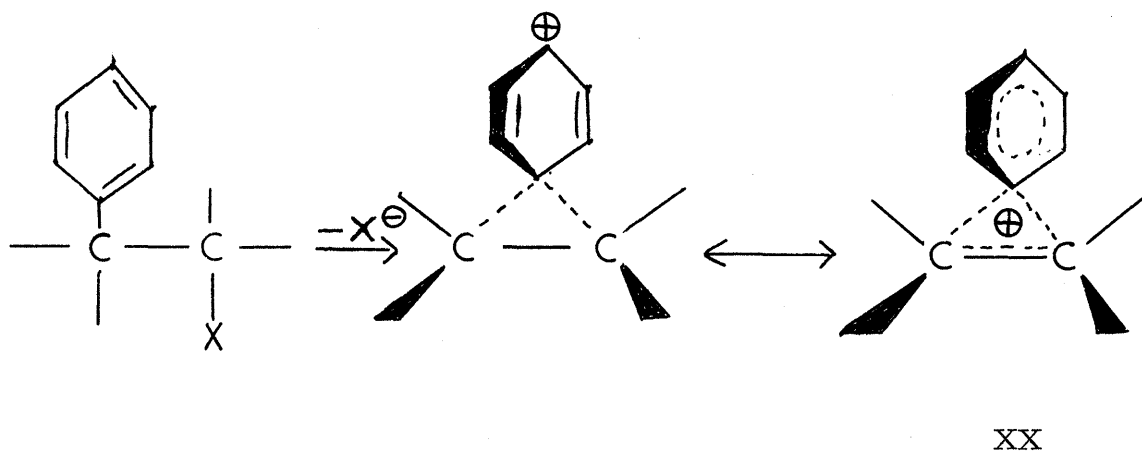
It was postulated that these three processes do not necessarily occur in distinct, consecutive steps, but may occur, in varying degrees, simultaneously.

More recent investigations of a great number of reactions involving 1,2-shifts about asymmetric centers have shown the rearrangement to be stereospecific with respect to the migration origin and migration terminus.^{16, 17}

¹⁶ M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, 1956, pp. 251, 253-254.

¹⁷ E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, 1959, p. 586.

The stereospecificity at these centers indicates that the Whitmore theory of a free carbonium ion intermediate is inadequate. A more concise view would require the migrating group to undergo, at least partially, bond formation to the migration terminus from the rear, either before or as the leaving group departs. An intermediate of this type would involve bonding between the migrating group and the migration origin and terminus simultaneously. This can be depicted by use of molecular orbital theory, and is exemplified in work by Cram.¹⁸ In XX and XXI the migration origin and

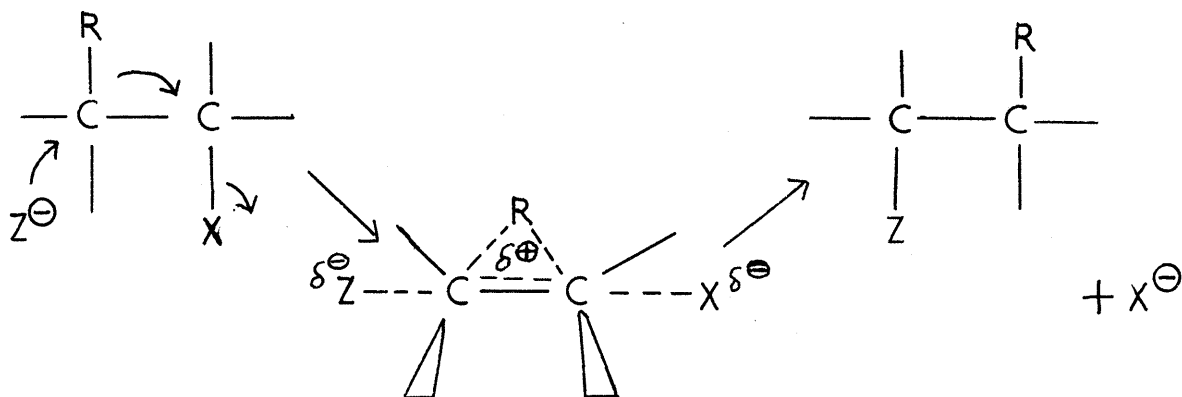


¹⁸ D. J. Cram, J. Am. Chem. Soc., 71, 3863 (1949).

terminus are sp^2 hybridized and are joined by a π -bond (represented by broken lines), which overlaps with a p-orbital of the central atom of the migrating group. These structures are resonance hybrids and are referred to as nonclassical ions or bridged intermediates.

The reaction product (or products) is then formed by a nucleophilic attack at one of the carbons of the bridged intermediate.

There exists the possibility that such a process might occur in a concerted manner in which the attack of the nucleophile, the migration, and the departure of the leaving group would occur simultaneously:

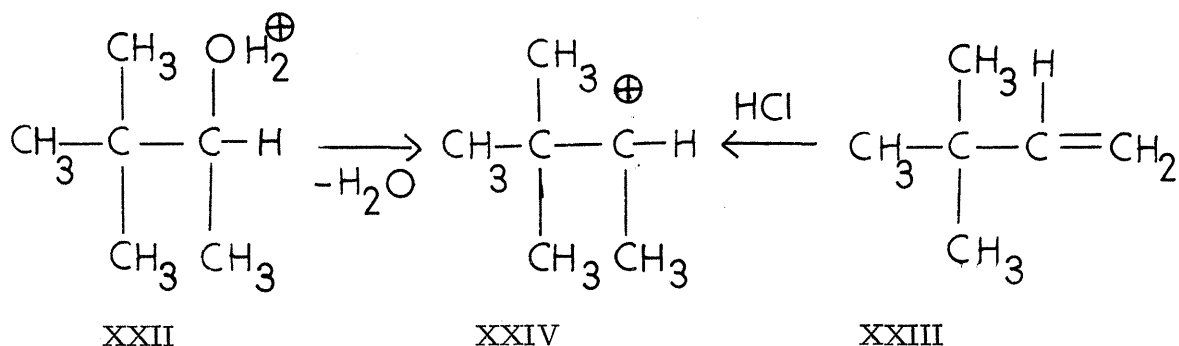


In such a process the two carbons comprising the origin and terminus would be sp^2 hybridized and surrounded by an envelope of π -electron density which is shared not only by the central carbon of the migrating group, but by the nucleophile and leaving group as well. The behavior of a concerted reaction of this type would be a function of the nucleophilic character of the attacking

group, the steric requirements of the groups about the beta carbon and their electrostatic field effects, the character of the leaving group, and the migratory aptitude of the migrating group.

This concerted type of mechanism which involves attack at a beta carbon has been advanced and applied by Scott¹⁹ to Wagner-Meerwein type rearrangements to account for otherwise anomalous results. The mechanism enables prediction of the migratory tendency of a particular group on the basis of steric or electrostatic effects about the carbon in a beta position to the leaving group.

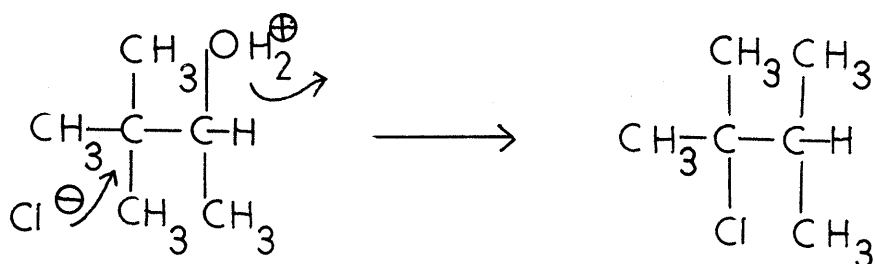
Evidence supporting this mechanism is found in the case of the action of hydrogen chloride on pinacolyl alcohol as compared to the addition of hydrogen chloride to tert-butylethylene (XXIII). If



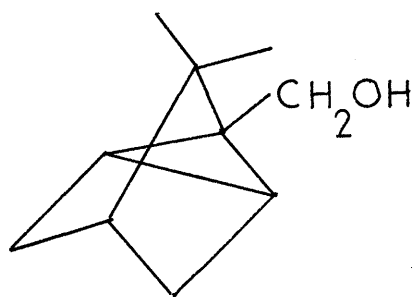
the instability of the intermediate carbonium ion were the only factor governing the rearrangement, then about the same degree of rearrangement should occur in both cases since the carbonium ion,

¹⁹R. B. Scott, Jr., and J. B. Gayle, J. Org. Chem., **18**, 740-744 (1953).

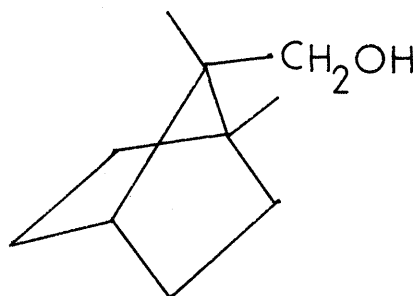
in both cases, is identical. In the first case, however, almost total rearrangement occurs; in the second only 60%. It can readily be seen that a beta attack on the oxonium ion would augment the formation of the rearranged product.



The effect of steric interaction due to bulky groups at a beta carbon accounts for non-rearrangement of such compounds as tricyclol (XXV) and 8-hydroxycamphane (XXVI) in their conversion to the chlorides by phosphorus pentachloride. The attack of a



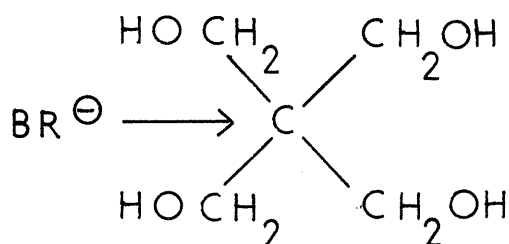
XXV



XXVI

chloride ion at the carbon beta to the hydroxyl group in either of the above compounds would be prohibited by the steric bulk of the bicyclic structures.

In view of the well known tendency of neopentyl alcohol²⁰ and its derivatives²¹ to rearrange in acidic media, pentaglycol would also be expected to undergo rearrangement under similar conditions. In preparation of the bromides of pentaglycol²² and pentaerythritol²³ good yields are obtained with no accompanying rearrangement. This suggests that the high electron density of the hydroxy groups repel the attacking nucleophile:



This electrostatic field effect is most likely enhanced by the ability of the electronegative group, or groups, to rotate about the axis of attack.

A case closely analogous to the retropinacol rearrangement might be adequately explained by the idea of an indirect attack at the

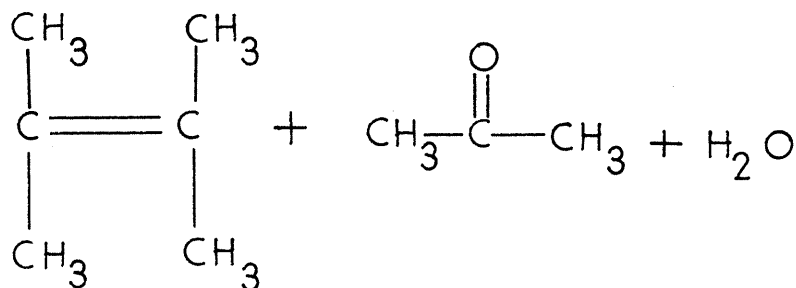
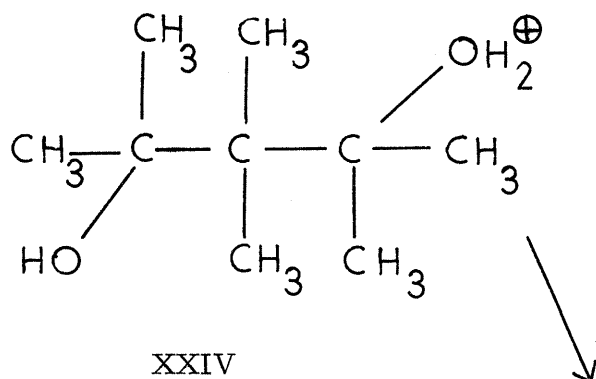
²⁰ F. C. Whitmore and H. S. Rothrock, J. Am. Chem. Soc., **54**, 3431 (1932).

²¹ F. B. Bordwell, B. N. Pitt and M. Knell, J. Am. Chem. Soc., **73**, 5004 (1951).

²² F. C. Whitmore, A. H. Popkin, H. I. Bernstein and J. P. Wilkins, J. Am. Chem. Soc., **63**, 124 (1941).

²³ A. H. Blatt, "Organic Syntheses," Collective Volume II, John Wiley and Sons, Inc., New York, 1943, p. 476.

beta carbon atom. Slavajanow²⁴ has shown that acidic dehydrations of 1-3-diols result in fragmentation. The course of the reaction is formally similar to a pinacol-pinacolone rearrangement. Hexamethyltrimethylene glycol (XXIV) gives acetone, tetramethylethylene, and water on acidic dehydration. In such a process, formation of a



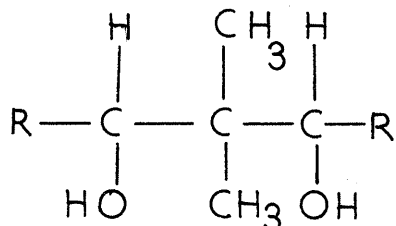
more stable carbonium ion, an idea inherent in Wheland's "intrinsic migratory aptitude," could hardly be an influence motivating the reaction.

²⁴ A. N. Slavajanow, *J. Russ. Phys. Chem. Sec.*, **39**, 140-60 (1907). *C.A.*, **1**, 2077 (1907).

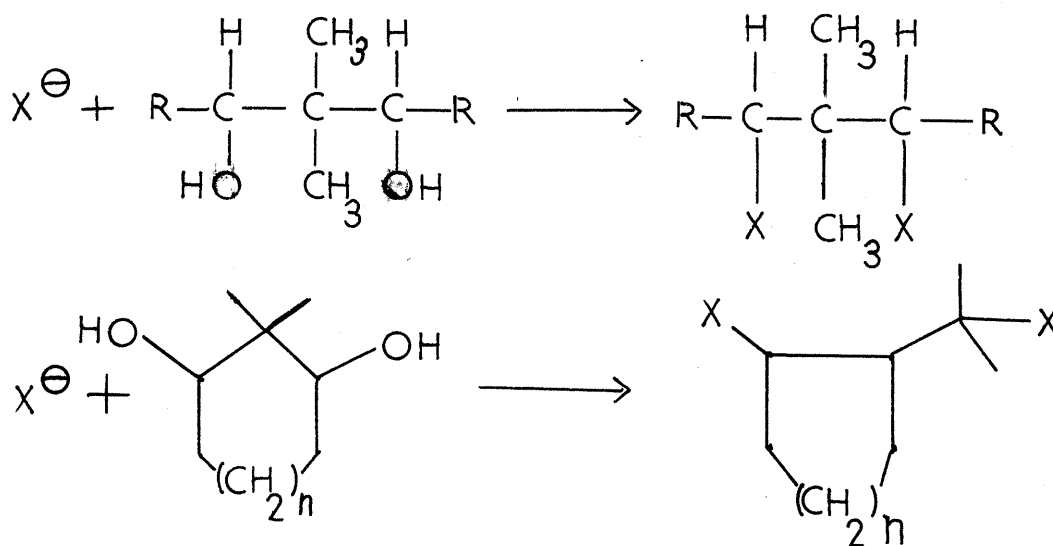
CHAPTER II

THEORETICAL

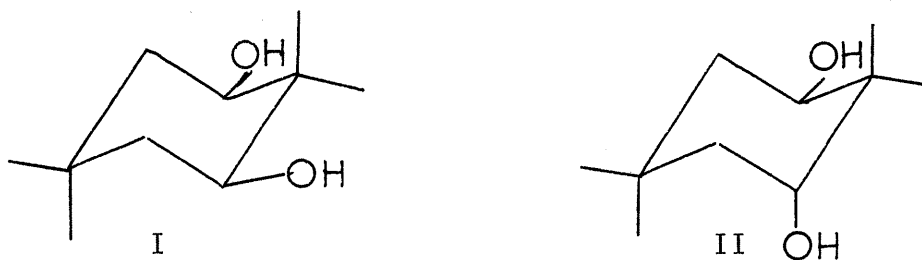
In order to ascertain the degree of the effect of electrostatic repulsion toward a nucleophile attacking at the beta carbon in a system of the type illustrated below, it is necessary to choose a cyclic system of this type such that the field effect would be held to a minimum due to restricted rotation about the site of attack.



If it could be shown that a Wagner-Meerwein type rearrangement occurs in such a cyclic system and does not occur in the analogous open chain compound under the same conditions, this would provide evidence for initiation of the rearrangement by a nucleophilic attack at the carbon alpha to the migration terminus. This is shown in the generalized formulation below.



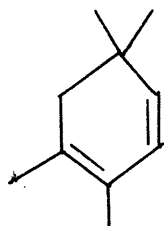
Rearrangements in cyclic 1,3-diol systems have been investigated by Scott and Hendrix.¹ Two isomers of the cyclic 1,3-diol, 2,2,5,5-tetramethyl-1,3-cyclohexanediol, (I) and (II), were subjected to dehydration with phosphoric acid:



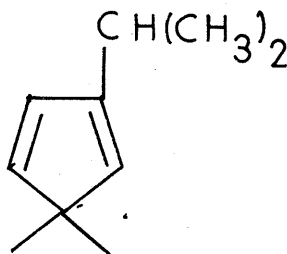
Olefinic products were obtained in both cases. Oxidative degradation indicated the cis isomer I to yield mainly 1,2,5,5-tetramethyl-1,3-cyclohexadiene III, and the trans isomer, a mixture of III and

¹W. R. Hendrix, "Retropinacol Rearrangements, The Effect of Structure," Master's Thesis, University of Alabama, 1956.

3-isopropyl-1,3-cyclopentadiene (IV).

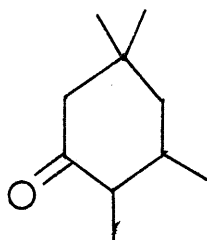


III

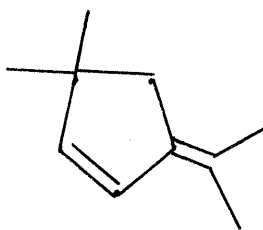


IV

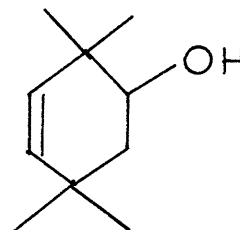
Similarly, Allan and Sneed² carried out the same type of acidic dehydration on I and II using potassium acid sulfate at a somewhat higher temperature. Three products, 2,3,5,5-tetramethylcyclohexanone (V), 1,1-dimethyl-3-isopropylidene-2-cyclopentene (VI), and 2,2,5,5-tetramethyl-3-cyclohexenol (VII), were obtained in varying amounts from each of the isomers.



V



VI



VII

²A. W. Allan, R. P. A. Sneed, and J. M. Wilson, J. Chem. Soc., 2186 (1959).

Though it is significant that retropinacol rearrangements occurred in each of these cases, it is not, at the same time, possible to unequivocally attribute the cause of the rearrangements to nucleophilic attack at the beta carbon for at least three reasons:

1. The hydroxyl group, involved in each case, is a poor leaving group in basic or neutral media.^{3,4} The ability of the hydroxyl as a leaving group in acidic media depends on an intermediate protonated specie, an oxonium ion, from which a neutral water molecule departs. Considering the facile formation of a carbonium ion under these conditions, it is difficult to preclude the possibility that the driving force of the reaction is the instability of this intermediate.
2. The reaction products are those resulting from elimination rather than from substitution reactions. This is not a strict cyclic analogy to the open chain compounds where the products are those of substitution, e. g., in the unrearranged conversion of pentaglycol into the bromide (p. 16).

³ E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, 1959, p. 261.

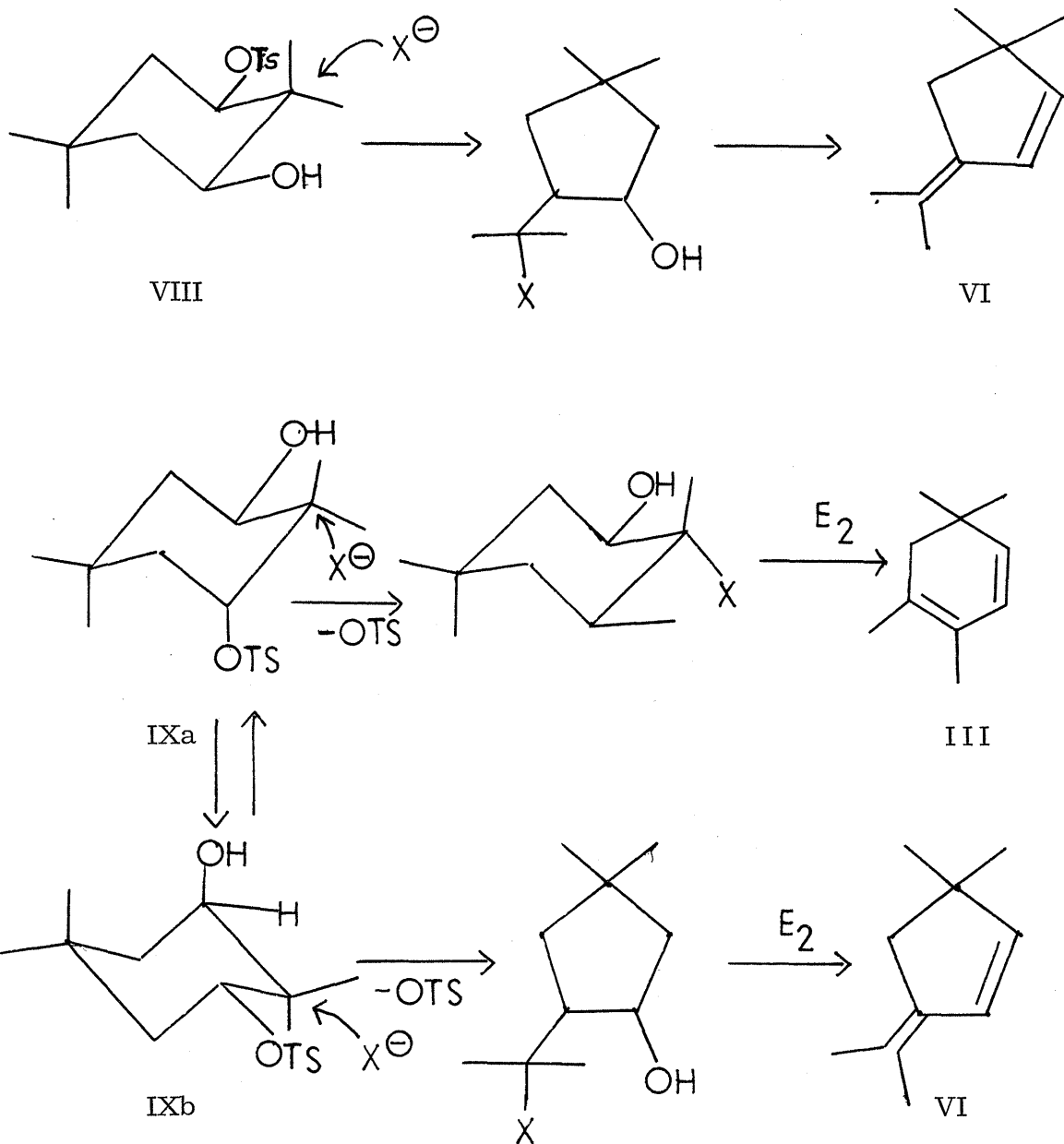
⁴ D. J. Cram and G. S. Hammond, "Organic Chemistry," McGraw-Hill Book Co., Inc., Boston, 1959, p. 216.

3. For a rigorous demonstration of the beta attack, kinetic data would be necessary showing the rate of reaction to be dependent on the concentration of both the nucleophile and the diol or at least that the overall rate expression include terms involving the attacking specie. The importance of the latter in the rate equation would determine the extent to which this mechanism intervenes in the course of rearrangement.

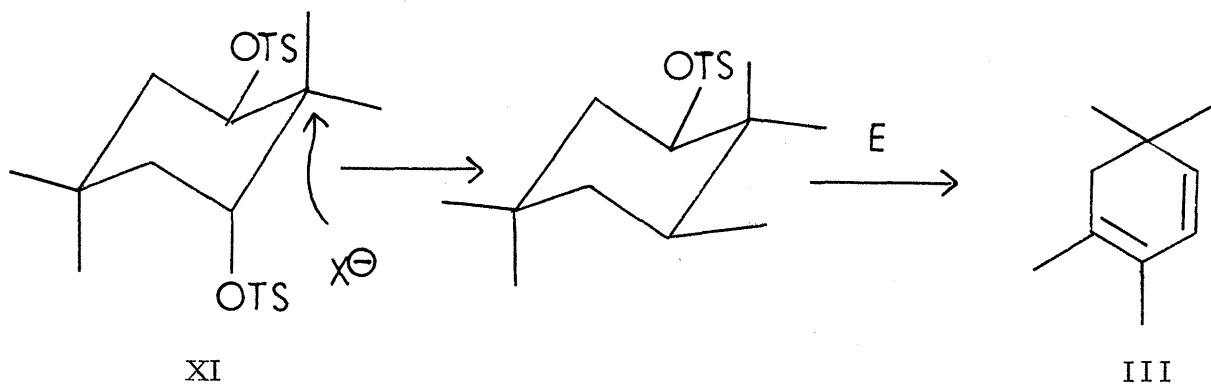
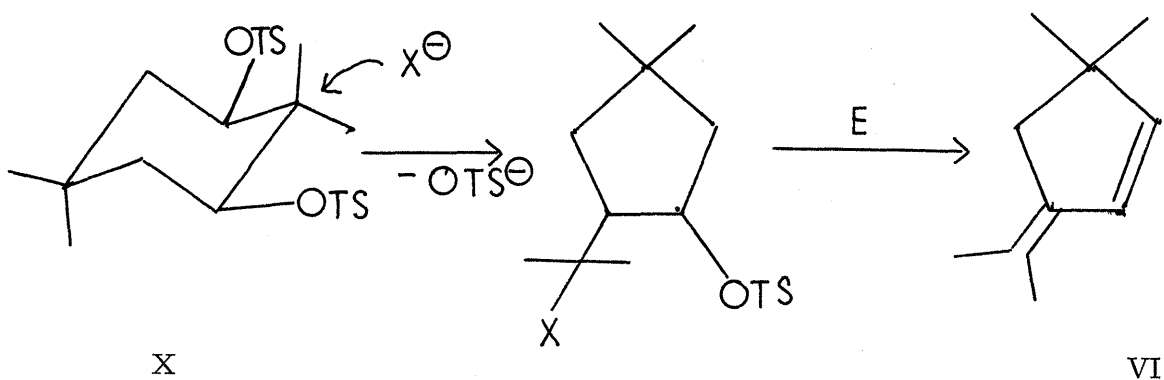
In order to investigate the further feasibility of this mechanism, it is necessary to acquire a molecular structure containing groups which are capable of departing readily as the beta attack occurs. The properties of p-toluenesulfonate and methanesulfonate substituents as leaving groups are well known.⁵ Such a system would be more likely to yield products resulting from substitution as well as those from elimination reactions. The recovery and characterization of substitution products would allow a more valid correlation with the starting material in regard to the driving force and the course of the rearrangement. For analogy to the reactions outlined on p. 19, the synthesis and study of the behavior of the p-toluenesulfonates and methanesulfonates of 2,2,5,5-tetramethyl-1,3-cyclohexanediol was undertaken.

⁵ E. S. Gould, op. cit., pp. 251, 261, 265.

If the mono-p-toluenesulfonates (tosylates) give rearrangement analogous to the retropinacol reaction, the following reaction types could be expected. X^- = a nucleophile, OH^- or OAc^- (acetate).



The bis-p-tosylates on undergoing the same type of rearrangement can be represented by the following sequence:



On the basis of an attack at the beta carbon, the cis-2,2,5,5-tetramethyl-1,3-cyclohexanediol mono-p-tosylate (VIII) should give predominantly one rearranged product with a five-membered ring or the olefin VI. There are two products possible from rearrangement of the trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol

mono-p-tosylate, depending on the reaction conformation of the tosylate. The conformation IXa in which the tosylate group occupies the axial position would be one of higher energy than IXb in which the tosylate group occupies the equatorial position. If rearrangement occurs with the more stable conformer, the reaction would proceed to give a substitution product with a five membered ring or olefin VI.

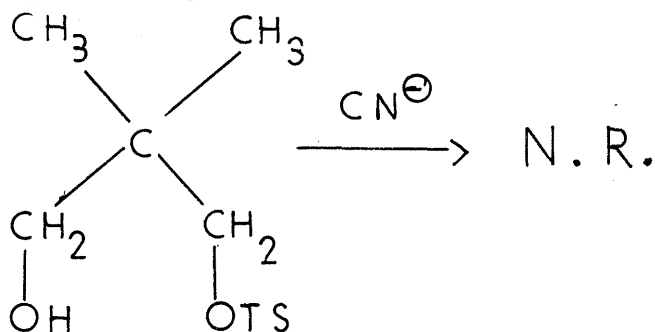
Accordingly, the cis- and trans-bistosylates might be expected to react in the same manner. Since large amounts of olefins arising from elimination reactions are usually formed on solvolytic and substitution reactions with cyclohexyl tosylate esters,⁶ the probable olefinic compounds are included in the above equations.

It is significant to note that skeletal rearrangement does not occur in an open chain compound of similar structure. The mono-⁷ and bis-p-toluenesulfonates⁸ of pentaglycol, (XII) and (XIII), on reflux with potassium cyanide in ethanol, give, in the first case, no reaction and in the second, a substituted cyanide. Two

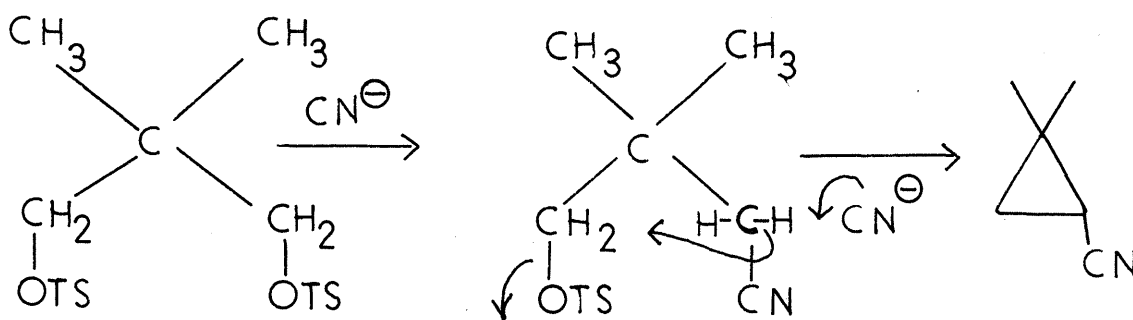
⁶ D. J. Cram, op. cit., p. 205-206.

⁷ R. F. Brown and N. M. van Gulick, J. Am. Chem. Soc., 77, 1089 (1955).

⁸ E. R. Nelson, M. Maienthal, L. A. Lane and A. A. Benderly, J. Am. Chem. Soc., 79, 3467-9 (1957).



XII



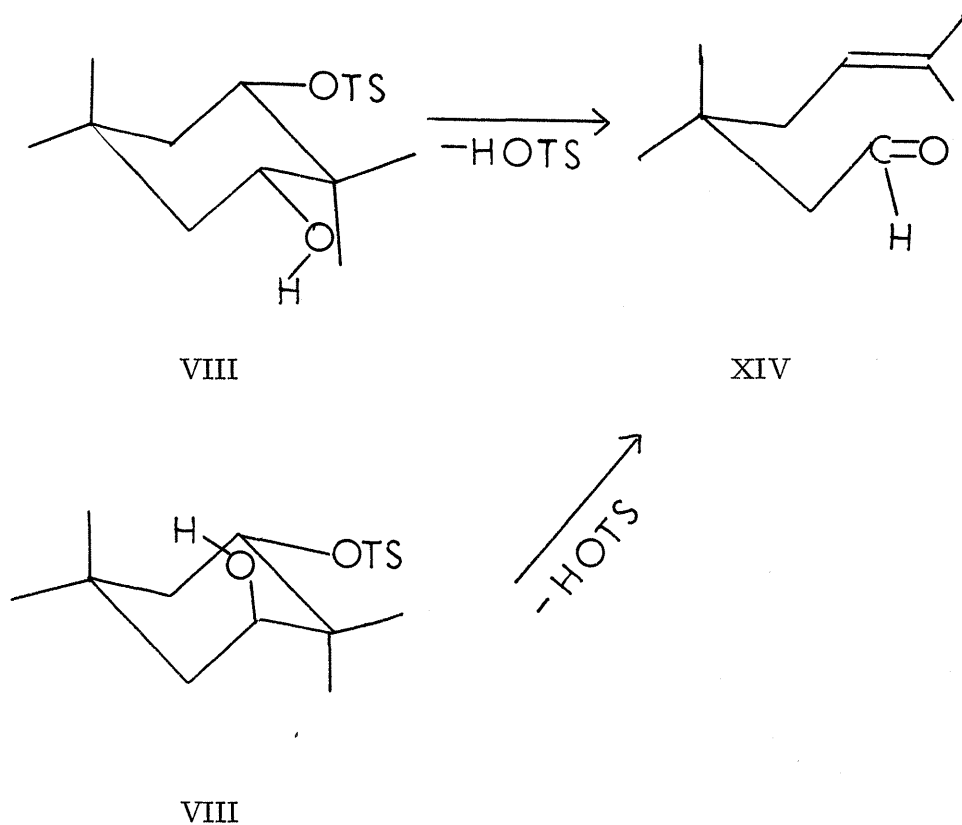
XIII

XIIIa

consecutive displacement reactions account for the formation of the 2,2-dimethylcyclopropyl cyanide (XIIIa). The behavior of these compounds serves as a basis for evaluating the tendency toward rearrangement of their cyclic analogs in terms of the beta attack proposition. Since there is no rearrangement in these esters on attack by a nucleophilic agent, i. e., the cyanide ion, and if the cyclic diol tosylates rearrange, it might be concluded that restricted rotation of the hydroxymethylene and tosylate groups reduce their electrostatic or field repulsion toward the attacking nucleophile and

hence the beta nucleophilic attack plays a significant role in retropinacol and pinacol rearrangements.

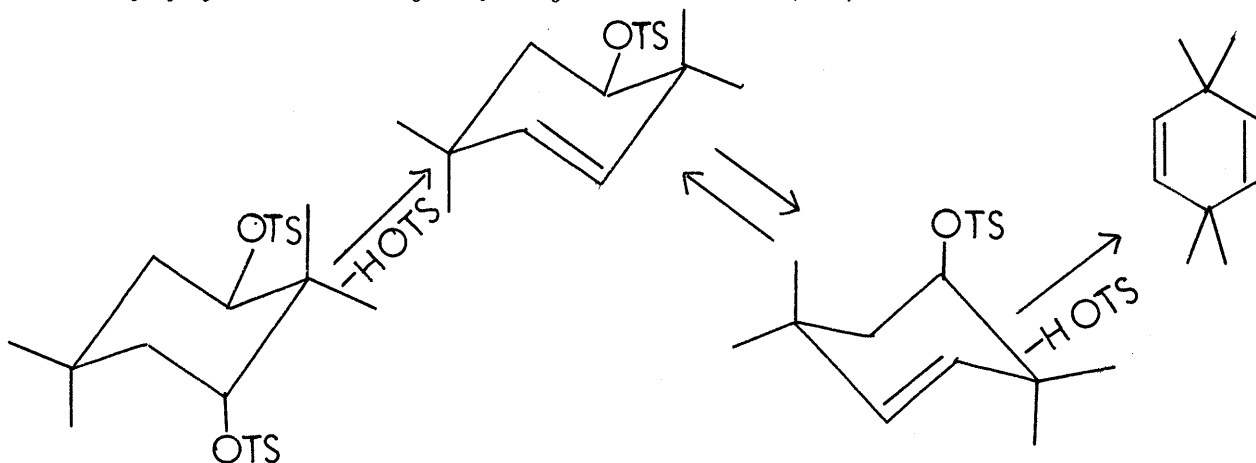
Among the further possibilities for reaction of the cyclic diol tosylates is a pinacol-like rearrangement in which an unsaturated aldehyde, 3,3,6-trimethyl-5-heptenal (XIV) is the product.



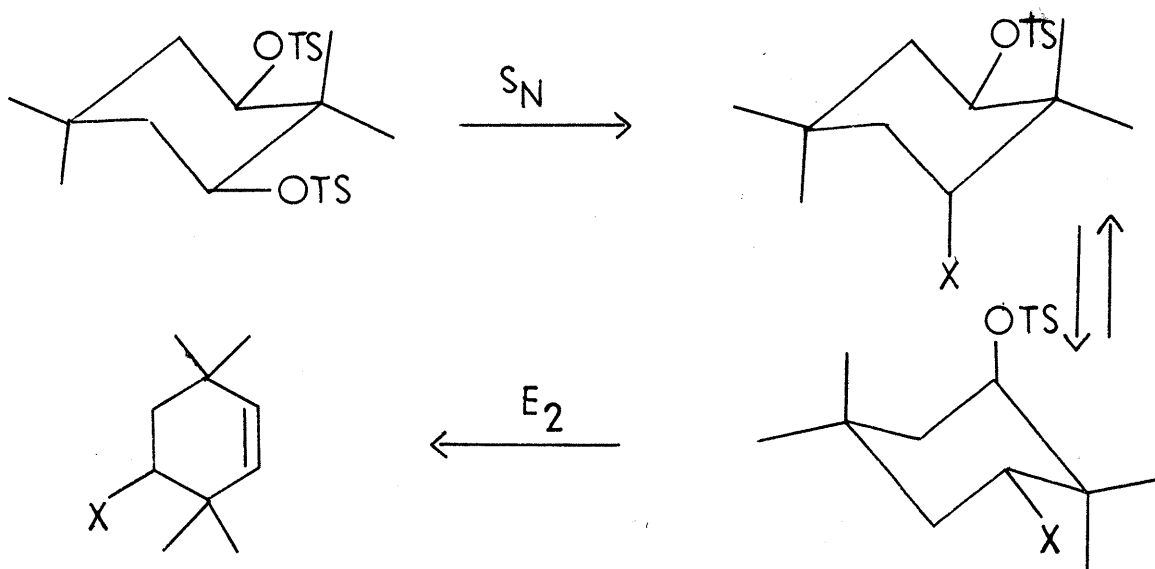
This reaction has the character of a pinacol rearrangement, ordinarily a 1,2-shift, but is unique in that the migration occurs in a transannular fashion giving a 1,3-shift of a bond and a simultaneous ring opening. In this reaction a gamma rather than beta attack occurs

where the attacking nucleophile, the electron pair forming the oxygen to hydrogen bond, is secondary to the nucleophilic specie X^- .

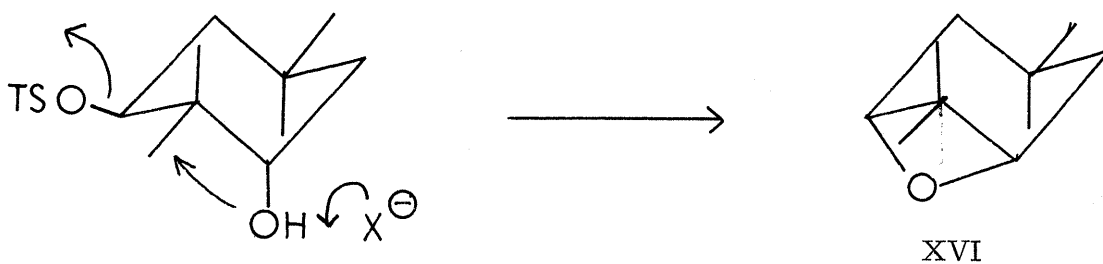
There are other possibilities for reaction in which no rearrangement occurs. An elimination reaction might result in an olefin, 3,3,6,6-tetramethyl-1,4-cyclohexadiene (XV). For elimination to



to occur to any appreciable extent, the H and tosylate groups must be in a trans configuration. Thus elimination would not be expected from the cis isomer unless a nucleophilic substitution precedes it.

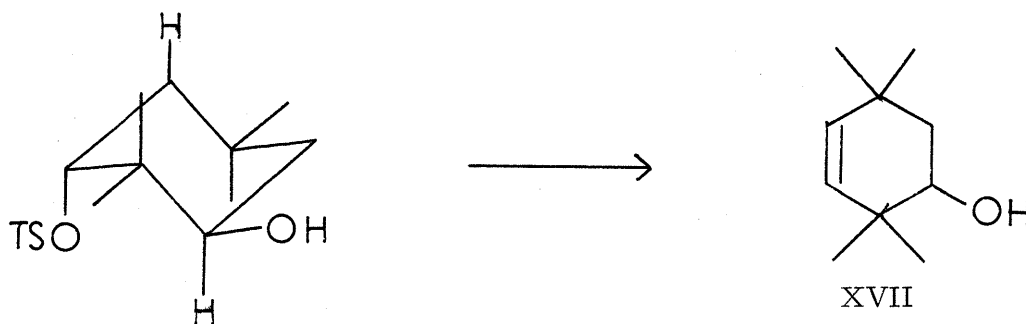


An intramolecular substitution might result from a conformation in which the tosylate group occupies an equatorial position and the hydroxy group, an axial position. This reaction giving a 1,3-epoxide



XVI would result only when substituents would constrain the ring of this conformation, causing the hydroxy group to be near the tosylate group.

From the conformation in which the positions of the groups are reversed, i. e., the inverted conformer, an elimination could give an unsaturated alcohol XVII. This conformation would not be favored



since it places the larger of the two functional substituents in the axial position.

The preparation of the tosylate esters of the 2,2,5,5-tetramethyl-1,3-cyclohexanediols and their reactions toward nucleophilic agents are discussed in Chapter III.

CHAPTER III

EXPERIMENTAL

Synthesis of 5,5-Dimethyl-1,3-cyclohexanedione

Since several preparations of this material were carried out, only a representative procedure will be described. 5,5-Dimethyl-1,3-cyclohexanedione, or dimedone, was prepared by the method of Vorlander¹ as described in Organic Syntheses.² In a 5000-ml three-neck flask equipped with a paddle stirrer mounted in a neoprene seal, a Friedrich's reflux condenser, a nitrogen inlet tube, and a 250-ml dropping funnel, was placed 800 ml of absolute ethyl alcohol which had been dried by refluxing over magnesium turnings and subsequent distillation.³ The flask was swept with dry nitrogen which was allowed to pass over the contents of the flask throughout the initial reaction. Sodium (46.0 g, 2.0 moles) was cut into chips and added slowly to the alcohol at such a rate as to maintain constant reflux. When the sodium had dissolved,

¹ D. Vorlander and J. Erig, Ann., 214, 302-316 (1897).

² A. H. Blatt, "Organic Syntheses," Collective Volume II, John Wiley and Sons, Inc., New York, 1943, pp. 200-202.

³ L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, 1955, p. 285.

ethyl malonate (340 g, 2.1 moles), (Fisher, purified), was slowly added to the mixture. The solution clouded due to formation of sodium malonate. Mesityl oxide (200 g, 2.04 moles), purified by two distillations through a 60-cm column packed with nickel chips and taking the fraction boiling at 127-128.5° C, was added dropwise. The mixture was stirred and refluxed for 3 hours. At the end of this time, the nitrogen was disconnected and potassium hydroxide (250 g, 4.4 moles), (Fisher, tech.), in 1150 ml of water was added.

The mixture was maintained at reflux for 12 hours. On cooling, the orange solution was made acidic to methyl orange paper by addition of 4N hydrochloric acid. Bubbles of carbon dioxide evolved rapidly at first and the solution became yellow. The reflux condenser was removed and the reaction flask was fitted with a condenser set for distillation. Approximately 1000 ml of ethanol and water was distilled. The residue was transferred, while hot, to three one-liter Erlenmeyer flasks, Nuchar (Fisher) was added, and the solutions were boiled and filtered. The material was made acidic to methyl orange paper and 5,5-dimethyl-1,3-cyclohexanedione precipitated. The solid was filtered, washed with water and dried in the suction flask. The crude material weighed 252 g. After recrystallization from acetone, the first fraction weighed 149.5 g, m.p. 148-150° C. A second fraction, 29.5 g, melted at 147.5-149° C. The yield, calculated on the basis of 179 g (1.28 moles), was 62.7%.

Synthesis of 2, 2, 5, 5-Tetramethyl-1, 3-cyclohexanedione by the
Method of Hirsjarvi and Toivonen⁴

Since ten preparations were made, only one will be described in detail. Absolute methanol (276 ml, 4.2 moles) which had been dried by refluxing over magnesium methoxide and distilling, was placed in a 2000-ml four-neck flask equipped with a 250-ml addition funnel, a Friedrich's reflux condenser, a wash bottle and benzene lock assembly, and a nitrogen inlet tube. After sweeping the apparatus with nitrogen, sodium (27.6 g, 1.2 moles) was added at such a rate as to maintain a constant reflux. The mixture was allowed to stop boiling and 5, 5-dimethyl-1, 3-cyclohexanedione (140 g, 1.0 mole), previously dried at 3 mm over phosphorus pentoxide, was added quickly to the hot solution. A distilling head with a thermometer was attached to the reaction flask and freshly distilled benzene was placed in the dropping funnel. The mixture was heated by means of a mantle until all the added material had gone into solution which had a light yellow color. The mixture was heated further until the methyl alcohol began to distill, at which point dropwise addition of benzene to the mixture was begun.

⁴ W. R. Hendrix, "Retropinacol Rearrangements, The Effect of Structure," Master's Thesis, University of Alabama, 1956, p. 46.

When the methyl alcohol had been displaced by benzene, the temperature rose to 80° C. The distillation was discontinued and the distilling head was replaced by a thermometer. The reaction apparatus was again swept with nitrogen and a slow stream was continued. Methyl iodide (213 g, 1.5 moles, 93.4 ml), (Fisher, Certified Reagent), was added dropwise from the addition funnel. The reaction mixture was allowed to reflux slowly for 24 hours. At this point a faint red color appeared and the reflux temperature was 64° C. Benzene (200 ml) was added in order to increase the reflux temperature. In the following 24 hours the reaction mixture had acquired a deep crimson color with a fine, powdery precipitate. Methyl iodide (20.0 ml) was added slowly. After 5 hours, the temperature had climbed to 72° C, at which point the color was a deep, dark red.

The reaction was cooled and the solid phase was filtered by suction. The precipitate, sodium iodide, was washed with a little benzene. Water (150 ml) was added to the filtrate causing the red color to turn yellow and precipitating dimedone and 2,5,5-trimethyl-1,3-cyclohexanedione. This was filtered, washed with water (150 ml) and with benzene (30 ml), and dried by suction yielding 56 g of material.

The benzene filtrate was extracted nine times with 50 ml of 10% aqueous sodium carbonate. The benzene solution, containing

2,2,5,5-tetramethyl-1,3-cyclohexanedione and small amounts of enol methyl ethers, was refluxed for two hours with 40 ml of dilute (3N) hydrochloric acid. The benzene and aqueous layers were separated. The aqueous layer was neutralized to methyl orange paper by addition of 10% aqueous sodium hydroxide. No precipitate was formed. The benzene layer was extracted four times with 50 ml of 10% aqueous sodium carbonate. These extracts were combined with the previous sodium carbonate washings and acidified to a pH 4-5. A yellow, sticky mass formed which crystallized on standing.

Isooctane (150 ml), (Phillips, Pure Grade), was added to the benzene solution of 2,2,5,5-tetramethyl-1,3-cyclohexanedione. The solution was evaporated under aspirator pressure to approximately 60 ml. The 2,2,5,5-tetramethyl-1,3-cyclohexanedione crystallized. A yield of 22.0 g (0.13 mole, 13%) of material melting at 97-99° C was obtained. The melting point observed by Hirsjarvi⁵ was 99.5-100.5° C. The 2,5,5-trimethyl-1,3-cyclohexanedione obtained above was combined with other such residues and recrystallized for further methylation.

⁵ V. P. Hirsjarvi, Ann. Acad. Sci. Fennicae, Ser. A II Chem. No. 23, 108 (1946). C. A. 42, 2936 (1948).

Synthesis of 2,2,5,5-Tetramethyl-1,3-cyclohexanedione by Sodium
Hydride-Methyl Iodide Alkylation⁶

Three procedures using this approach were tried. The most promising of the three will be described. Sodium hydride (6.0 g, 0.25 moles; 12 g in 54% oil dispersion), (Metal Hydrides), was dispersed by shaking in dimethylformamide, freshly purified by distillation from calcium hydride. The dispersion was placed in a three-neck, 500-ml round-bottom flask, equipped with a 250-ml dropping funnel, a Friedrich's condenser with drying tube, a nitrogen inlet, and magnetic stirrer. The apparatus was swept by allowing nitrogen to pass through for 20 minutes. Benzene (125 ml), dried by distillation from calcium hydride was added. 5,5-Dimethyl-1,3-cyclohexanedione, (dimedone), (17.7 g, 0.125 mole), dried by desiccation over phosphorus pentoxide at 3 mm, was dissolved in 75 ml of dimethylformamide, placed in the dropping funnel, and added slowly to the hydride dispersion during 25 minutes. Heat and bubbles of hydrogen evolved profusely. When the initial reaction subsided, a heating mantle was applied and the reaction mixture was cautiously heated for 1.5 hours.

⁶ F. J. Marshall and N. Cannon, J. Org. Chem., 21, 245 (1956).

The reaction mixture was cooled to room temperature and methyl iodide (38.9 g, 0.25 mole), (Fisher, Certified Reagent), was added dropwise during vigorous stirring. The methylation displayed an induction period by suddenly reacting vigorously after the addition of approximately 1 ml. The reaction mixture was cooled to 50° C before cautiously completing the addition. The mixture was heated at reflux for 5 days, then cooled and poured into a 500-ml Erlenmeyer flask containing 250 ml of benzene. The precipitate in the mixture was filtered and the benzene filtrate was extracted nine times with 50-ml portions of 10% aqueous sodium carbonate, and refluxed for two hours with 20 ml of 6N hydrochloric acid. The acid layer was separated and the benzene layer was extracted with two 50-ml portions of 10% aqueous sodium carbonate, followed by two 50-ml portions of water. The benzene layer was evaporated to about 20 ml and 150 ml of isooctane was added. The solution was evaporated to 50 ml and set aside to crystallize.

Acidification of the sodium carbonate washings gave 4.4 g of a mixture of dimedone and 2,5,5-trimethyl-1,3-cyclohexanedione. The initial precipitate was dissolved in water, which removed sodium iodide, and filtered to 6.0 g of a brownish, badly discolored material.

On crystallization from isooctane, 2,2,5,5-tetramethyl-1,3-cyclohexanedione (1.7 g, 0.010 mole) was obtained (8%), m. p. 97-99° C.

Synthesis of cis- and trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol

Sodium borohydride (7.89 g, 0.214 mole), (Metal Hydrides), and 140 ml of water were placed in a 1000-ml, three-neck flask equipped with a 250-ml addition funnel, neoprene seal stirrer, and reflux condenser. 2,2,5,5-Tetramethyl-1,3-cyclohexanedione (36.0 g, 0.214 mole) was dissolved in absolute ethanol (250 ml) and added dropwise to the stirred aqueous solution of the borohydride. It was necessary to heat the alcoholic solution of the dione by means of an infrared lamp to prevent its precipitation. During the exothermic reaction, bubbles of hydrogen copiously evolved. After the period of effervescence, 20 minutes, the reaction mixture was heated at 80° C for 4 hours.

The material was evaporated under aspirator pressure to approximately one-half its volume, at which point a cis-rich fraction precipitated. After its removal by filtration, the trans-rich filtrate was extracted twice with 150-ml portions of ethyl ether and dried over anhydrous sodium sulfate (Allied Chemical, N.F. VII), and then evaporated to dryness under aspirator pressure.

The cis fraction was dissolved in a mixture of 250 ml of benzene and 60 ml of acetone which was evaporated to 200 ml giving 10.0 g of the cis isomer, m.p. 203-205° C.

Two successive crystallizations of the parent solution gave 2.0 g, m.p. 203-205° C, and 1.3 g, m.p. 202-204° C. Two successive recrystallizations of the trans isomer from benzene gave 4.0 g, m.p. 105.5-108.5° C. In this instance a few of the fluffy crystals of the cis were decanted before the trans was collected. The parent solution, on two further evaporations, gave 1.0 g of the trans, m.p. 104-107° C. In the first of these operations, the cis and trans isomers could be separated manually, since the trans crystals were, fortunately, relatively large and heavy and the cis crystals were fine and light.

A total of 14.3 g (0.083 mmole, 38.9%) of the cis isomer and 16.0 g (0.093 mmole, 43.4%) of the trans isomer, a total yield of 82.3% of the two isomers, was obtained. This result is representative among six similar runs.

Infrared Anal. (IR-I).⁷ trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol. The -O-H absorption frequency appears at 3630 cm⁻¹, with hydrogen bonding at 3480 cm⁻¹. CH₃-C absorbs at 1475 cm⁻¹ and (CH₃)₂C at 1365 and 1395 cm⁻¹. C-O absorbs at 1165 cm⁻¹.

⁷The infrared analyses were carried out by double beam operation on a Beckman IR-7 Infrared Spectrophotometer at a speed of 200 cm⁻¹min⁻¹, gain of 2%, coarse gain 10, period 0, and slit on automatic select. The cell path was 0.09 mm and the reference beam passed through a wedge cell. Unless otherwise indicated chloroform was used as the solvent and in the reference cell.

Infrared Anal. (IR-II). --⁸ cis-2,2,5,5-Tetramethyl-1,3-
cyclohexanediol. The -O-H group is obscured by nujol bands in
the -O-H absorption range. The other bands are essentially the
same except for the C-O- band which is shifted to 1150 cm^{-1} .

Attempted Chromatographic Resolution of the cis and trans Isomers
of 2,2,5,5-Tetramethyl-1,3-cyclohexanediol

The chromatographic column, 3 x 57 cm, was prepared by filling with petroleum ether (30-60° C), (Baker Analyzed Reagent), placing a glass wool plug, covered by a disc of filter paper, at the bottom and filling with 90 g of absorption alumina (Fisher, Chromatographic 80-200 mesh). A 3.0-g mixture of the two isomers was dissolved in 100 ml of chloroform, (Allied Chemical, U.S.P.), and introduced into the column. Elution was begun with benzene. Nine 75-ml portions failed to elute the diols. Eleven 75 ml fractions of chloroform eluate were collected. The results are tabulated below. The greater part of the material was eluted in fractions 1-5. Fractions 6-11 were very small. The rates of absorption and elution are seen to be approximately the same. Thus little separation is afforded by this technique. The total recovery from the column was 76.7%.

⁸ This analysis was kindly carried out by Dr. Nelson Lloyd on a Perkin-Elmer 21 Spectrophotometer, using a sample mull in nujol. Gain 64. Speed 3 microns min^{-1} .

<u>Fraction No.</u>	<u>Weight of Material (g)</u>	<u>Melting Point (° C)</u>
1.	0.0	
2.	0.25	96-108
3.	0.75	103-108
4.	1.05	106-112
5.	0.25	104-110
6.	—	—
7.	—	—
8.	—	—
9.	—	96-112
10.	—	—
11.	—	106-125

Synthesis of trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol

Bis-p-toluenesulfonate^{9, 10}

trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol (1.0 g, 5.8 mmoles) was dissolved in 10 ml of pyridine (Allied Chemical, Reagent). This solution was placed in a 300-ml, three-neck flask equipped with reflux condenser and drying tube, magnetic stirrer, addition funnel and thermometer. p-Toluenesulfonyl chloride (4.44 g, 23.2 mmoles), (Eastman, Pract.) which had been recrystallized three times from petroleum ether (30-60° C), was dissolved in 10 ml of pyridine and placed in the dropping funnel. The reaction mixture was kept at 50° C during dropwise addition of the p-toluenesulfonyl chloride solution. On

⁹ S. Winstein, H. V. Hess, and R. E. Buckles, J. Am. Chem. Soc., **64**, 2798 (1942).

¹⁰ A. S. Hussey, H. P. Liao and R. H. Baker, J. Am. Chem. Soc., **75**, 4727 (1953).

addition of the first few drops, a transient green color developed. After addition (1 hour), the reaction mixture was stirred at 50-60° C for 20 hours.

On cooling the reaction mixture to room temperature, a precipitate of pyridine hydrochloride was observed. This gummy, deliquescent, water soluble material was removed by filtration. The filtrate was poured into 150 ml of water, extracted twice with 75-ml portions of chloroform, which was then washed with an equal volume of water, twice with 200-ml portions of dilute sulfuric acid (6N), once with 100 ml of 10% aqueous sodium bicarbonate, once with 100 ml of water and then dried for 30 minutes over anhydrous sodium sulfate (5 g), (Allied Chemical, N.F. VII).

The chloroform solution was evaporated to dryness under aspirator pressure. The residue was recrystallized from ethanol, m.p. 139-142° C. A second recrystallization gave 1.9 g (4.0 mmole, 69%), m.p. 140-142° C. After three recrystallizations, the melting point was constant at 141-142° C. Two further recrystallizations were made for an analytical sample and infrared spectrum.

Anal.¹¹ Calculated for $C_{24}H_{32}O_6S_2$: C 59.97%; H 6.71%; S 13.34%
 Found: C 59.87%; H 6.74%; S 13.34%.

¹¹ E. Thommen, Basel, Switzerland.

Infrared Anal. (IR-III). -- Absorptions for the sulfonate group are found at 1365 and 1180 cm^{-1} . These coincide with the absorption frequencies for sulfonates quoted by Bellamy.¹²

An alternative preparation of this compound was also found to be effective. The reagents used were of the same source as those described above. trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol (5.0 g, 0.029 mole) was dissolved in 90 ml of pyridine and placed in a glass-stoppered 500 -ml flask. p-Toluenesulfonyl chloride (11.2 g, 0.058 mole) was dissolved in 30 ml of pyridine and mixed with the diol solution. This was allowed to stand for 11 days. The product was recovered by the same method as described above, 9.0 g (0.019 mole, 65%).

Synthesis of cis-2,2,5,5-Tetramethyl-1,3-cyclohexanediol Bis-p-toluenesulfonate

cis-2,2,5,5-Tetramethyl-1,3-cyclohexanediol (1.0 g, 5.8 mmoles) was dissolved in 15 ml of pyridine (Allied Chemical, Reagent) and placed in a glass-stoppered 150-ml flask. p-Toluenesulfonyl chloride (1.1 g, 5.8 mmole), (Eastman, Pract.), which had been recrystallized three times from petroleum ether (30-60° C), was

¹² L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, 1958, p. 364.

dissolved in 10 ml of pyridine and added to the flask.

After the reaction mixture stood for 24 hours, p-toluene-sulfonyl chloride (1.1 g, 5.8 mmoles) was added. The mixture was allowed to stand with occasional shaking for 48 hours. The mixture was poured into 150 ml of water, extracted twice with 75-ml portions of chloroform which was then washed with 100 ml of water, twice with 200 ml of 3N sulfuric acid, once with 100 ml of 5% aqueous sodium bicarbonate, again with 100 ml of water and then dried over 5 g of anhydrous sodium sulfate (Allied Chemical, N.F. VII). The chloroform solution was evaporated to dryness and the residue was crystallized from absolute ethanol, m. p. 146-151° C. After two recrystallizations, the melting point was constant, m. p. 155.5-157° C, 1.7 g (3.5 mmoles, 61.1%).

Anal.¹³ Calculated for C₂₄H₃₂O₆S₂ : C 59.97%; H 6.71%; S 13.34%
Found: C 60.10%; H 6.78%; S 13.31%.

Infrared Anal. (IR-IV). -- Absorptions for the sulfonate group are found at 1175 and 1375 cm⁻¹.

An alternate preparation was carried out in which cis-2,2,5,5-tetramethyl-1,3-cyclohexanediol (5.0, 0.029 mole) was dissolved in 90 ml of pyridine (Allied Chemical, Reagent). p-Toluenesulfonyl

¹³ E. Thommen, loc. cit.

chloride (11.2 g, 0.058 mole), (Eastman, Tech., recrystallized) was dissolved in 30.0 ml of pyridine. The two solutions were combined and allowed to stand 11 days. The product was recovered as described above, 11.5 g (0.025 mole, 82.7%).

Synthesis of trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol Bis-methanesulfonate

trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol (1.0 g, 5.8 mmoles) dissolved in pyridine (10 ml), (Allied Chemical, Reagent), was placed in a 300-ml, three-neck flask, fitted with dropping funnel, reflux condenser, thermometer and magnetic stirrer. Methanesulfonyl chloride (4.5 g, 38 mmoles, 3.0 ml), (Eastman, 5388) was dissolved in 10 ml of chloroform (Allied Chemical, Reagent), placed in the dropping funnel and added slowly to the stirred solution of the diol. On addition of 10 drops, a transient green color was observed. The temperature of the reaction mixture climbed to 31° C. The reaction mixture was stirred for 12 hours, at the end of which time it had a dark brown color. Heat was evolved as the mixture was poured into 150 ml of water. Two extractions were made with 100-ml portions of chloroform. The extract was washed with two 200-ml portions of 3N sulfuric acid, then with 100 ml of 10% aqueous sodium bicarbonate. The chloroform solution was dried over 10 g of anhydrous sodium sulfate (Allied Chemical, N.F. VII).

The solution was evaporated under aspirator pressure to a viscous yellow oil, which crystallized, partially, after standing 8 hours. The material was recrystallized twice from absolute ethanol, 1.20 g (3.6 mmoles 63.1%), m.p. 103-106° C. On the fifth recrystallization from absolute ethanol the melting point was constant at 105.5-107° C.

Anal.¹⁴ Calculated for C₁₂H₂₄O₆S₂ : C 43.88%; H 7.36%; S 19.52%
Found: C 44.08%; H 7.48%; S 19.40%.

Infrared Anal. (IR-V). --Absorptions characteristic of sulfonate groups are found at 1175 and 1370 cm⁻¹.

Synthesis of cis-2,2,5,5-Tetramethyl-1,3-cyclohexanediol Bis-methanesulfonate

cis-2,2,5,5-Tetramethyl-1,3-cyclohexanediol (1.0 g, 5.8 mmoles) was dissolved in 15 ml pyridine (Allied Chemical, Reagent) and placed in a three-neck flask equipped with dropping funnel, condenser, magnetic stirrer and thermometer. Methanesulfonyl chloride (4.5 g, 38 mmoles, 3.0 ml), (Eastman, 5388), was dissolved in 10 ml of chloroform (Allied Chemical, Reagent) and placed in the dropping funnel. Addition was carried out slowly, during stirring, over a period of 12 hours at 28-31° C.

¹⁴ E. Thommen, loc. cit.

The mixture was stirred 4 hours after addition and poured onto 40 g of ice. Extraction was carried out with two 100-ml portions of chloroform. The extract was washed with two 200-ml portions of 3N sulfuric acid, then with 75 ml of 5% aqueous sodium bicarbonate. The solution was dried over 5 g of anhydrous sodium sulfate (Allied Chemical, N. F. VII). On evaporation of solvent, a solid remained which was recrystallized from absolute ethanol, 1.50 g (4.6 mmoles, 78.8%), m. p. 159-161° C. On recrystallizing three times from absolute ethanol, the material had a constant m. p., 160.5-162° C.

Anal.¹⁵ Calculated for $C_{12}H_{24}O_6S_2$: C 43.88%; H 7.36%; S 19.52%
 Found: C 44.09%; H 7.48%; S 19.27%.

Infrared Anal. (IR-VI). --Absorption bands for the sulfonate group are found at 1183 and 1355 cm^{-1} .

Synthesis and Rearrangement of cis- and trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol Mono-p-toluenesulfonates to 3,3,6-Trimethyl-5-heptenal

Since the same compound, 3,3,6-trimethyl-5-heptenal, was obtained from each of the isomeric diols in identical procedures, only one synthesis will be described in detail as to purification of the

¹⁵ E. Thommen, loc. cit.

product. In neither of these procedures were the compounds, cis- and trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol mono-p-tosylate actually isolated. These are proposed as logical intermediates in the course of formation of the final product, 3,3,6-trimethyl-5-heptenal.

trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol (3.0 g, 17.4 mmoles) was dissolved in 50 ml of pyridine (Allied Chemical, Reagent) and placed in a three-neck, 300-ml flask equipped with reflux condenser, dropping funnel, magnetic stirrer and thermometer. In the dropping funnel was placed p-toluenesulfonyl chloride (3.33 g, 17.4 mmoles), (Eastman, Pract.), which had been recrystallized three times from petroleum ether (30-60° C), dissolved in 30 ml of pyridine. The addition was carried out slowly over a period of 11 hours at 35° C.

The reaction mixture was stirred 14 days, after which it was poured into 150 ml of ice water and extracted twice with 75-ml portions of chloroform. The extract then was washed successively with 100 ml of water, two 100-ml portions of 1N sulfuric acid, 75 ml of 5% aqueous sodium bicarbonate and finally with 100 ml of water. The washed solution was then dried over 5 g of anhydrous sodium sulfate (Allied Chemical, N.F. VII). The chloroform was evaporated under aspirator pressure until a volume of 75 ml of solution remained.

A yellow precipitate was formed when a few drops was placed in an alcoholic solution of 2,4-dinitrophenylhydrazine. The solution was chromatographed on a column (3 x 52 cm) filled with 70 g of alumina (Fisher Chromatographic Alumina, 80-200 mesh) in petroleum ether (30-60° C), (Baker, Analyzed). Elution was begun with petroleum ether, and fourteen 120-ml fractions were taken. Evaporation gave an aromatic liquid. The process was repeated with four fractions of benzene-petroleum ether, six benzene fractions, four benzene-chloroform fractions and finally with seven fractions of chloroform. Except for the chloroform fractions which gave 0.9 g of a solid melting at 135-139° C, which was the impure bistosylate (m. p. pure, 141-142° C), only a fragrant liquid was obtained. The material was distilled under reduced pressure. 3,3,6-Trimethyl-5-heptenal, 1.61 g (10.4 mmole, 60.0%), b. p. 40-42° C/4-5 mm, n_D^{25} 1.4509, was obtained.

Infrared Anal. (IR-VII). --¹⁶ The aldehyde carbonyl absorption lies at 1725 cm^{-1} . The C-H stretching frequency for the group, CHO, is found at 2750 cm^{-1} . An olefinic absorption at 1680 cm^{-1} is indicative of the group, $R_1R_2C = CR_3$.

Qualitative Tests. --Positive tests for unsaturation were given by addition of bromine in carbon tetrachloride, and by addition of

¹⁶ L. J. Bellamy, op. cit., pp. 34, 132-133.

potassium permanganate in acetone. A positive reaction for the aldehyde group was given by Benedict's test.

cis-2,2,5,5-Tetramethyl-1,3-cyclohexanediol (6.0 g, 35 mmoles) was allowed to react with p-toluenesulfonyl chloride (6.6 g, 35 mmoles) in the same manner as described above for the trans diol. The reaction was carried out over a period of 4 days at 50° C. The purification and chromatographic procedures were identical to those described above. The material was distilled under reduced pressure giving 1.9 g (12 mmoles, 35%), b. p. 37-39° C/3.5 mm, of 3,3,6-trimethyl-5-heptenal. n_D^{25} 1.4470; n_D^{35} 1.4440, d_4^{35} 0.8522, M_D observed 48.07, M_D calculated 47.92.

Anal.¹⁷ Calculated for $C_{10}H_{18}O$: C 77.86%; H 11.76%

Found: C 77.77%; H 11.95%.

Infrared Anal. (IR-VIII). -- The spectrum is essentially identical to IR-VII.

Preparation of the 2,4-Dinitrophenylhydrazone of 3,3,6-Trimethyl-5-heptenal

The derivative was prepared from samples of the aldehyde derived from both the cis and trans diols by the method described by

¹⁷ E. Thommen, loc. cit.

Shriner.¹⁸ The derivative obtained from the trans diol melted at 94-95° C. That obtained from the cis diol was recrystallized three times from 95% aqueous ethanol and sent for analysis, m. p. 94.5-95.7° C.

Anal.¹⁹ Calculated for $C_{16}H_{23}O_4N_4$: C 57.29%; H 6.91%; N 16.70%
Found: C 57.03%; H 6.68%; N 16.92%.

Infrared Anal. (IR-IX). -- A band for -CH = N- is found at 1625 cm^{-1} . A band at 3325 cm^{-1} is due to the nitro groups.

Ozonolysis of 3, 3, 6-Trimethyl-5-heptenal

A 1-ml sample of 3, 3, 6-trimethyl-5-heptenal was dissolved in 50 ml of ethyl acetate (Baker, Reagent) and placed in the ozonolysis apparatus.²⁰ Oxygen was passed through the apparatus at approximately 4 bubbles/sec. for 10 minutes. The discharge was begun and continued 30 minutes, after which the apparatus was again swept with oxygen for 10 minutes. The flask containing the ozonized sample was placed on a magnetic stirrer behind a safety shield. The ozonides were decomposed by addition of a mixture of 7.0 g zinc dust

¹⁸ R. L. Shriner, R. C. Fuson and D. L. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., 1956, p. 219.

¹⁹ E. Thommen, loc. cit.

²⁰ The apparatus for ozonolysis was built by Dr. R. B. Scott, Jr. from a design by Dr. W. A. Bonner, J. Chem. Ed., 30, 452 (1953).

(Fisher, Reagent), 12 ml of dioxane (Allied Chemical, Tech.), 2.0 ml water, a trace of silver nitrate and a trace of hydroquinone.²¹ The solution was stirred by a magnetic stirrer for 1 hour, after which it was filtered and added to 70 ml of an alcoholic solution of 2,4-dinitrophenylhydrazine.²² Since no precipitate was formed immediately, the solution was evaporated under reduced pressure until the precipitate formed. This was filtered and recrystallized three times from a mixture of ethyl alcohol and ethyl acetate, m.p. 236.5-238.5° C. This corresponds to the bis-(2,4-dinitrophenylhydrazine) of 3,3-dimethylglutaraldehyde, the melting point of which is quoted as 238-9° C.²³

Reaction of cis-2,2,5,5-Tetramethyl-1,3-cyclohexanediol Bis-p-toluenesulfonate with Potassium Hydroxide in Methanol

cis-2,2,5,5-Tetramethyl-1,3-cyclohexanediol bis-p-toluene-sulfonate (6.0 g, 12.5 mmoles) was placed in a one-neck, 500-ml flask equipped with reflux condenser, heating mantle and drying tube. Methyl alcohol (190 ml), (Fisher, Purified), was added. Potassium hydroxide (7.9 g, 141 mmoles), (Allied Chemicals, Reagent), was

²¹W. T. Smith and R. L. Shriner, "The Examination of New Organic Compounds," John Wiley and Sons, Inc., New York, 1956, p. 120.

²²R. L. Shriner, op. cit., p. 111.

²³J. Meinwald and P. Chuan, J. Am. Chem. Soc., 82, 699-704 (1960).

dissolved in methyl alcohol (50 ml), and added to the flask. The contents were heated at reflux for 7 days.

The reaction mixture, on cooling, gave a precipitate of the bistosylate, 2.80 g, m.p. 154-157° C (m.p. pure, 155.5-157° C). The filtrate was extracted with two 200-ml portions of chloroform which was washed twice with 200-ml portions of water. The chloroform solution was dried over 5 g of anhydrous sodium sulfate for 30 minutes and evaporated to 20 ml. An infrared spectrum showed the characteristic carbonyl band at 1725 cm⁻¹ for 3,3,6-trimethyl-5-heptenal. The residue was poured into a solution of alcoholic 2,4-dinitrophenylhydrazine,²⁴ giving a yellow precipitate which was filtered and recrystallized from 95% ethyl alcohol, 0.2 g (6 mmoles, 4.78%, yield from the bistosylate). After two recrystallizations the material melted at 94-95° C, as compared to 94.5-95.7° C for the authentic sample.

Infrared Anal. (IR-X). -- The spectrum is identical to that of the 2,4-dinitrophenylhydrazone of 3,3,6-trimethyl-5-heptenal, IR-IX.

Attempted Isolation of cis- and trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol Mono-p-toluenesulfonates

Since the preparation of both the trans- and cis-monotosylates resulted in immediate rearrangement, two other methods were tried

²⁴R. L. Shriner, op. cit., p. 111.

in an attempt to isolate and characterize the compound.²⁵

trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol (1.0 g, 5.8 mmoles) was dissolved in 50 ml acetone (Baker, N.F.) and placed in a 300-ml three-neck flask equipped with stirrer, reflux condenser, and dropping funnel. Potassium carbonate (2.6 g, 20 mmoles), (Fisher, Reagent), was added and put into a suspension by stirring. p-Toluenesulfonyl chloride (1.1 g, 5.8 mmoles), (Eastman, Pract.) recrystallized from petroleum ether (30-60° C), was dissolved in 20 ml of acetone and placed in the addition funnel. Addition was carried out slowly at 50° C during 3 hours. The material was stirred at 50° C during 24 hours.

The mixture was poured into 150 ml of water and extracted twice with 150 ml of chloroform, washed twice with 150 ml of water and dried over anhydrous sodium sulfate. The mixture was evaporated to dryness and recrystallized from absolute ethyl alcohol yielding 0.3 g of the unchanged diol, starting material, m.p. 105-108° C (m.p. pure, 107-108° C).

A second method involved an attempt to prepare the sodium salt of cis-2,2,5,5-tetramethyl-1,3-cyclohexanediol. In a 500-ml flask equipped with heating mantle, magnetic stirrer, reflux condenser, dropping funnel and thermometer was placed the diol

²⁵ V. K. Ahluwalia, S. K. Mukerjee, and T. R. Seshadri, J. Chem. Soc., 3988 (1954).

(1.0 g, 5.8 mmole_s). Toluene (60 ml), purified by treatment with calcium hydride and distilling at 110° C, was added and the mixture was heated to 108° C. After the diol dissolved, sodium (0.13 g, 5.8 mmole_s) was added and the mixture was stirred until the sodium disappeared and then stirred for 12 hours at 70° C. The mixture contained a dispersed black precipitate. p-Toluenesulfonyl chloride (1.1 g, 5.8 mmole_s) dissolved in 30 ml of toluene was added during 2 hours. The mixture was stirred 48 hours, after which it was heated to 105° C and the black material (assumed to be sodium) disappeared. The heating was continued 5 hours after which the reaction mixture was poured into water, extracted with two 50-ml portions of ether, dried over anhydrous sodium sulfate, and evaporated to dryness yielding only 0.55 g of the unchanged cis-diol, m. p. 202-204° C (m. p. pure, 206-207° C).

Reaction of trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol Bis-p-toluenesulfonate with Potassium Hydroxide in Methanol

Since several repetitions of this reaction were carried out, the results of only two will be described. In a 500-ml, one-neck flask with a reflux condenser and drying tube was placed trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol bis-p-toluenesulfonate (6.0 g, 12.5 mmole_s), 190 ml of methanol (Fisher, purified) and a

solution of potassium hydroxide (6.0 g, 107 mmole_s), (Fisher, Reagent), in 30 ml of methanol. The mixture was heated at reflux 7 days.

As the reaction mixture was cooled, potassium p-toluenesulfonate precipitated. After filtration and drying, 3.9 g (19 mmole_s, 74.3%) was obtained. The filtrate was poured into 150 ml of water and extracted twice with 100-ml portions of chloroform. The extract was washed twice with 200-ml portions of water and dried 2 hours over anhydrous sodium sulfate. After filtering, the solution was evaporated to 30 ml and distilled under reduced pressure. Two fractions were obtained: 0.2 g, b. p. 40-55° C/13 mm, n_D^{25} 1.4502, and 0.40 g of 4-methoxy-3,3,6,6-tetramethylcyclohexene (2.4 mmole, 19%), b. p. 64-67° C/13 mm, n_D^{25} 1.4458.

Anal.²⁶ (Second fraction). Calculated for C₁₁H₂₀O : C 78.51%;
H 11.98%

Found: C 78.98%; H 11.96%.

Infrared Anal. (IR-XI). --²⁷ (First fraction). An absorption at 1650 cm⁻¹ indicates unsaturation. A faint carbonyl group absorption is found at 1720 cm⁻¹. CH₃-C is found at 1475 and (CH₃)₂C is indicated

²⁶ E. Thommen, loc. cit.

²⁷ L. J. Bellamy, op. cit., pp. 14, 34, 114, 132.

by absorption at 1360 and 1387 cm^{-1} . An ether linkage is indicated at 1075 cm^{-1}

Infrared Anal. (IR-XII). --(Second fraction). The olefinic absorption at 1650 cm^{-1} is weaker and the carbonyl absorption is absent. The ether absorption is equally strong as well as the other absorptions noted above.

Qualitative Tests. --Unsaturation is indicated in both fractions by decolorization of bromine in carbon tetrachloride and potassium permanganate in acetone. No derivative is given with an alcoholic solution of 2,4-dinitrophenylhydrazine. From ozonolysis of the second fraction by the same procedure described on p. 51, no 2,4-dinitrophenylhydrazine derivatives were isolated. It is possible that such derivatives might have been present in small amounts.

In another reaction, the bistosylate (10.0 g, 20.8 mmole) and potassium hydroxide (13.1 g, 234 mmole) in 310 ml of methanol was refluxed for 11 days. A precipitate of potassium p-toluenesulfonate (5.0 g, 238 mmole) was obtained. This corresponds to 57.2% of the theoretical yield of the salt. The same procedure as described on p. 56 was used for isolation of the reaction product. The reaction residue was distilled under reduced pressure giving 1.2 g (7.2 mmole, 34.4%) of 4-methoxy-3,3,6,6-tetramethylcyclohexene, b. p. 60-65° C/12 mm. The material was redistilled giving 0.5 g,

b. p. 62-65° C/12 mm, n_D^{20} 1.4473. The following analytical data were obtained from this sample.

Anal.²⁸ Calculated for $C_{11}H_{20}O$: C 78.51%; H 11.98%

Found: C 78.77, 78.63%; H 11.72, 11.79% (in duplicate).

Infrared Anal. (IR-XIII). --²⁹ This spectrum is essentially identical to IR-XII.

Nuclear Magnetic Resonance and Gas Chromatographic Data. --³⁰

The NMR spectrum was recorded, using a Varian A-60 instrument. Peaks near -325 cps are due to olefinic protons. Peaks near -185 cps indicate O-CH₃ resonances. Peaks near -60 cps are due to methyl groups attached to saturated carbons. It is concluded that a large percentage of the material contains two olefinic protons per molecule. A gas chromatographic study showed the material to contain at least three impurities in significant amounts.

²⁸ G. Weiler and F. B. Strauss, Oxford, England.

²⁹ This spectrum was run by Dr. Nelson Lloyd on a Perkin-Elmer 21 Spectrophotometer. The sample was run as a film; gain 64; speed 3 microns min⁻¹.

³⁰ The nuclear magnetic resonance spectrum was run and interpreted through the courtesy of J. B. Dickey, Director, Research Laboratories, Tennessee Eastman Co., Kingsport, Tenn.

Results of Solvolytic Reactions of cis- and trans-2,2,5,5-Tetra-
methyl-1,3-cyclohexanediol Bis-p-toluenesulfonates in Acetic and
and Formic Acids^{31, 32}

Acetolysis. -- The bistosylates showed considerable inertia toward solvolysis in acetic acid at moderate temperatures. Appreciable reaction could only be obtained at higher temperatures and long reflux periods, the result of which was extensive decomposition. Some correlations from the infrared spectra of the residues are presented.

cis-2,2,5,5-Tetramethyl-1,3-cyclohexanediol bistosylate (0.95 g, 1.9 mmole $\frac{1}{2}$) was placed in a three-neck, 300-ml flask equipped with reflux condenser, heating mantle and magnetic stirrer. Glacial acetic acid (31.2 g, 30.0 ml, 0.52 mole), (Allied Chemical, Reagent), acetic anhydride (1.2 g, 12 mmole, 1.16 ml), (Allied Chemical, Reagent), and anhydrous sodium acetate (1.0 g, 12 mmole $\frac{1}{2}$), (Baker Chemical, C.P.), were added and the mixture was heated at 100° C for 24 hours.

On Cooling, the mixture was poured into 150 ml of water and extracted with 200 ml of ethyl ether (Fisher, solvent grade). The

³¹ J. D. Roberts and V. C. Chambers, J. Am. Chem. Soc., 73, 5034 (1951).

³² E. Grunwald and S. Winstein, J. Am. Chem. Soc., 79, 3278 (1957).

ether extract was washed with two 150-ml portions of water and two 150-ml portions of 10% aqueous sodium bicarbonate. After drying over 5.0 g of anhydrous sodium sulfate, the solution was evaporated to dryness, leaving a solid, which was dissolved in chloroform and again dried over anhydrous sodium sulfate. This solution was evaporated to a few ml (~ 10) and an infrared spectrum was taken. This was seen to be almost identical to that for the cis-diol tosylate. The residue was again subjected to acetolysis in the same manner as described above, except that the material was heated for 48 hours at 114° C. The recovery procedure, same as above, gave a small amount of a dark brown oil. This was dissolved in chloroform, treated with decolorizing carbon, filtered and evaporated to an oil.

Infrared Anal. (IR-XIV). --³³ The carbonyl band at 1735 cm⁻¹ corresponds to that for the acetate group. A strong band at 1250 cm⁻¹ is indicative of the C-O stretching frequency for an acetate. Bands at 1375 and 1470 cm⁻¹ indicate presence of (CH₃)₂C and CH₃-C groups. The broad, strong band for the carbonyl absorption and absence of the proportionately strong absorptions at 1175 and 1375 cm⁻¹ characteristic of the tosylate group indicate the presence of 2,2,5,5-tetramethyl-1,3-cyclohexanediol bisacetate. Absence of bands in the range

³³ L. J. Bellamy, op. cit., pp. 14, 132, 179.

of 1650 cm^{-1} shows definite lack of olefinic structure.

Qualitative Tests. -- The oil gave a negative 2,4-dinitrophenylhydrazine test. The carbonyl band is therefore not likely due to presence of ketone nor aldehyde, but to an ester.

The trans isomer of 2,2,5,5-tetramethyl-1,3-cyclohexanediol bistosylate was similarly subjected to acetolysis.

Infrared Anal. (IR-XV). -- This shows a product spectrally identical with that obtained from the cis isomer, (IR-XIV).

Formolysis. -- In order to dissolve the diol tosylates in formic acid, it was necessary to heat the mixture to 70°C . Shortly after this temperature was reached, a blackening of the material occurred indicating extensive decomposition.

trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol (3.0 g, 6.2 mmole), 70 ml of formic acid (Allied Chemical, C. P. 98-100%) and sodium formate (1.0 g, 14.7 mmole), (Coleman and Bell, C.P.), were placed in a 250-ml flask with condenser, thermometer and heating mantle.

On heating the mixture to 70°C , a black-purple color developed. The mixture was cooled and the bistosylate crystallized. The material was again heated to 65°C and the temperature was maintained at this point for 25.5 hours. On cooling, the material crystallized. Heat at 65°C was again applied for 16 hours. The reaction mixture

was worked up in the same manner as described for the acetolysis procedures.

Infrared Anal. (IR-XVI). --³⁴ A weak carbonyl band at 1730 cm^{-1} and a C-O band at 1180 cm^{-1} is indicative of the presence of a formate. No unreacted tosylate remains since absorption at 1600 cm^{-1} is absent (benzene ring absorption frequency characteristic of the tosylates). The band intensity of the carbonyl absorption is weaker in relation to the C-O, the $\text{CH}_3\text{-C}$, and the $(\text{CH}_3)_2\text{C}$ bands at 1445 and 1365 cm^{-1} than might be expected if only a formate ester were present. Unsaturation is absent as indicated by lack of absorption in the 1650 cm^{-1} range.

Qualitative Tests. --A negative test was given with an alcoholic solution of 2,4-dinitrophenylhydrazine.

An equivalent formolysis of the cis-2,2,5,5-tetramethyl-1,3-cyclohexanediol bistosylate gave a residue of the unreacted material as shown by infrared analysis.

Attempted Preparation of trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol Monomethanesulfonate

A solution of trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol (3.0 g, 17 mmol) in 75 ml of pyridine (Allied Chemical, Reagent)

³⁴ L. J. Bellamy, op. cit., p. 179.

was placed in a three-neck, 300-ml flask equipped with reflux condenser, thermometer, magnetic stirrer and dropping funnel.

Methanesulfonyl chloride (2.0 g, 17 mmoles, 1.3 ml), (Eastman, 5388), dissolved in 30 ml of chloroform (Allied Chemical, Reagent) and placed in the dropping funnel, was added slowly to the stirred diol solution over 12 hours.

The reaction mixture, after being stirred 5 days at room temperature was poured slowly into 150 ml of ice water. The solution was extracted twice with 100-ml portions of chloroform, which was washed twice with 100-ml portions of water, twice each with 200 ml of 3N sulfuric acid, once with 5% aqueous sodium bicarbonate, then with 100 ml of water. The solution was dried over 5 g of anhydrous sodium sulfate and evaporated to a mixture of a viscous oil and solid. The material gave a negative 2,4-dinitrophenylhydrazine test. The oil-solid mixture was triturated with pentane and filtered. A solid, (0.35 g, 1 mmole), the bismesylate melting at 105-108° C, was obtained. The filtrate, a heavy oil, was dissolved in chloroform, dried, and evaporated again. An infrared spectrum was run on the product. A hydroxy group was indicated at 3640 cm^{-1} .

Since the oil would not crystallize from any of the common solvents, it was chromatographed. An oil was eluted in the

chloroform-benzene fraction. An attempt was made to convert the material to a solid by acetylation with acetic anhydride (10.0 g, 0.10 mole), (Baker, Reagent), and 35 ml of pyridine. The mixture was heated at 50° C for 10 hours and worked up in the same way as the mesylation process described above. No solid derivative was obtained from the dark viscous oil that remained.

Infrared Anal. (IR-XVII). ³⁵ An OH frequency is found at 3640 cm⁻¹ and intermolecular hydrogen bonding is indicated at 3440-3570 cm⁻¹. The absorptions at 1350 and 1180 cm⁻¹ indicate the sulfonate group. CH₃-C is indicated at 1475 cm⁻¹. Unsaturation is absent.

Reaction of trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol Bis-methanesulfonate with Potassium Hydroxide in Methanol

The bismesylate (2.77 g, 8.4 mmoles) in 120 ml of methanol (Fisher, Purified) was placed in a 500-ml one-neck flask fitted with reflux condenser, heating mantle and drying tube. Potassium hydroxide (5.3 g, 94 mmoles), (Fisher, Reagent), dissolved in 40 ml of methanol (Fisher, Purified) was added.

The mixture was heated at reflux. After 18 hours, a white precipitate appeared in the flask. The reaction was heated for a

³⁵ L. J. Bellamy, op. cit., pp. 14, 95, 179.

total of 35 hours, after which it was cooled and filtered. A precipitate of potassium methanesulfonate (1.60 g, 12 mmole), 71.0% of the theoretical amount, was obtained. The filtrate, after adding 150 ml of water, was extracted with 100 ml of chloroform, which was washed twice with 100-ml portions of water and dried over 5 g of anhydrous sodium sulfate. The solution was evaporated to 10 ml and distilled under reduced pressure with the aid of a dry-ice acetone trap. Only one fraction was collected, 0.7 g (0.0042 mole, 49.6%), b. p. 46-49° C/7 mm, n_D^{25} 1.4494. The physical constants are comparable to those obtained for the product, 4-methoxy-3,3,6,6-tetramethylcyclohexene, from the reaction of the trans-bistosylate with potassium hydroxide under the same conditions, (p. 57). The somewhat higher refractive index suggests presence of an impurity, very likely the same as that in fraction one (p. 56). This is indicated by a comparison of spectra XI, XII, and XVIII.

Infrared Anal. (IR-XVIII). -- This spectrum is closely comparable to spectra XI and XII. The band positions are identical and except for the olefinic absorption at 1650 cm^{-1} and a band at 900 cm^{-1} , the relative intensity of the bands are the same as those of XII. The purity of this material appears to be intermediate between that of fractions one and two, (p. 56), spectra XI and XII.

Qualitative Tests. -- Unsaturation is indicated by decolorization of potassium permanganate in acetone and bromine in carbon tetrachloride. A negative 2,4-dinitrophenylhydrazine test is given.

Reaction of cis-2,2,5,5-Tetramethyl-1,3-cyclohexanediol Bismethanesulfonate with Potassium Hydroxide in Methanol

The cis bismesylate (2.77 g, 8.4 mmoles) and 120 ml of methanol (Fisher, Purified) was placed in a one-neck, 500-ml flask fitted with reflux condenser and heating mantle. Potassium hydroxide (5.3 g, 0.095 mole), dissolved in 40 ml of methanol, was added and the mixture was heated at reflux for 11 days.

On cooling and filtering, a precipitate, potassium methanesulfonate (0.70 g, 5.3 mmoles), 31.1% of the theoretical amount was obtained. The filtrate, was worked up in the same manner as that from the trans isomer, p. 65, and the chloroform solution was evaporated to about 20 ml. An infrared spectrum was taken showing presence of the unreacted bismesylate and presence of a carbonyl group. Ethanol (30 ml), 95%, was added and the solution was evaporated to a few ml. On standing, the bismesylate precipitated, 1.1 g (2.2 mmoles), m. p. 158-161° C (m. p. pure, 160.5-162° C).

The ethanolic filtrate was added to a solution of 2,4-dinitrophenylhydrazine in alcohol.³⁶ No derivative was obtained.

³⁶ R. L. Shriner, loc. cit.

Infrared Anal. (IR-XIX). -- A band at 1725 cm^{-1} and a very weak band at 2750 cm^{-1} indicate the presence of 2,2,6-trimethyl-5-heptenal whose carbonyl and aldehyde C-H bands occur at these positions.³⁷ On comparing the intensities of these bands to those of the methanesulfonate group occurring at 1350 and 1180 cm^{-1} , it is apparent that only a small amount of the aldehyde is present.

Reaction of 2,2-Dimethyl-1,3-propanediol with p-Toluenesulfonyl Chloride in Pyridine³⁸

2,2-Dimethyl-1,3-propanediol (10.4 g, 0.1 mole), (Eastman, Pract.), dissolved in 33 ml of pyridine, was placed in a three-neck, 300-ml flask equipped with a reflux condenser and drying tube, addition funnel and a gas trap connected to the drying tube. A solution of 2,4-dinitrophenylhydrazine was placed in the trap such that any gas escaping from the reaction would bubble through this solution. p-Toluenesulfonyl chloride (19.0 g, 0.1 mole), (Eastman, Pract. recrystallized), dissolved in 50 ml of pyridine (Allied Chemical, Reagent) was placed in the dropping funnel. Addition was carried out slowly with stirring at room temperature over a period of 12 hours. If decomposition of the 2,2-dimethyl-1,3-propanediol mono-p-toluenesulfonate had occurred, on its formation, in the same

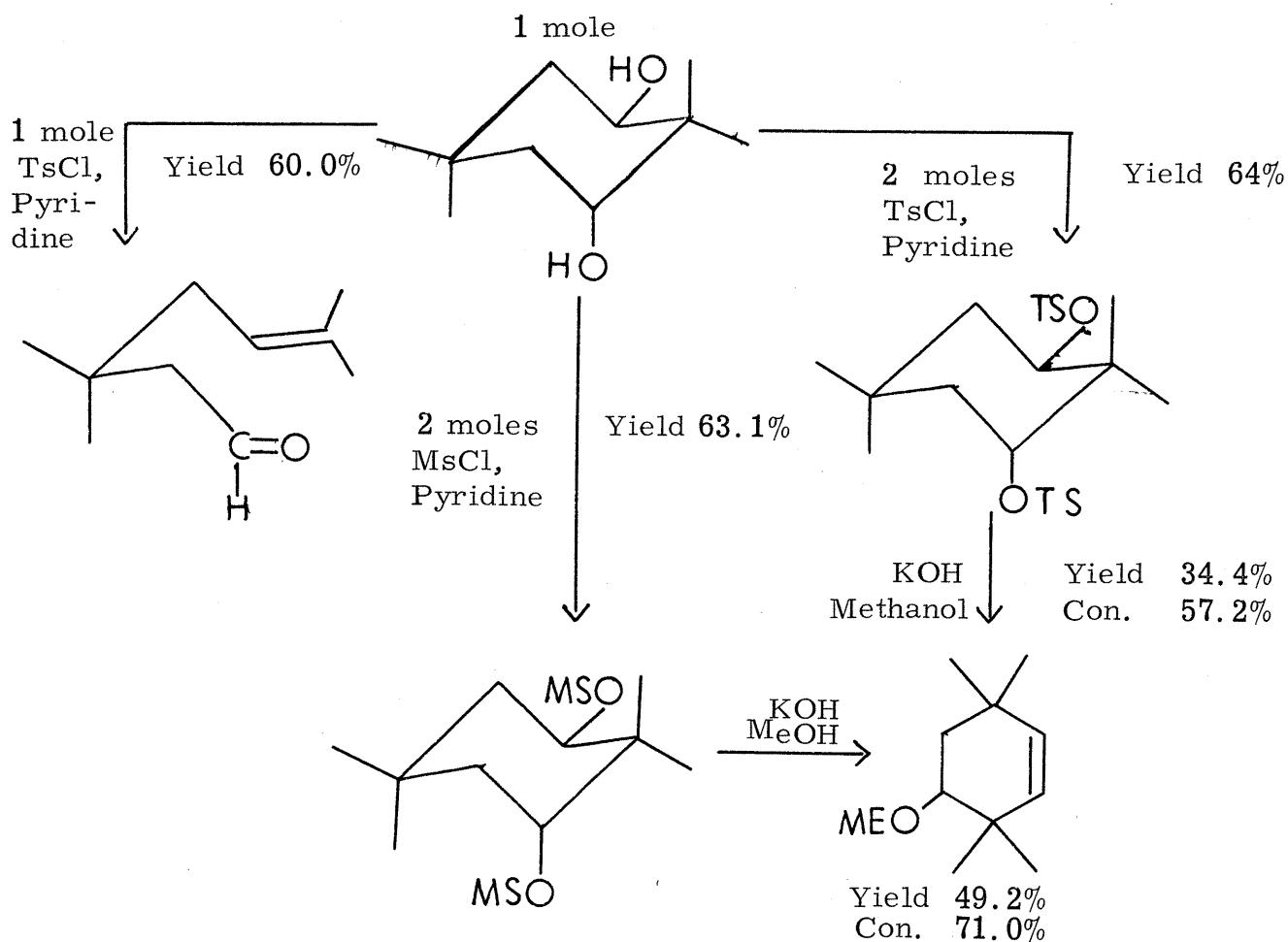
³⁷ See Spectrum VII.

³⁸ R. F. Brown and N. M. van Gulick, J. Am. Chem. Soc., 79, 3467-9 (1957).

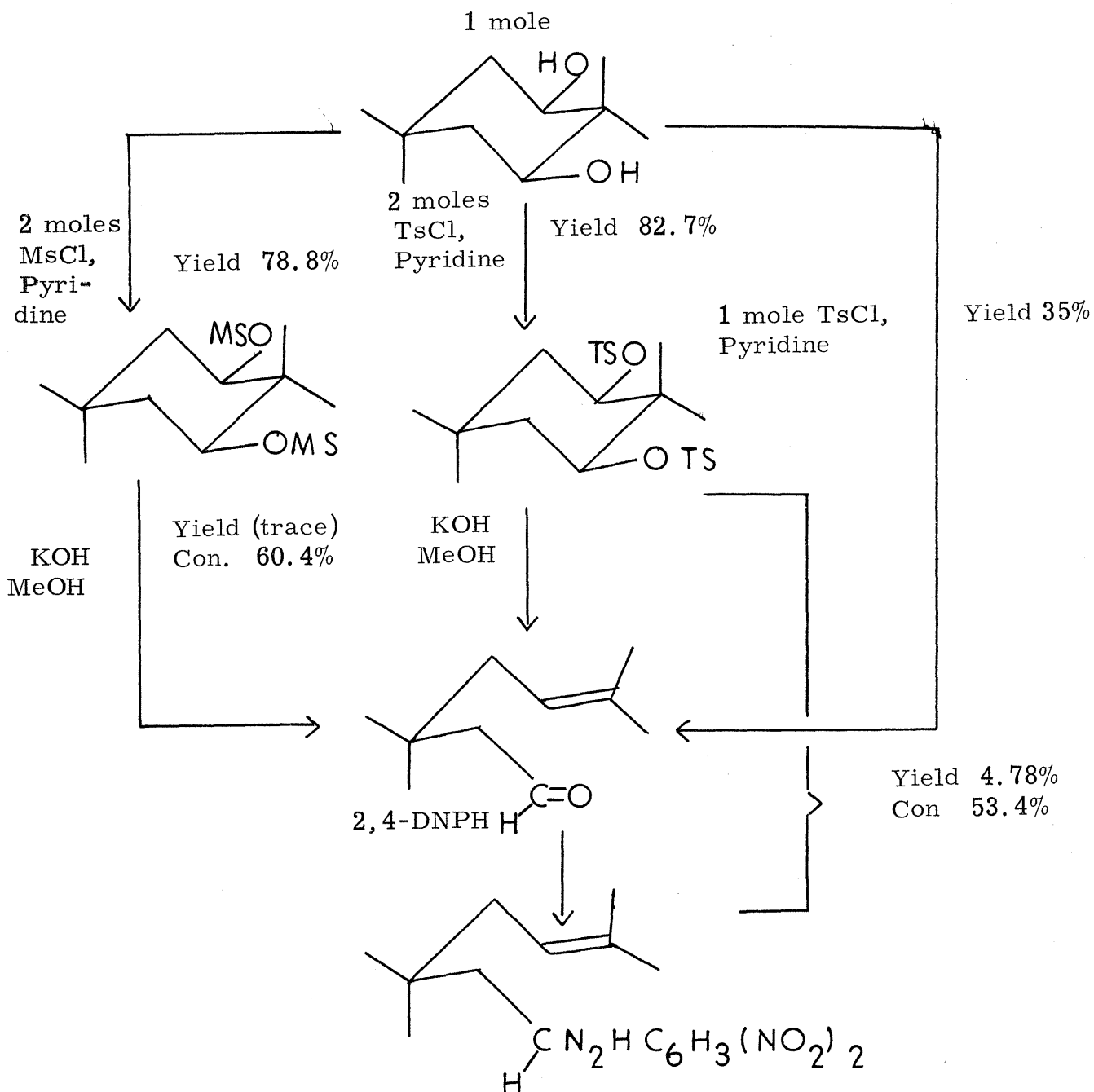
manner as with the cyclic analogues, cis- and trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol mono-p-toluenesulfonates, formaldehyde would have evolved and reacted to form a yellow precipitate in the trap. No such reaction occurred.

Schematic Diagram of Yields and Conversions

Substances derived from trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol:



Substances derived from cis-2,2,5,5-tetramethyl-1,3-cyclohexanediol:

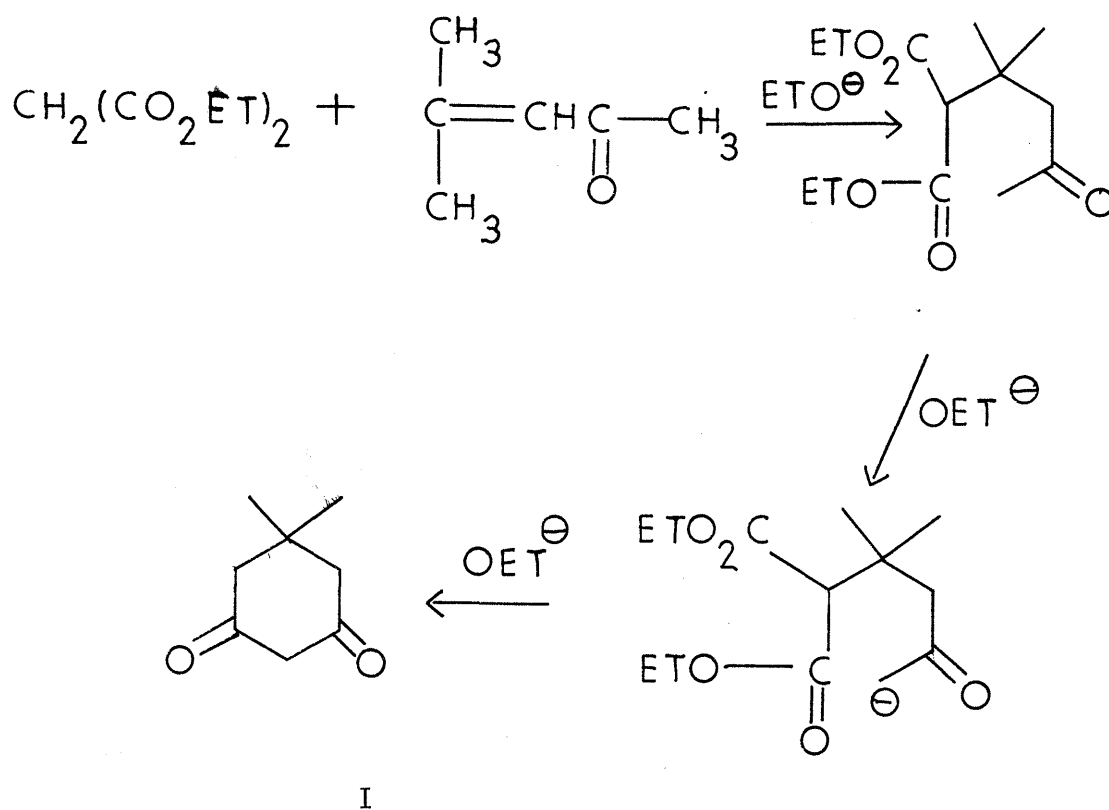


Ts = Tosylate, Ms = Mesylate, MeOH = Methanol, 2,4-DNPH = 2,4-Dinitrophenylhydrazine

CHAPTER IV

DISCUSSION OF EXPERIMENTAL

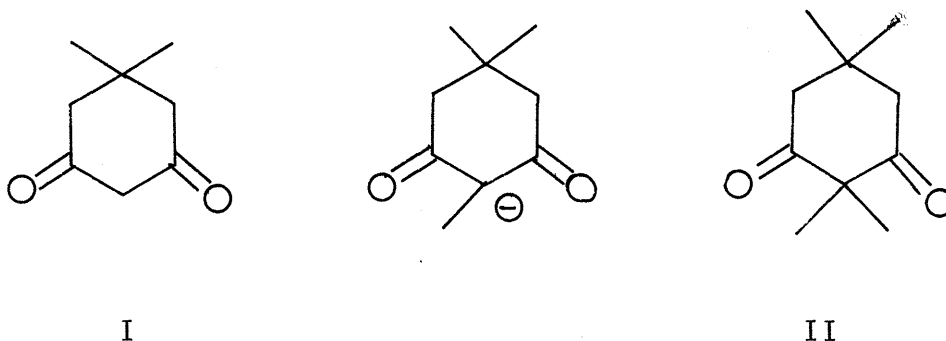
2,2,5,5-Tetramethyl-1,3-cyclohexanedione (II) was synthesized by preparation and methylation of dimedone (I) according to the following reaction sequence. The last three steps occur



without isolation of intermediates.

The methylation of the 2-position was carried out by the

procedure of Hirsjarvi and Toivonen¹ which gave yields in the range of 13-20%. Another method, using methyl iodide and sodium hydride was tried in order to improve the yield. However, this was found to be somewhat less efficient since yields of the order of 8% were obtained.



Reduction of 2,2,5,5-tetramethyl-1,3-cyclohexanedione to the diols was effected by use of sodium borohydride in alcohol and water. This procedure gives both cis and trans isomers, III and IV, which were separated by fractional crystallization. The higher melting of



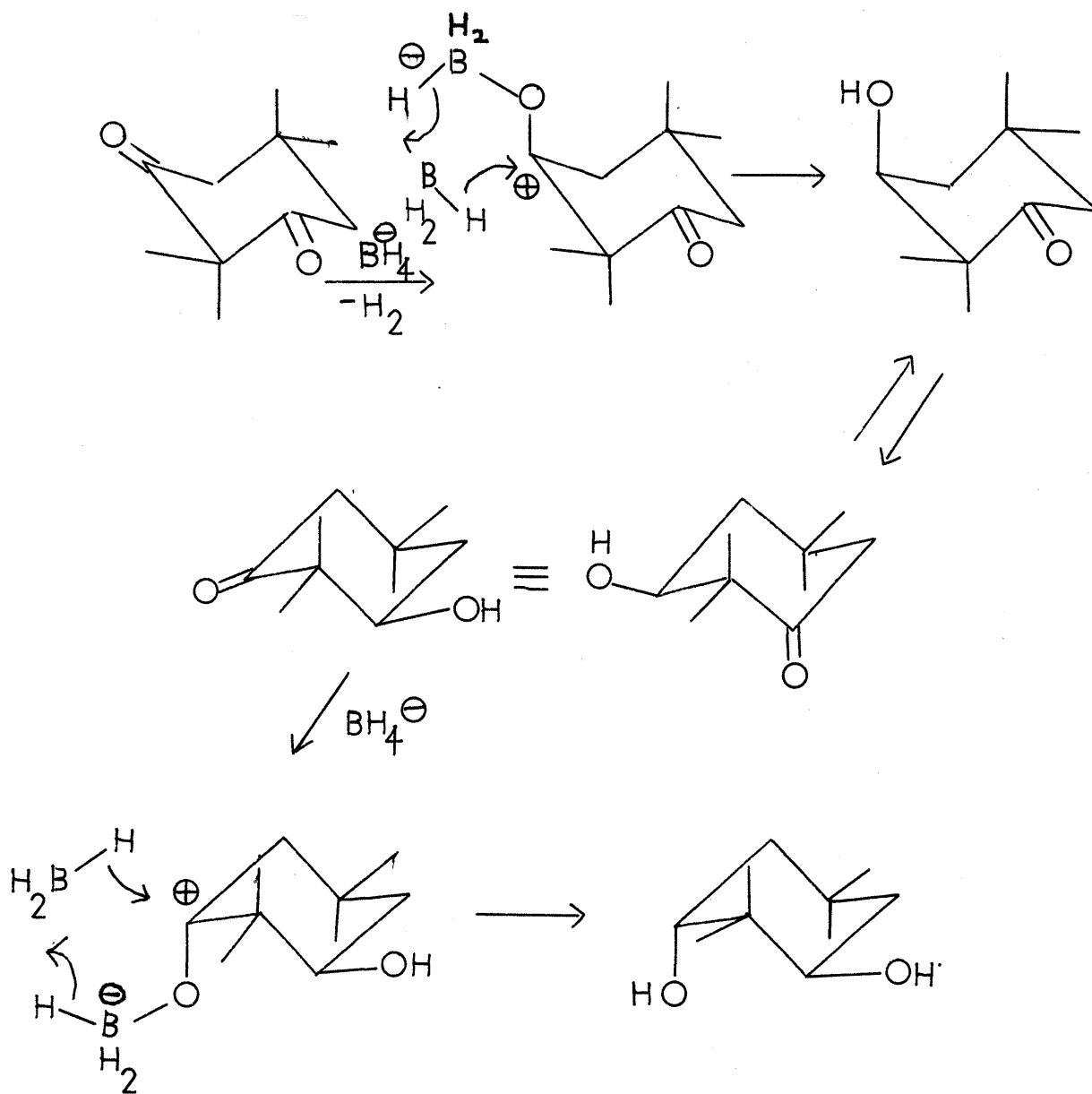
¹ W..R. Hendrix, "Retropinacol Rearrangements, The Effect of Structure," Master's Thesis, University of Alabama, 1956, pp. 47-48.

these isomers, m.p. 205-6° C, has been shown to have the cis configuration and the lower melting, m.p. 107-8° C, the trans, by resolution of the asymmetric trans isomer into its optical enantiomers.²

A predominance of the trans isomer was noted in all reductions carried out, of which a typical result gave 38.9% cis and 43.4% trans. From a consideration of the mechanism for sodium borohydride reduction³ and the conformational structure of the diketone, this result can be ascribed to a steric requirement for the transition state of the reduction. For a cyclic or concerted mechanism, the transition state would be most stable when the six-member group is spatially oriented away from the cyclohexane ring. The most favorable position for this would place the -O- in the axial position. The intervention of such a mechanism is possibly responsible for the predominance of the trans isomer.

² A. W. Allan, R. P. A. Sneeden and J. Colvin, J. Chem. Soc. 557-9 (1958).

³ D. J. Cram and G. S. Hammond, "Organic Chemistry," McGraw-Hill, Inc., Boston, 1959, pp.205-6.

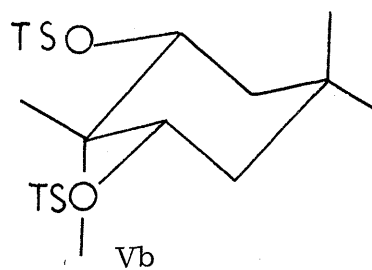
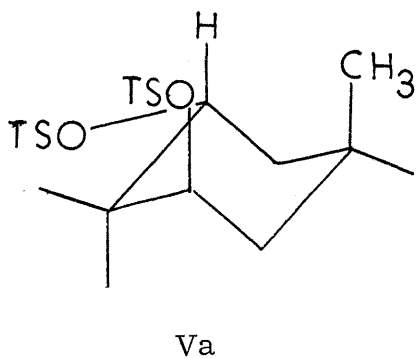


III

Fractional crystallization was found to be the most expedient means for separation of the cis- and trans-diols. A chromatographic procedure, in which the diols were eluted from an alumina column, was tried without success. There was little or no enrichment of the diols in the separated fractions.

The synthesis of the p-toluenesulfonates (tosylates) of these cyclic diols using p-toluenesulfonyl chloride and pyridine required more stringent conditions and more careful purification of the starting materials than is ordinarily needed for preparation of tosylates.⁴ The standard use of low temperature (0-15° C) and relatively short reaction periods was of no avail. trans-2,2,5,5-Tetramethyl-1,3-cyclohexanediol bistosylate was obtained in 69% yield by heating the reaction mixture 20 hours at 50-60° C. The corresponding cis isomer was prepared in 61% yield by allowing the reactants to stand at room temperature 72 hours.

In an alternate procedure the cis- and trans-bistosylates were prepared in 82.7% and 64.0%, respectively, by allowing the reactants to stand for 11 days. The lower yield of the trans isomer is probably due to the relative instability of the trans as compared to the cis. The introduction of a p-toluenesulfonate group on the axial oxygen causes steric strain due to non-bonded interaction between this group, the axial methyl group on carbon 5, and the axial hydrogen on



⁴ R. S. Tipson, J. Org. Chem., 9, 235-241 (1949).

carbon 1. No such interaction would be incurred with the formation of the cis isomer since both tosylate groups are in equatorial positions.

The characteristic absorption frequencies for the sulfonate group, in the cis isomer, occur at 1175 and 1375 cm^{-1} , and at 1180 and 1365 cm^{-1} in the trans isomer. The 10 cm^{-1} shift toward a lower frequency in the trans might be a result of the steric opposition mentioned above. The opposing methyl and hydrogen groups probably place a constraint on the vibrational modes of the p-toluene-sulfonate group.

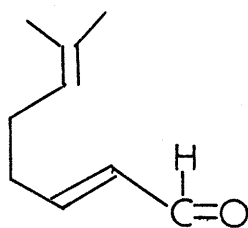
It is significant, however, that the effect of 1,3 steric interactions in cyclohexane systems appears to have little effect on rates of $\text{S}_{\text{N}}2$ reactions. Eliel⁵ found the rates of displacement of the tosylate group from trans-3,3,5-trimethylcyclohexyl tosylate and 4-tert-butylcyclohexyl tosylate to be approximately the same.

The bismesylates of cis- and trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol were prepared by the same method used for the tosylates. The reactions were carried out at room temperature. The cis-bismesylate was prepared in 78.8% yield during a reaction period of 16 hours. The trans-bismesylate was prepared in 63.1% yield during a period of 12 hours. The shorter reaction periods

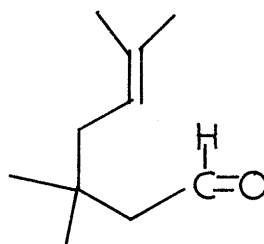
⁵ E. L. Eliel and R. P. Gerber, Tetrahedron Letters, 1961, 473-6.

required for the mesylates is a result of the higher reactivity of methanesulfonyl chloride as compared to p-toluenesulfonyl chloride. Again, the relative yields of the two isomers are probably determined by steric factors, although to a lesser degree than in the case of the tosylates.

In attempts to prepare the monotosylates of the cis- and trans-diols by slow addition of a 1:1 molar quantity of p-toluenesulfonyl chloride to the diol in pyridine, a liquid with an exotic odor was consistently obtained. This was found to be due to an aldehyde based upon its carbonyl absorption at 1725 cm^{-1} , H-CO absorption at 2750 cm^{-1} , and qualitative tests, i. e., a derivative from 2,4-dinitrophenylhydrazine and Benedict's test. Unsaturation was indicated by absorption at 1680 cm^{-1} and by a positive test with bromine in carbon tetrachloride and with potassium permanganate in acetone. The odor of the material, reminiscent of lemon-grass oil, suggested a structure close to that of citral (VI), a natural product occurring in lemon-grass oil. An inspection of the possible mechanisms for

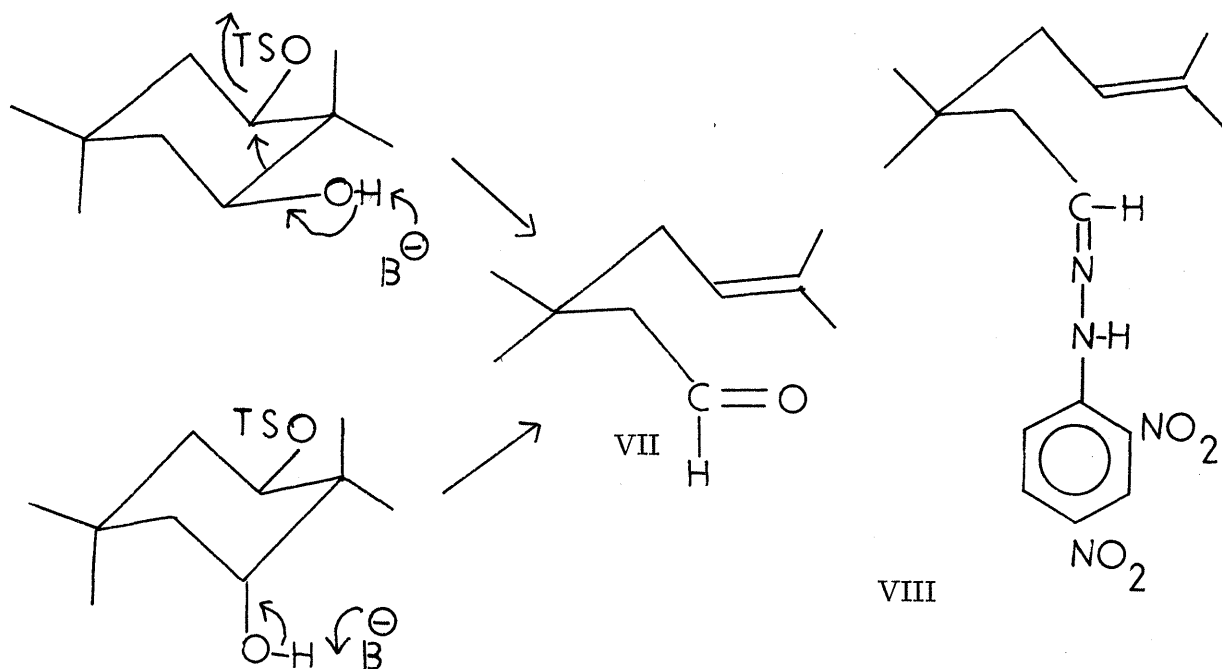


VI



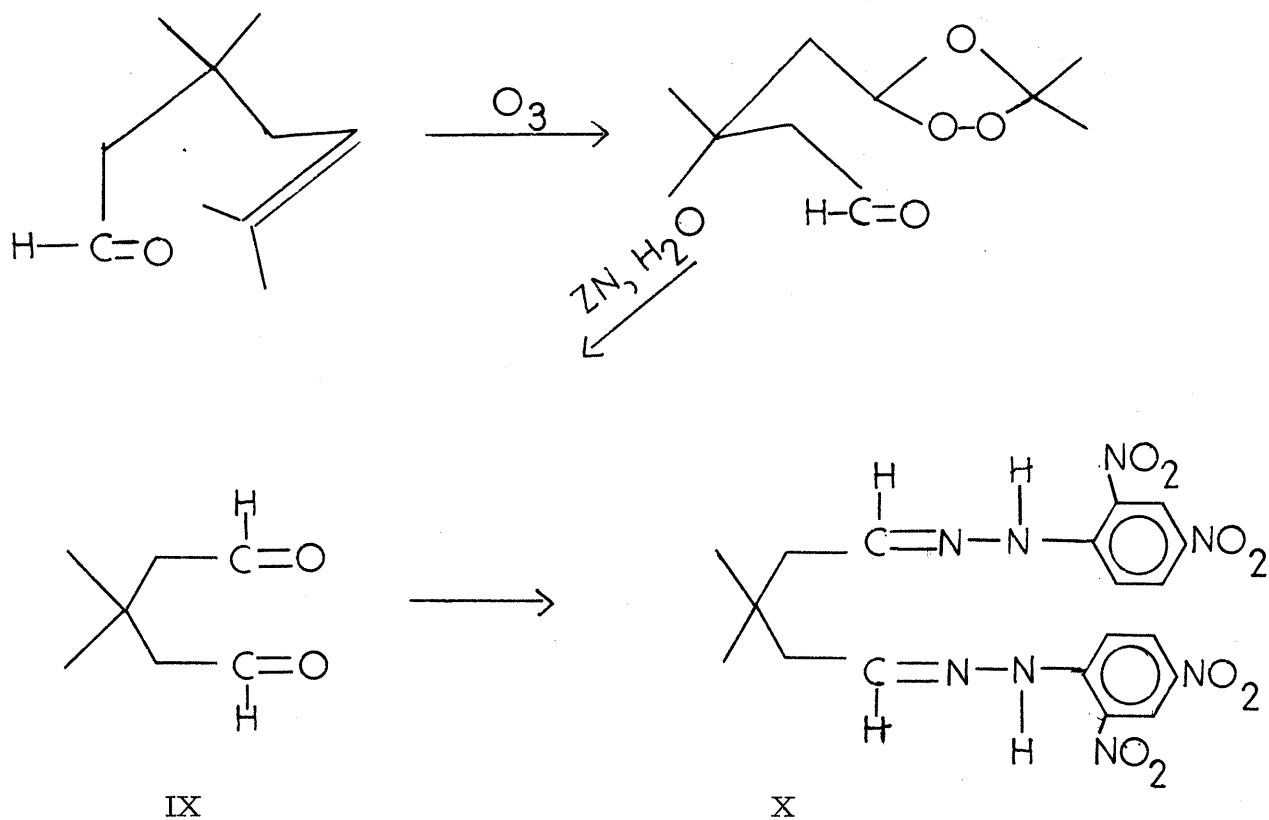
VII

rearrangement of 2,2,5,5-tetramethyl-1,3-cyclohexanediol mono-tosylate, an assumed intermediate, suggested a possible structure, 3,3,6-trimethyl-5-heptenal (VII), for this compound:



Elemental analysis for the aldehyde is consistent with the empirical formula, $C_{10}H_{18}O$, VII, while that for the 2,4-dinitrophenylhydrazone is consistent with the formula, $C_{16}H_{23}O_4N_4$, VIII. The absorption at 1680 cm^{-1} falls in the range quoted by Bellamy⁶ for the olefin type, $RR_1C = CHR_2$. The presence of the terminal isopropylidene group is further substantiated by the results of ozonolysis:

⁶ L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., 1956, p. 36.



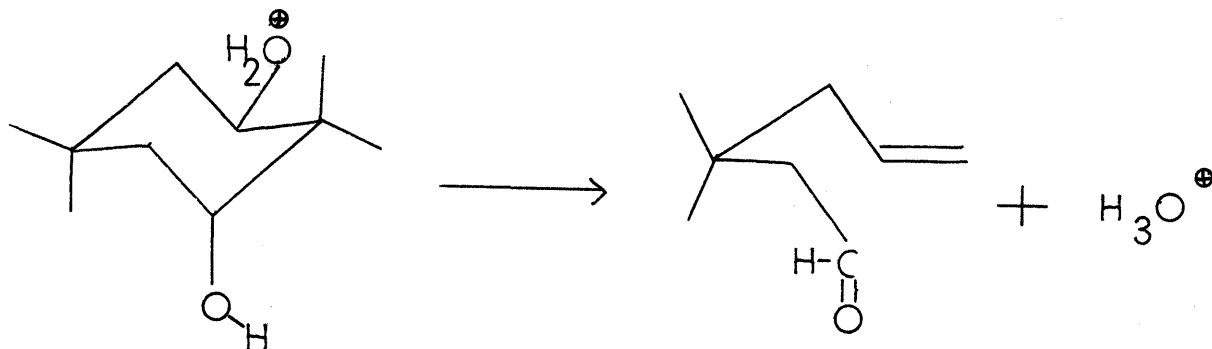
The aldehyde VII was ozonized to 3,3-dimethylglutaraldehyde (IX). Without isolating IX, the bis-(2,4-dinitrophenylhydrazone), (X), was made directly. The melting point, 236.5-238.5° C, agrees closely with that reported for X, 238-239° C by Meinwald.⁷

This reaction represents a case of a unique rearrangement. Such a reaction was thought by Allan⁸ to be probable in acidic

⁷ J. Meinwald and P. Chuan, J. Am. Chem. Soc., **82**, 699 (1960).

⁸ A. W. Allan, R. P. A. Sneeden, J. M. Wilson, J. Chem. Soc., 2186 (1959).

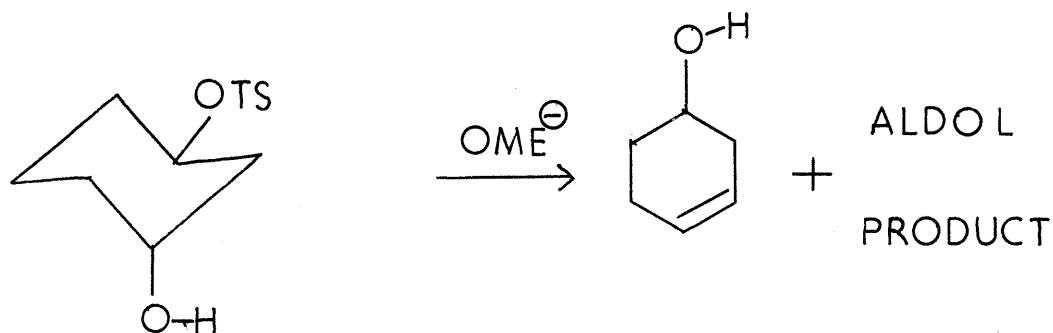
dehydration of the 2,2,5,5-tetramethyl-1,3-cyclohexanediols. However, these workers detected no such rearrangement in actual experiment. In the present case, the efficiency of the tosylate as a leaving



VII

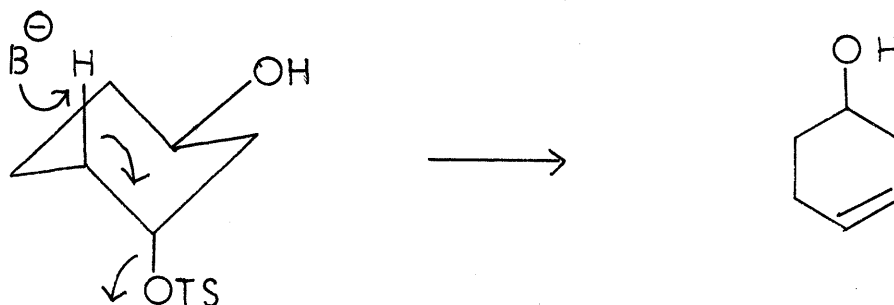
group is probably the driving force of the reaction which, in turn, is assisted by base attack on the hydroxyl hydrogen, the base, in this case, being pyridine.

Brutcher and Cenci⁹ propose a similar mechanism to account for results obtained from basic solvolysis of cyclohexanediol monotosylates:

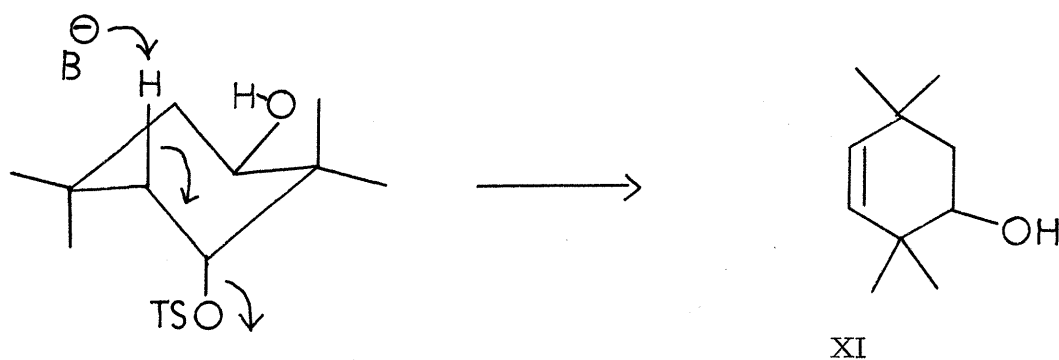


⁹ F. V. Brutcher and H. J. Cenci, Chem. and Ind., 1625-6 (1957).

The simple aldehyde was not isolated in this case, instead the aldol condensation product of the aldehyde was obtained. In addition an unsaturated alcohol was a second product. This resulted from the ability of the relatively non-constrained cyclohexane ring to assume a conformation in which the tosylate group occupies an axial position such that a planar 4-center elimination might occur.

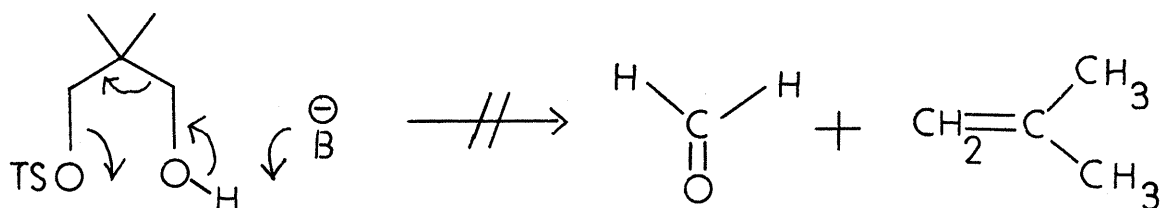


With the cis- or trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol tosylate a planar 4-center elimination conformation is sterically unfavorable. None of the alcohol, 2,2,5,5-tetramethyl-3-cyclohexenol



(XI), was obtained as denoted by absence of O-H absorptions in the spectra of the reaction residues and products.

It is significant to note that the open chain tosylate analogue of 2,2,5,5-tetramethyl-1,3-cyclohexanediol monotosylate, i. e., 2,2-dimethyl-1,3-propanediol monotosylate, (XII), does not undergo an analogous rearrangement:



On preparation of this compound under the same conditions by which rearrangement was effected with the monotosylates, no formaldehyde was detected in a gas trap containing 2,4-dinitrophenylhydrazine.

In the attempted preparation of trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol monomethanesulfonate, no aldehyde was isolated. Instead a heavy oil, presumably the impure monomesylate, which could not be distilled nor crystallized was obtained. The infrared spectrum, (IR-XVIII), shows an O-H group at 3640 cm^{-1} and hydrogen bonding at $3440\text{-}3570\text{ cm}^{-1}$. Absorptions at 1350 and 1180 cm^{-1} are indicative of the sulfonate group. The mesylate group apparently is not as effective a leaving group as the tosylate. Hence, the rearrangement does not occur to give the aldehyde under these conditions. This leaves little doubt that the driving force of the reaction is the leaving ability of the tosylate group.

The bistosylates of 2,2,5,5-tetramethyl-1,3-cyclohexanediol were found to be relatively inert toward mild solvolytic conditions with acetic acid using the general methods of Grunwald¹⁰ and Roberts.¹¹ However, at higher temperatures and longer heating periods, spectral evidence, IR-XIV and IR-XV, of substitution of the tosylate by the acetate ion was obtained. The identity of the infrared spectra of the products from acetolysis of cis (IR-XIV) and trans (IR-XV) bistosylates indicates that acetates were obtained from both isomers, although it must be noted that these were obtained in very small amounts. This is consistent with the results usually obtained, i. e., in solvolysis of tosylates, the substituted products often are present in a small ratio to the elimination products.^{12, 13} No evidence for rearrangement could be ascertained from the spectra.

Formolysis of the bistosylates was less rewarding since the solubility of the tosylates could be effected only after 70° C had been reached, at which point extensive decomposition occurred. Spectral evidence of substitution of the tosylate group by formate was obtained from the trans-bistosylate (IR-XVI).

¹⁰ E. Grunwald and S. Winstein, J. Am. Chem. Soc., 79, 3278 (1957).

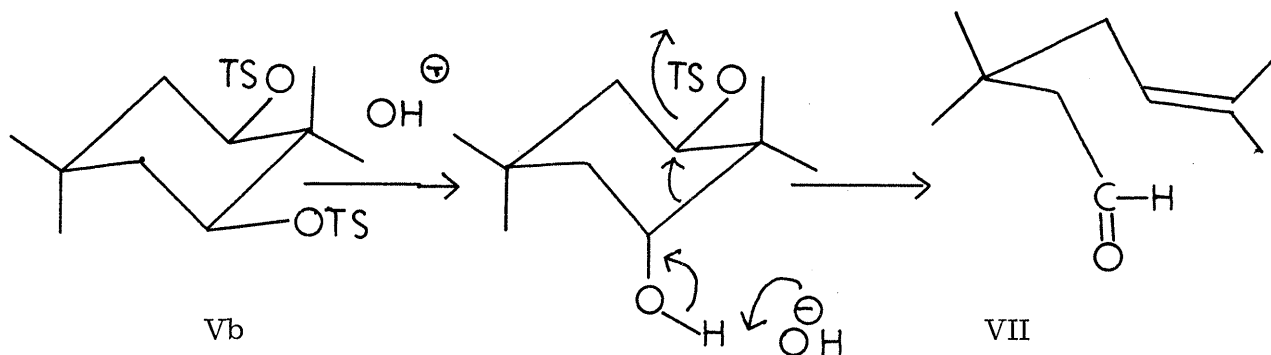
¹¹ J. D. Roberts and V. C. Chambers, J. Am. Chem. Soc., 73, 5034 (1951).

¹² E. Grunwald and S. Winstein, loc. cit.

¹³ J. D. Roberts and V. C. Chambers, loc. cit.

The reaction of the diol bistosylates with potassium hydroxide and methanol occurred with rearrangement in the case of the cis and with substitution and elimination in the case of the trans isomer.

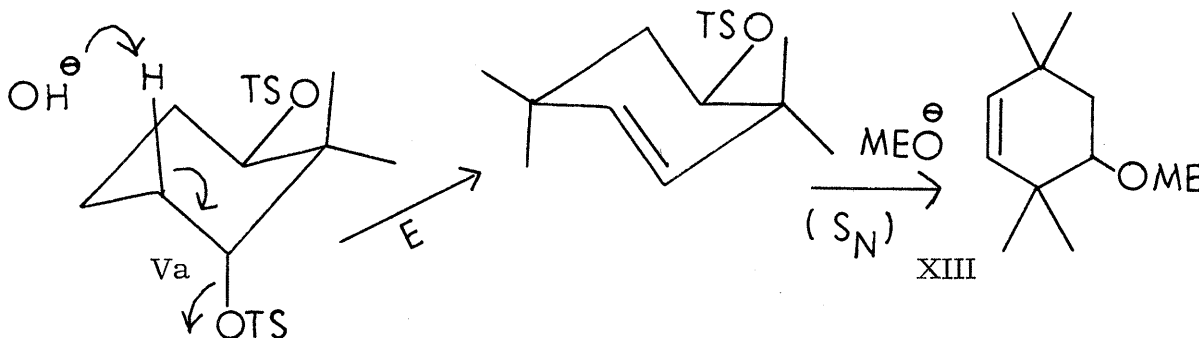
cis-2,2,5,5-Tetramethyl-1,3-cyclohexanediol bistosylate (Vb) was refluxed 7 days in 0.58N KOH in methanol. 3,3,6-Trimethyl-5-heptenal was detected in the residue by its spectral absorption at 1725 cm^{-1} . The material was converted directly to its 2,4-dinitrophenylhydrazone, the weight of which represented a 4.8% yield of the aldehyde. The spectrum of the 2,4-dinitrophenylhydrazone (IR-X) is found to be identical to that taken previously of the analyzed sample (IR-IX). The reaction is assumed to proceed through an initial



substitution of a tosylate group by hydroxide ion and rearrangement occurs in the same manner as described previously for the mono-tosylation reaction. No products of elimination were detected. The inertness of the cis tosylate to basic methanolysis was also considerable since much (47%) of the cis-tosylate was recovered.

In contrast, the trans-2,2,5,5-tetramethyl-1,3-cyclohex-
 anediol bistosylate (Va) under identical conditions, gave none of the
 aldehyde VII but gave, instead, an unsaturated ether together with a
 lower boiling product. An ether group is indicated by absorption
 at 1075 cm^{-1} and unsaturation is indicated at 1650 cm^{-1} . $\text{CH}_3\text{-C}$
 group absorption is found at 1475 cm^{-1} and $(\text{CH}_3)_2\text{C}$ at 1360 and
 1387 cm^{-1} .

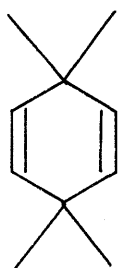
Elemental analysis on a repeatedly distilled sample was con-
 sistent with the formula $\text{C}_{11}\text{H}_{20}\text{O}$. Tests for unsaturation were positive.
 These data together with nuclear magnetic resonance studies (p. 58)
 indicate that a large percentage of the material has the structure,
 4-methoxy-3,3,6,6-tetramethylcyclohexene (XIII).



In this reaction potassium p-toluenesulfonate was precipitated
 on cooling; 57.2% of the theoretical amount was obtained. None of
 the trans-bistosylate was recovered. The trans isomer is apparently
 more reactive toward basic methanolysis than is the cis.

The material obtained in the lower boiling range is most likely
 the ether contaminated with a more olefinic product. A comparison

of infrared spectra XI and XII shows a relatively stronger olefinic absorption at 1650 cm^{-1} for this fraction but otherwise the bands are essentially the same. The impurity could be 3,3,6,6-tetramethyl-1,4-cyclohexadiene (XIV) which would result from total elimination, whereas XIII was a result of elimination and substitution.



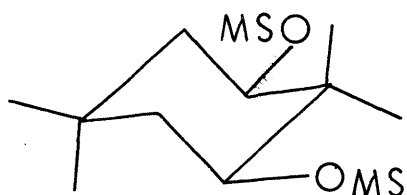
XIV

An almost identical result was obtained on basic methanolysis of trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol bismesylate. 4-Methoxy-3,3,6,6-tetramethylcyclohexene was obtained in 46.9% yield, though in somewhat less purity. Comparison of the spectrum (IR-XVIII) and physical constants to those obtained (IR-XII) for the product derived from the trans-bistosylate shows these products to be, within limits of purity, the same. Qualitative tests for unsaturation were positive. A negative test was obtained with 2,4-dinitrophenylhydrazine.

cis-2,2,5,5-Tetramethyl-1,3-cyclohexanediol bismesylate (XV) was very inert toward basic methanolysis. An absorption at

1725 cm^{-1} and a very weak absorption at 2750 cm^{-1} (IR-XIX) indicate the presence of a trace of 3,3,6-trimethyl-5-heptenal.

This reluctance toward rearrangement is likely a consequence of the lesser ability of methanesulfonate as a leaving group. Elimination is also unfavorable since both methanesulfonate groups are in equatorial positions.

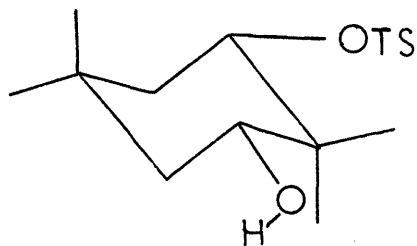


XV

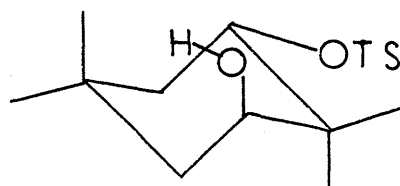
CHAPTER V

INTERPRETATION OF EXPERIMENTAL RESULTS

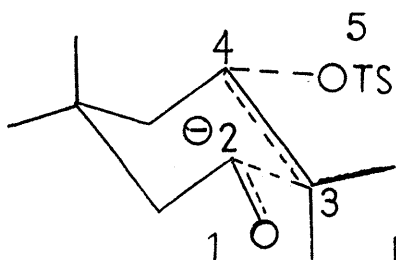
The mechanism of rearrangement of the unstable cis- and trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol monotosylates (I) and (II) can be described as a 5-center, base-catalyzed reaction.¹ Transition states are represented by Ia and IIa. A preference for coplanarity



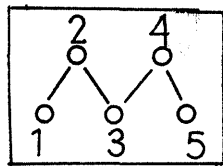
I



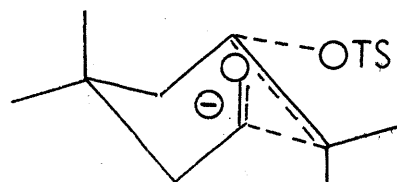
II



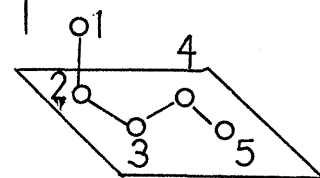
Ia



Ib



IIa



IIb

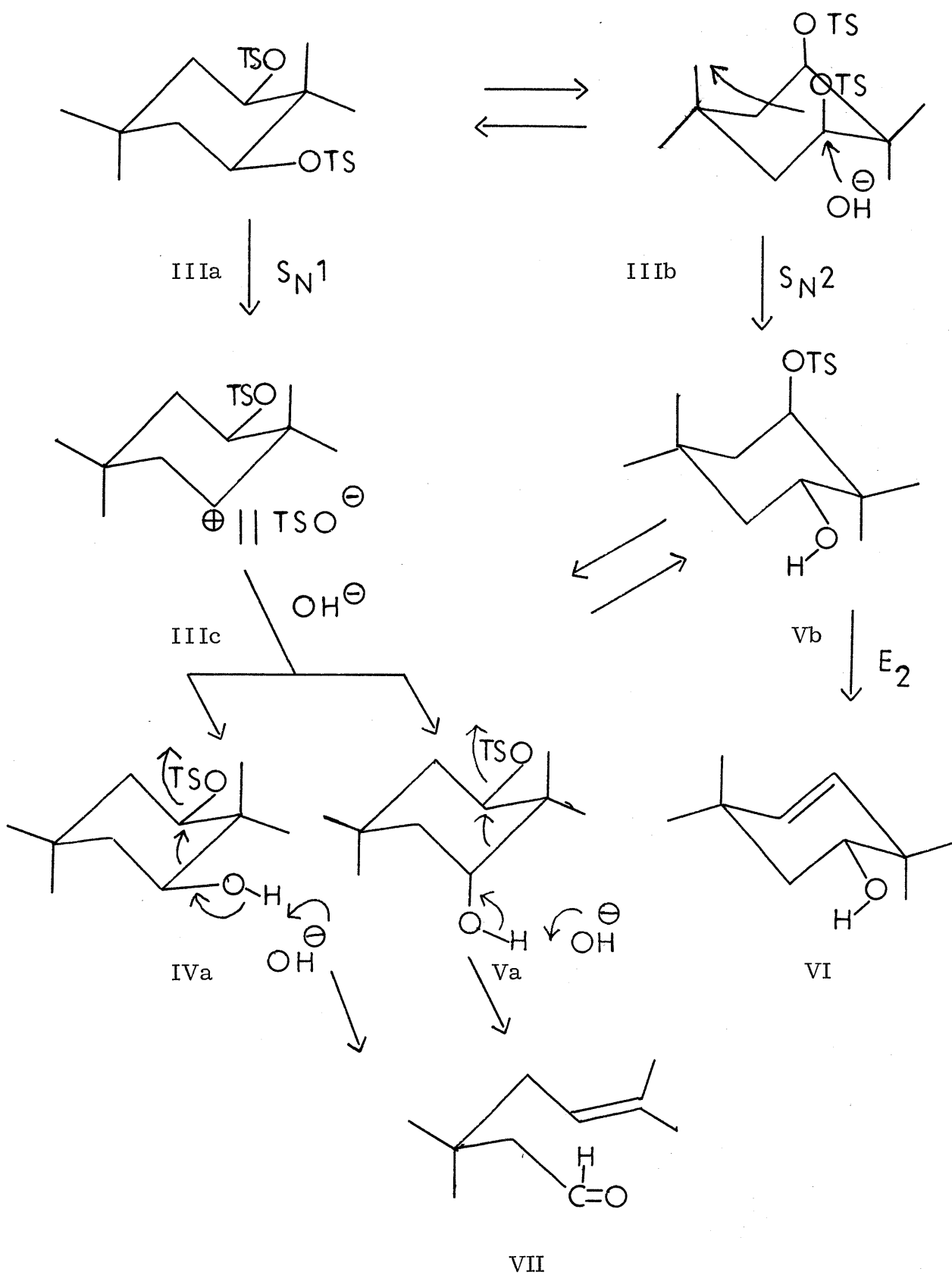
¹F. V. Brutcher and H. J. Cenci, Chem. and Ind., 1625-6 (1957).

of the five atoms in the transition states is probable since a linear transition state is preferred for 3-center reactions (Walden inversions) and a coplanar transition state for 4-center reactions (E_2 -type eliminations).^{2,3} The transition state may be stabilized to a greater extent by distribution of electron charge density where the five centers lie in an extended plane as shown in Ia and Ib (in which heavy dots represent the numbered coplanar atoms) than in the case where four centers lie in a plane and one out of the plane, IIa and IIb. The less favored of the two transition states would be the one in which the anionic oxygen lies out of the plane of the other four members. This would occur if the transition state for the trans isomer were to retain the configuration of the ground state such that the anionic oxygen remains in the axial position (IIb). Rate data would be necessary to more rigorously study the nature of these transition states.

The conversion of cis-2,2,5,5-tetramethyl-1,3-cyclohexanediol bistosylate to 3,3,6-trimethyl-5-heptenal apparently proceeds in the same manner after substitution of one of the tosylate groups by a hydroxide ion. Replacement of the tosylate group possibly could occur either by an S_N1 or S_N2 reaction.

² E. D. Hughes and C. K. Ingold, J. Chem. Soc., 2093, 2117, (1948).

³ D. H. R. Barton and R. C. Cookson, Quart. Rev. Chem. Soc., 1956, 10, 44.



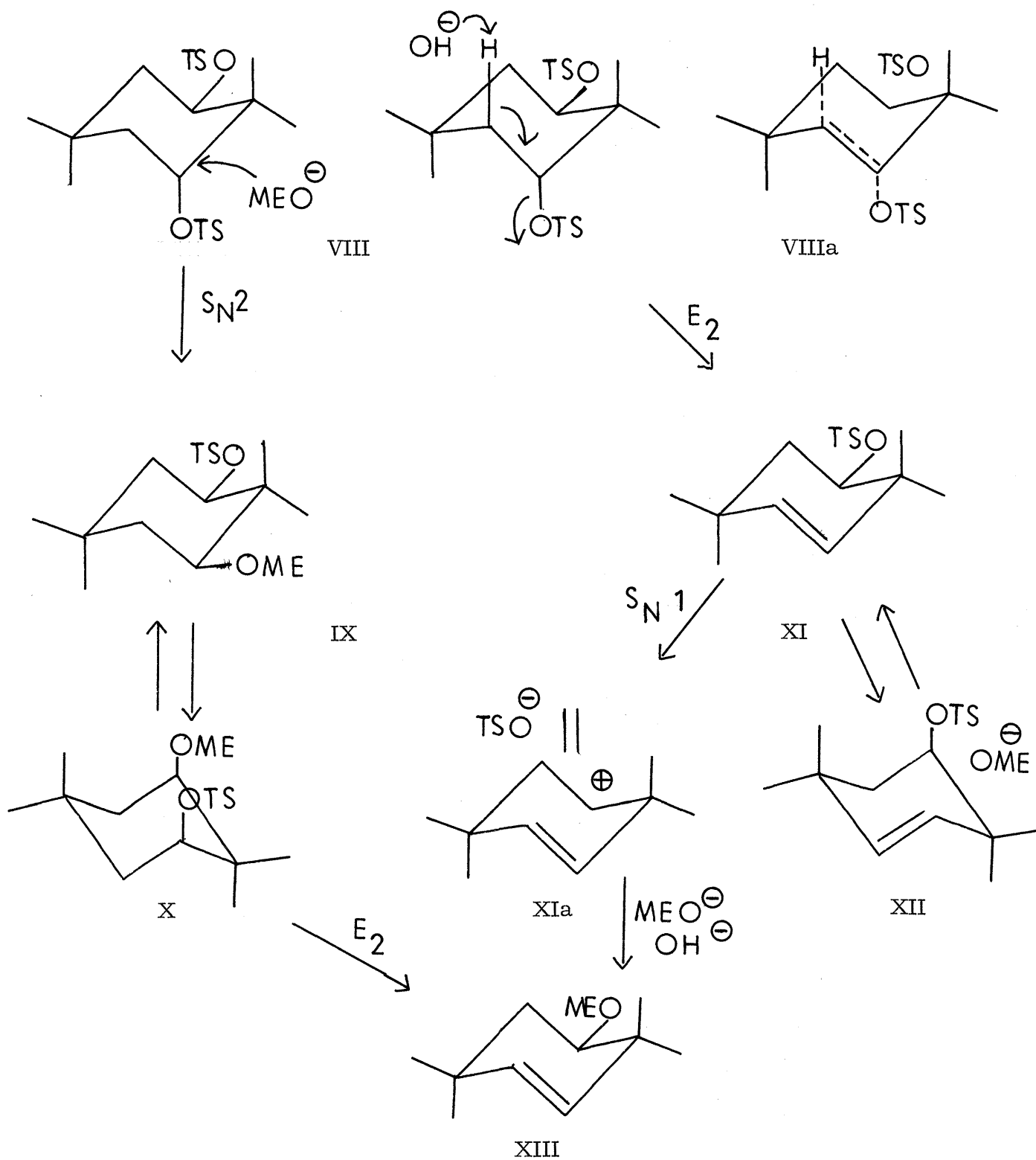
For an S_N2 reaction to occur, attack must take place at the back side of the carbon bonded to the leaving group. Such an attack would be sterically impossible with the cis (e, e) conformation (IIIa). S_N2 attack might occur on the cis (a, a) conformation, however, this conformation with both tosylate groups in axial positions is highly unfavorable because of non-bonded interaction among the tosylates and the axial 5-methyl group. The more logical course of reaction would be an S_N1 displacement, in which ion pair formation occurs (IIIc). Substitution by the OH^- ion would give both cis- and trans-monotosylates, IVa and Va, which rearrange to the aldehyde. The small amount of product obtained suggests that the S_N1 reaction occurs to only a limited extent. This is consistent with the solvating action of methanol, resulting in its poor ability to induce ionization, which is more conducive to S_N2 than S_N1 reactions in general.⁴

The conformation Vb would afford a facile elimination (E_2) reaction to give 2,2,5,5-tetramethyl-3-cyclohexenol VI. Since no material was obtained, the intervention of an intermediate of this conformation is unlikely.

The basic methanolysis of both trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol bistosylate (VIII) and trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol bismesylate to give 4-methoxy-3,3,6,6-tetramethylcyclohexene involves both substitution and elimination. The order in

⁴E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, 1959, p. 253.

which these processes occur is not certain. Two possible routes are presented in the following scheme. An initial substitution would



require, subsequently, an unfavorable conformation X in order for elimination to occur. The steric opposition of the tosylate, the methoxy and methyl groups together with the unfavorable parallel dipoles of the methoxy and tosylate groups make this conformation extremely unlikely. On the other hand a planar 4-center transition state VIIIa, favorable for initial elimination, could be attained with a smaller activation energy than would be required for conformation X.

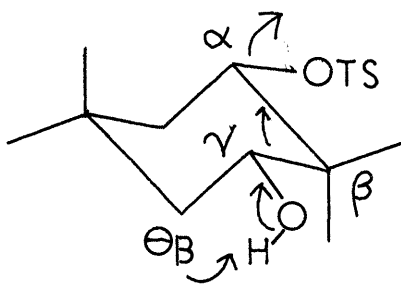
The simultaneous occurrence of the two processes is hardly feasible in view of the possibility of a common transition state which could give either result.

The substitution reaction is thought to occur by an S_N2 mechanism. If it were S_N1 proceeding through intermediate ion-pairs, the collapse of the ion-pairs should result in substitution by the hydroxide ion as in the case of the cis isomer. In the latter, selectivity of the more basic hydroxide ion by the substrate carbonium ion probably occurred.⁵ Since the hydroxide and methoxide ions have comparable nucleophilic character and the less basic methoxide ion is the more prevalent specie, it is reasonable that the product obtained, i.e., the methyl ether XIII, was derived through an S_N2 reaction. The amount of product (19-34%) derived from the

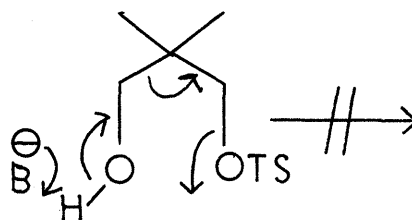
⁵ E. S. Gould, op. cit., p. 261.

trans isomer as opposed to that from the cis isomer (4.8%) indicates a more rapid reaction in the case of the former. Since a methanol medium is more conducive to an S_N2 reaction (p. 90) than an S_N1 , it is most likely that the substitution is S_N2 .

In relation to the original proposition of this dissertation, i. e., demonstration of skeletal rearrangement of cis- and trans-2,2,5,5-tetramethyl-1-3-cyclohexanediol monotosylate initiated by nucleophilic attack at a beta carbon (p. 22), no 1,2-shifts were actually observed. However, the rearrangement of the cis- and trans-monotosylates can be regarded as a 1,3-shift, a pinacol type rearrangement (p. 27), initiated by attack at a gamma carbon, where the attacking nucleophile is the electron pair of the O-H bond.



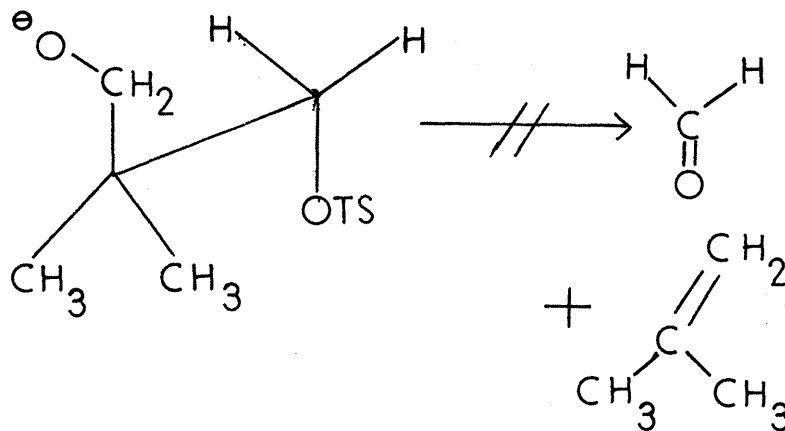
I



XIX

The analogous rearrangement does not occur in the open chain compound XIX. The reason for this is possibly a result of an increased field effect, due to free rotation, repelling an attacking nucleophile. Still another explanation is tenable. As pointed out

previously (p. 87), a 5-center transition state requires that the centers be coplanar. In the cyclic system, the reaction conformation is virtually that of the ground state which resembles the reaction conformation of XIX:



The freedom of rotation of the hydroxymethylene group does not allow the reaction to occur.

CHAPTER VI

SUMMARY

The bis-p-toluenesulfonates and bis-methanesulfonates of cis- and trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol were synthesized. The mono-p-toluenesulfonates, derived from both cis- and trans-diols, were found to be unstable and on formation in presence of base gave immediate ring-cleavage rearrangement to 3,3,6-trimethyl-5-heptenal.

Acetolysis of the bistosylates, found to be slow under the usual conditions of acetolysis, yielded traces of acetates at higher temperatures.

Basic methanolysis of cis-2,2,5,5-tetramethyl-1,3-cyclohexanediol bistosylate gave rearrangement to 3,3,6-trimethyl-5-heptenal while the trans isomer, under the same conditions gave 4-methoxy-3,3,6,6-tetramethylcyclohexene, a product resulting from elimination and substitution.

New compounds were cis-2,2,5,5-tetramethyl-1,3-cyclohexanediol bis-p-toluenesulfonate, trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol bis-p-toluenesulfonate, cis-2,2,5,5-tetramethyl-1,3-cyclohexanediol bis-methanesulfonate, trans-2,2,5,5-tetramethyl-1,3-cyclohexanediol bismethanesulfonate, 3,3,6-trimethyl-5-heptenal, 3,3,6-trimethyl-5-heptenal 2,4-dinitrophenylhydrazone, and 4-methoxy-3,3,6,6-tetramethylcyclohexene.

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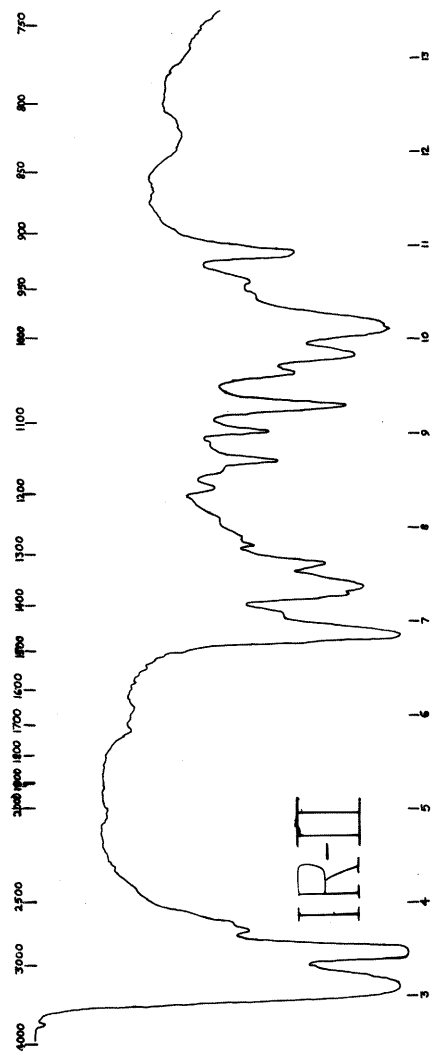
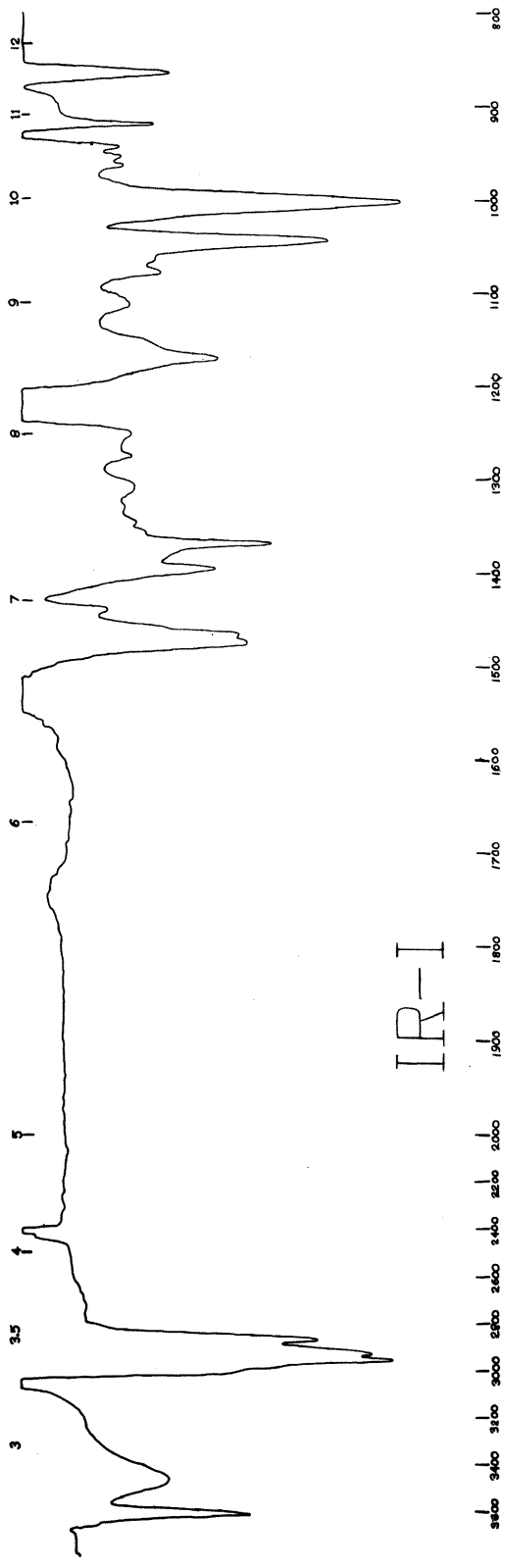
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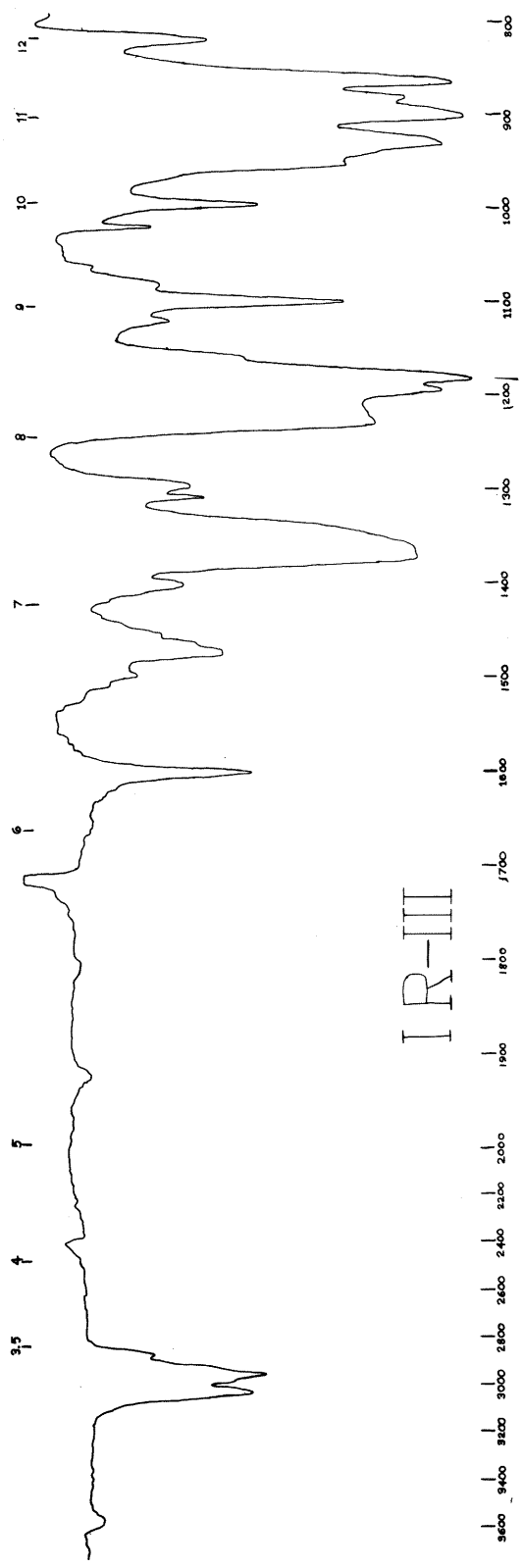
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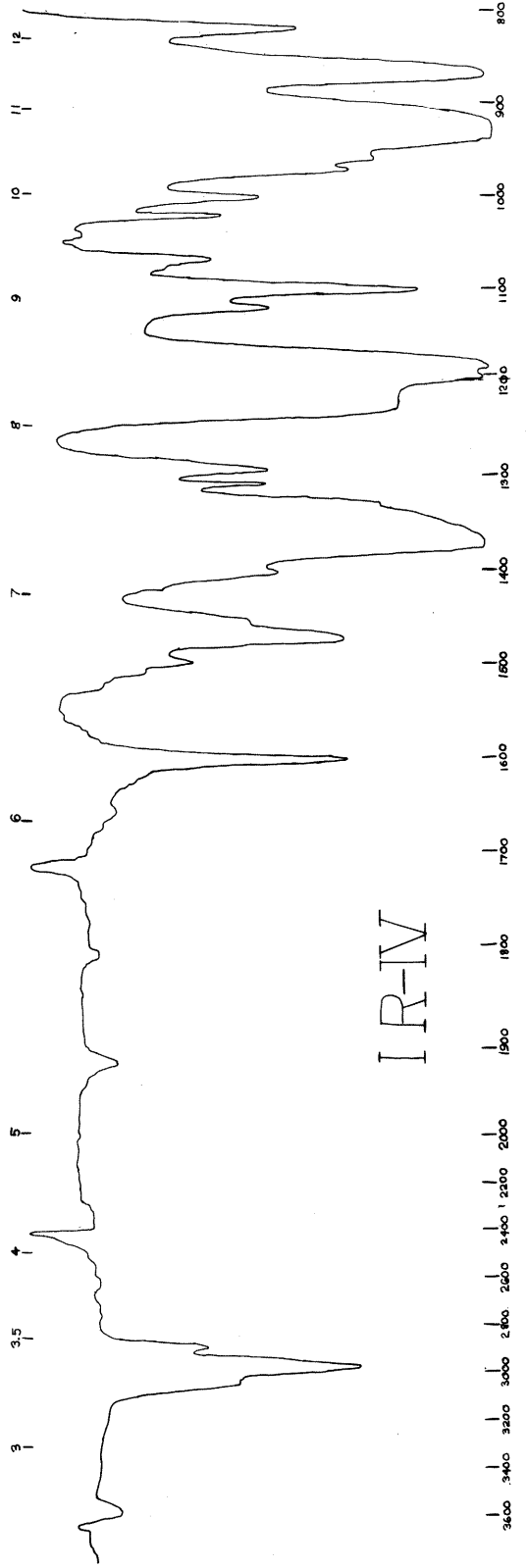
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APPENDIX

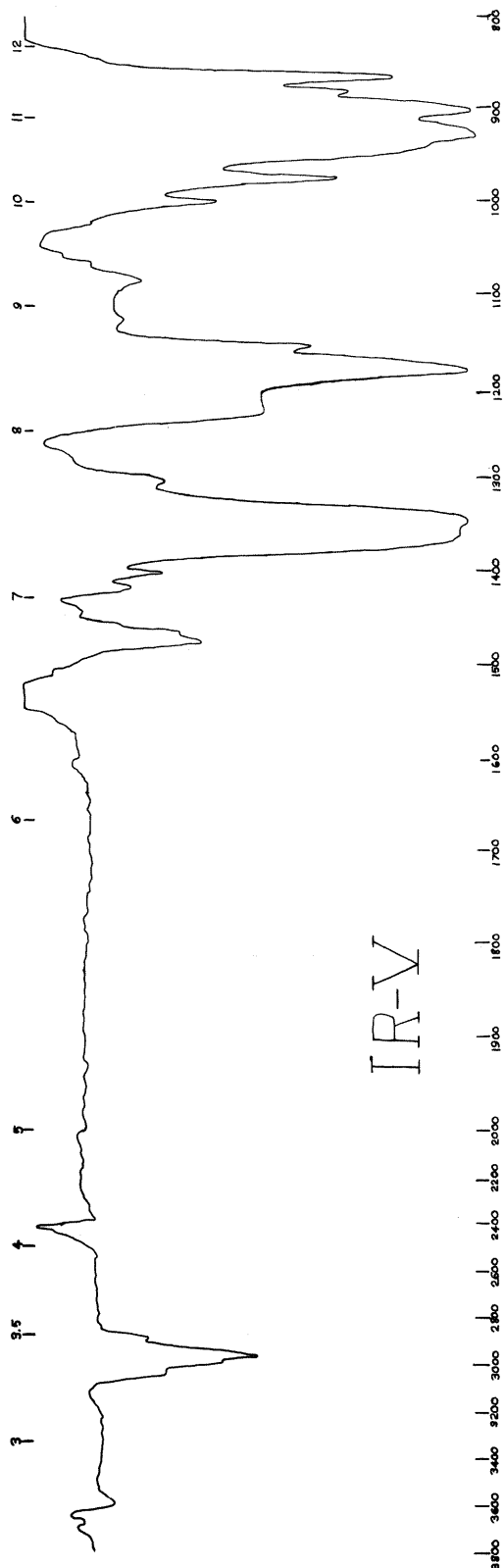




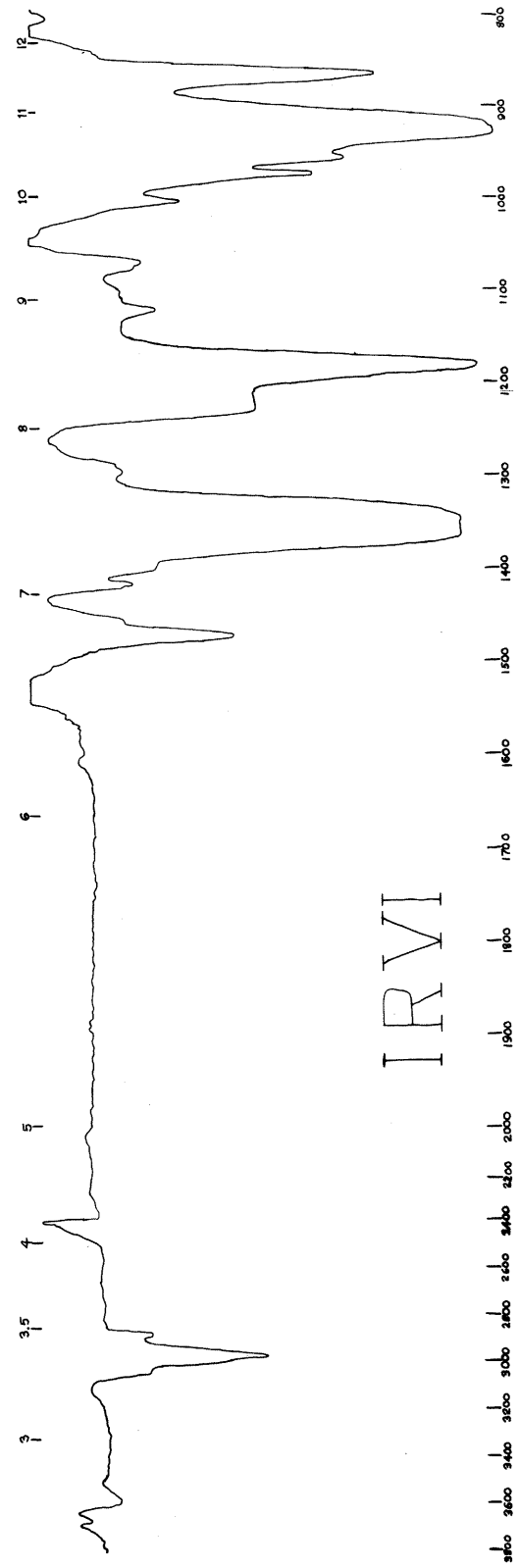
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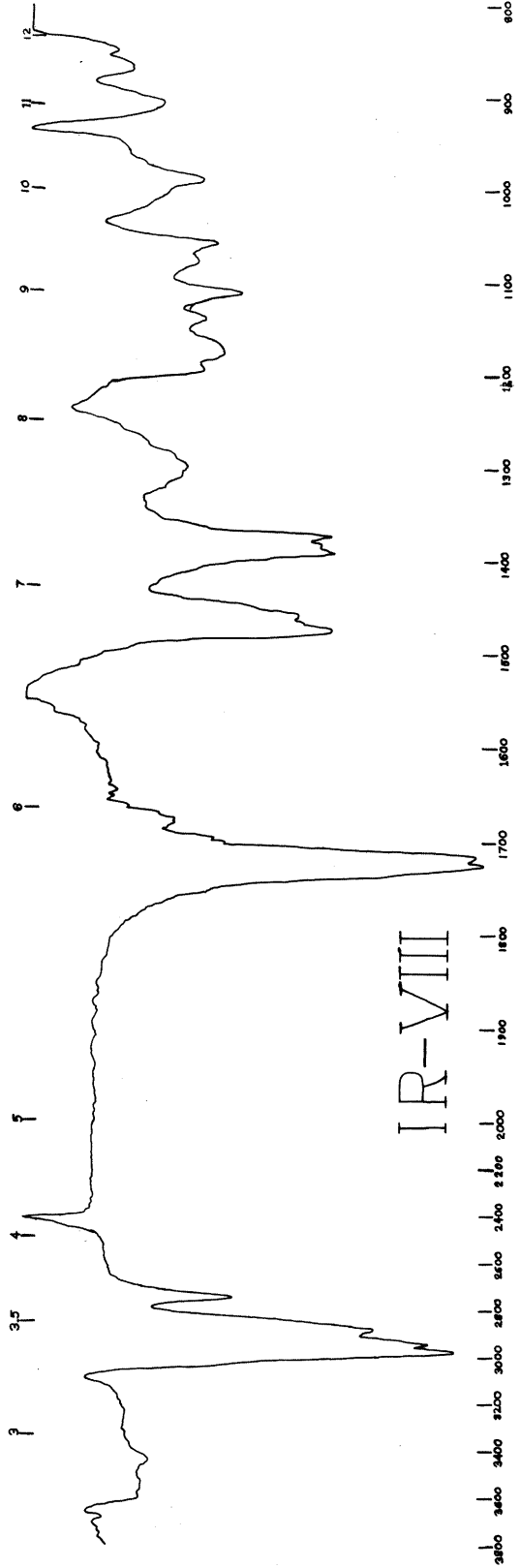
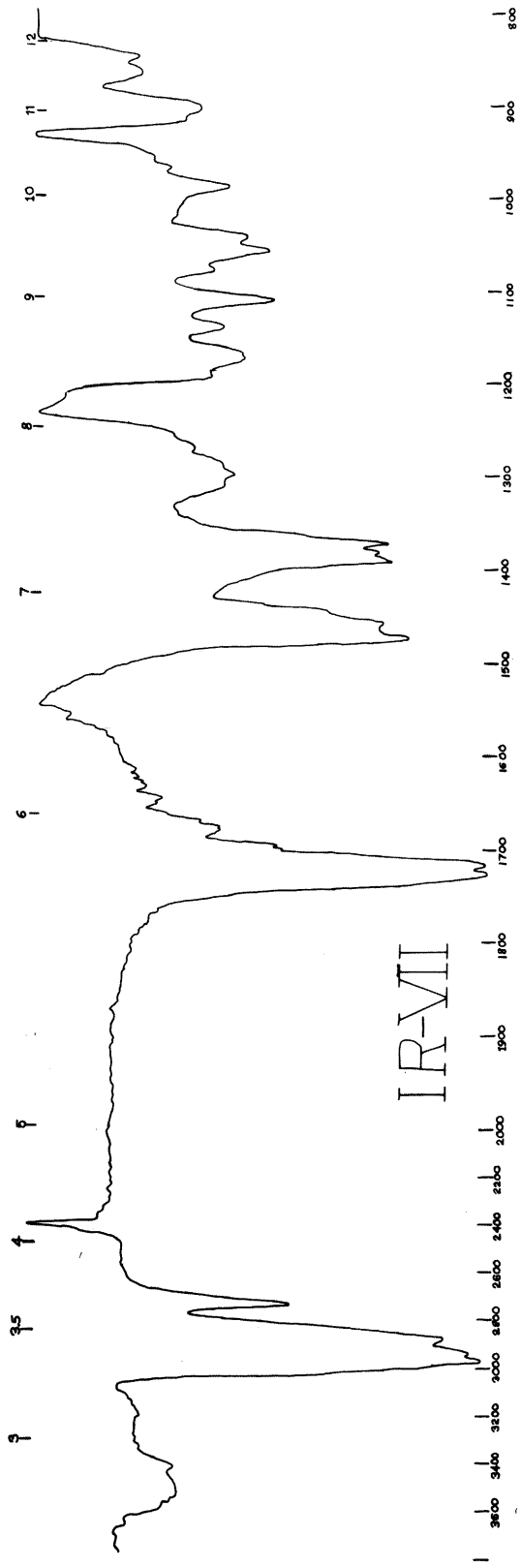
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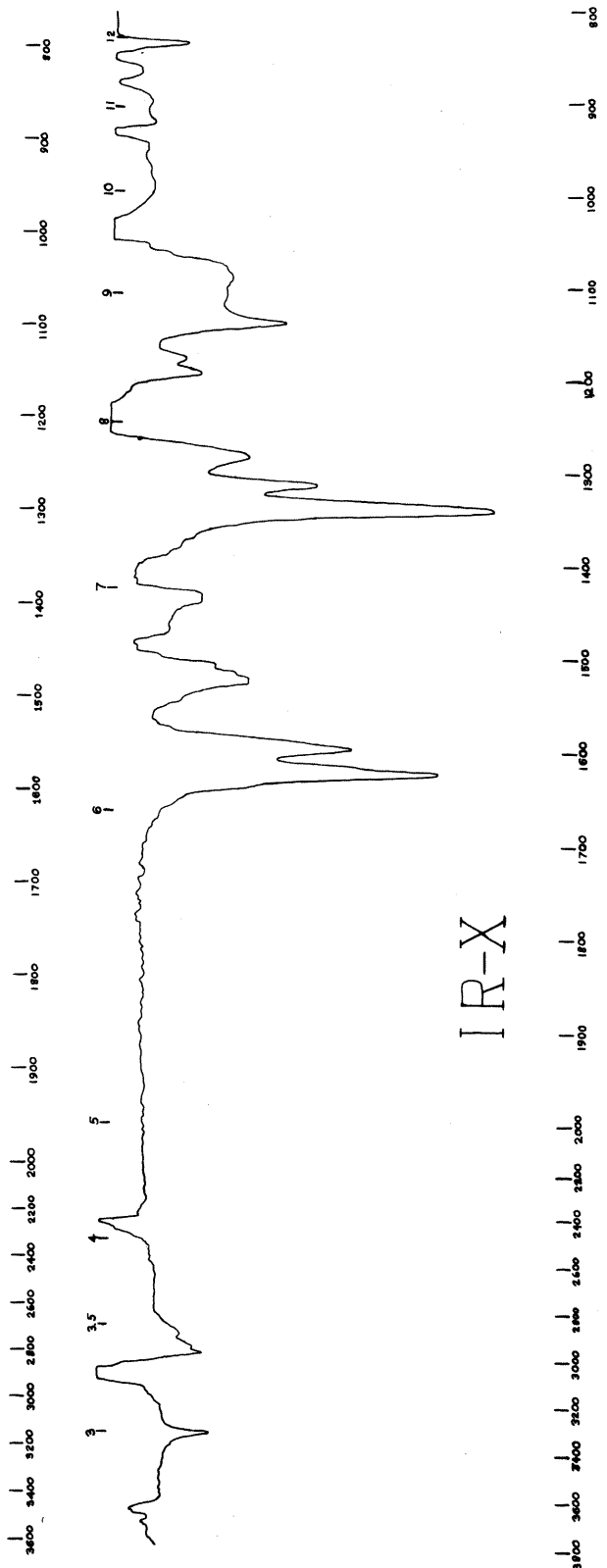
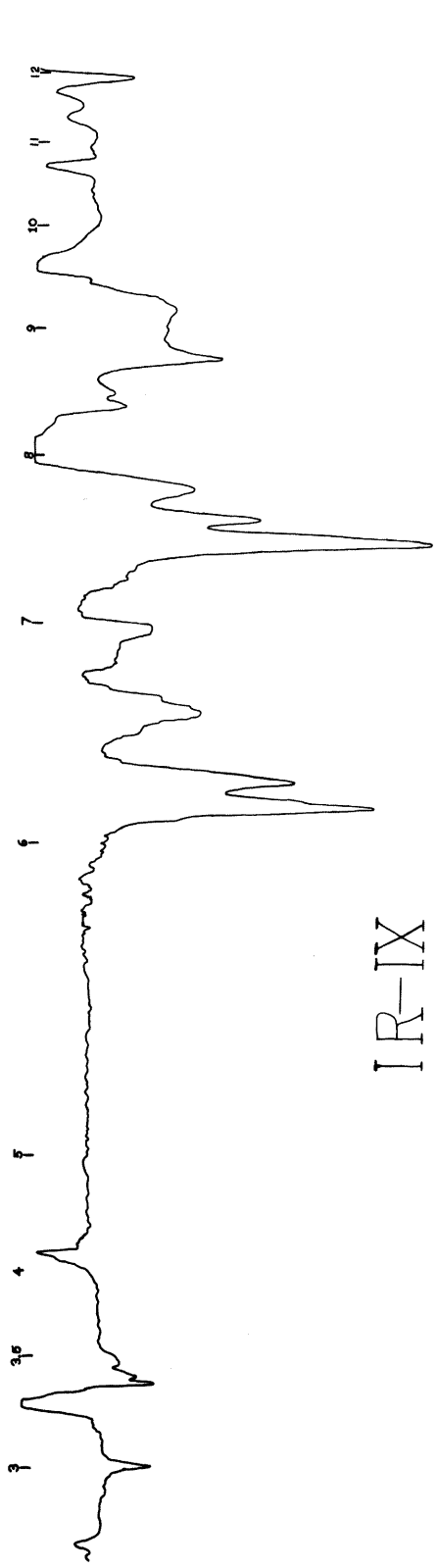


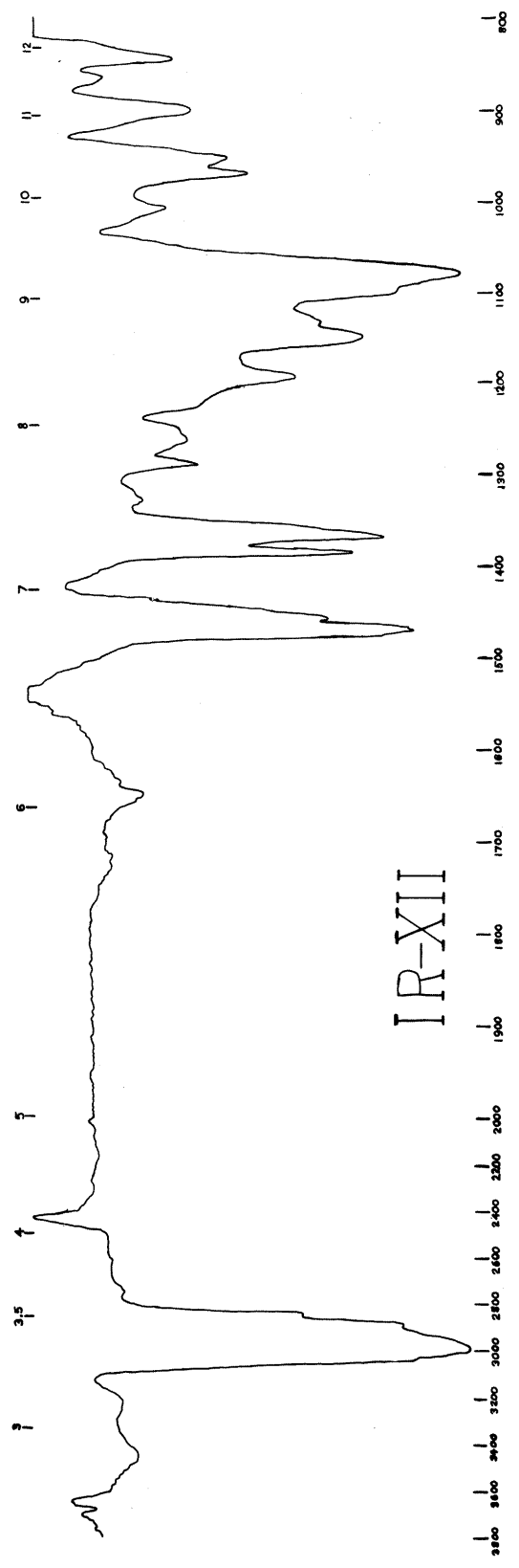
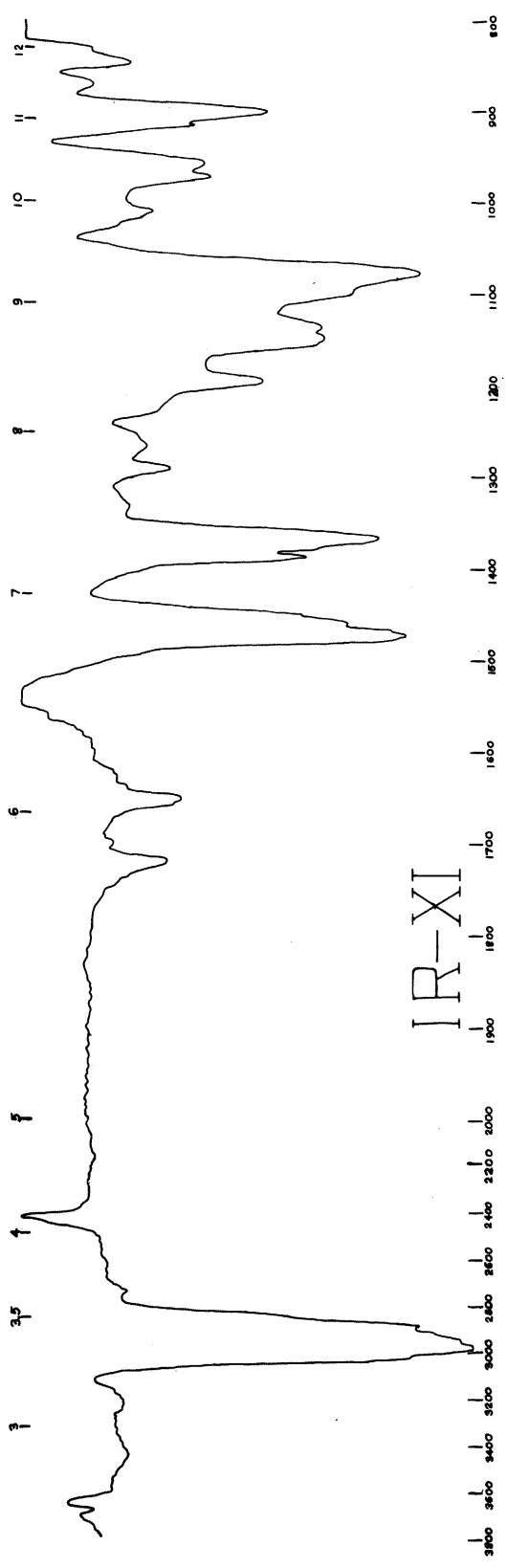
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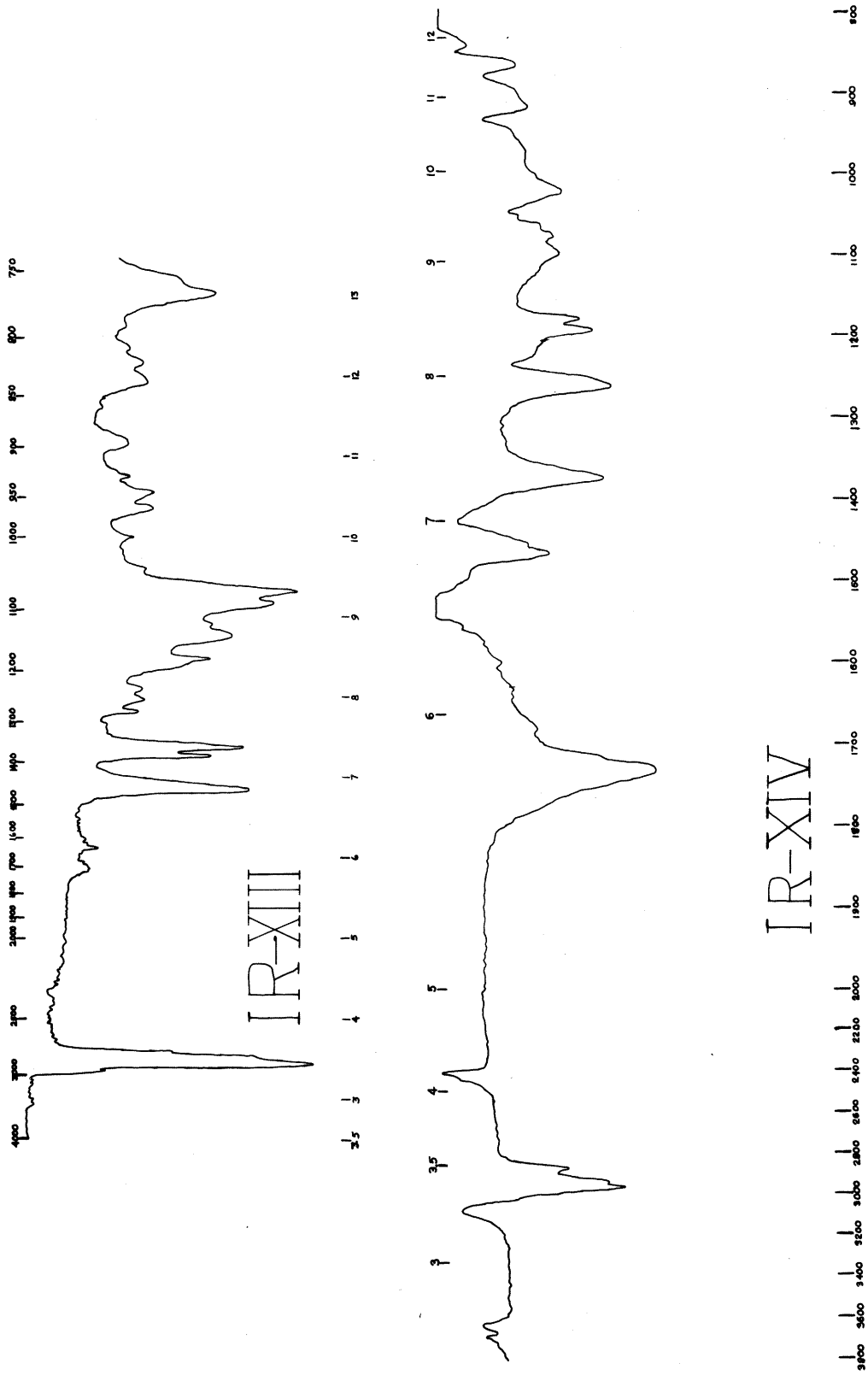


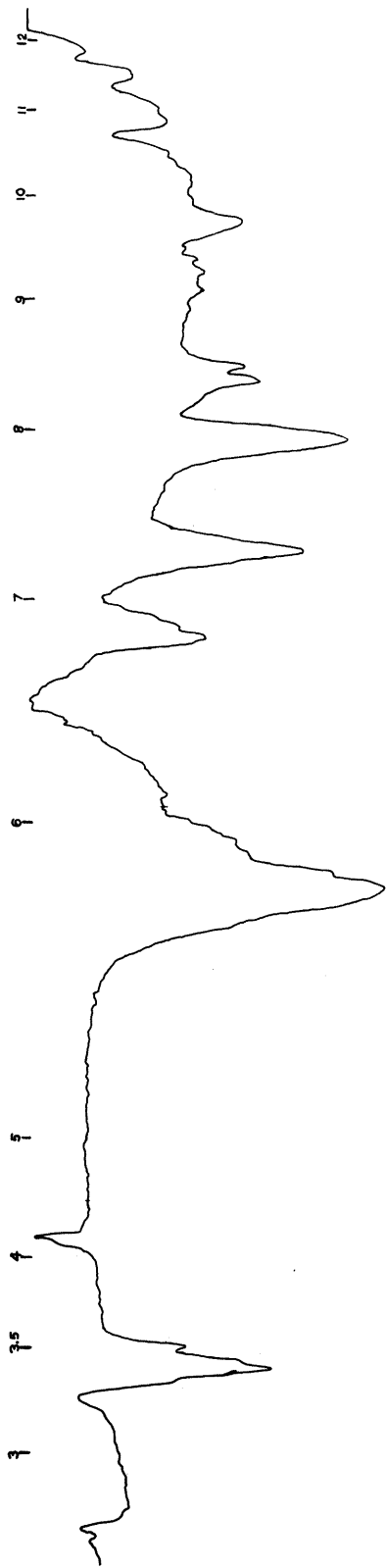
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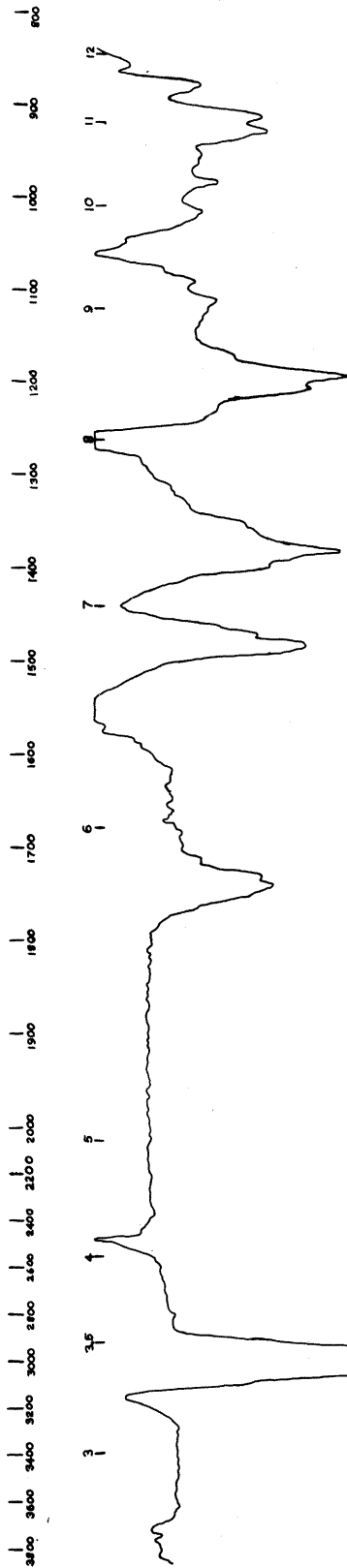




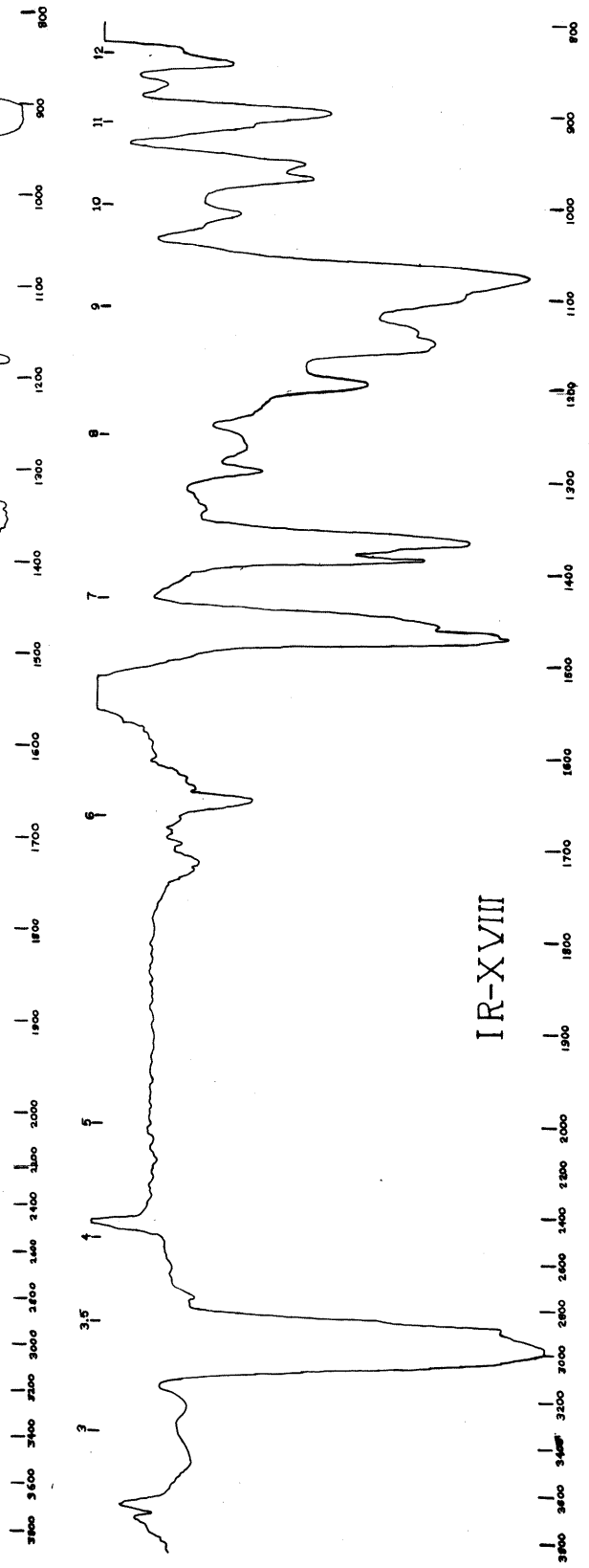
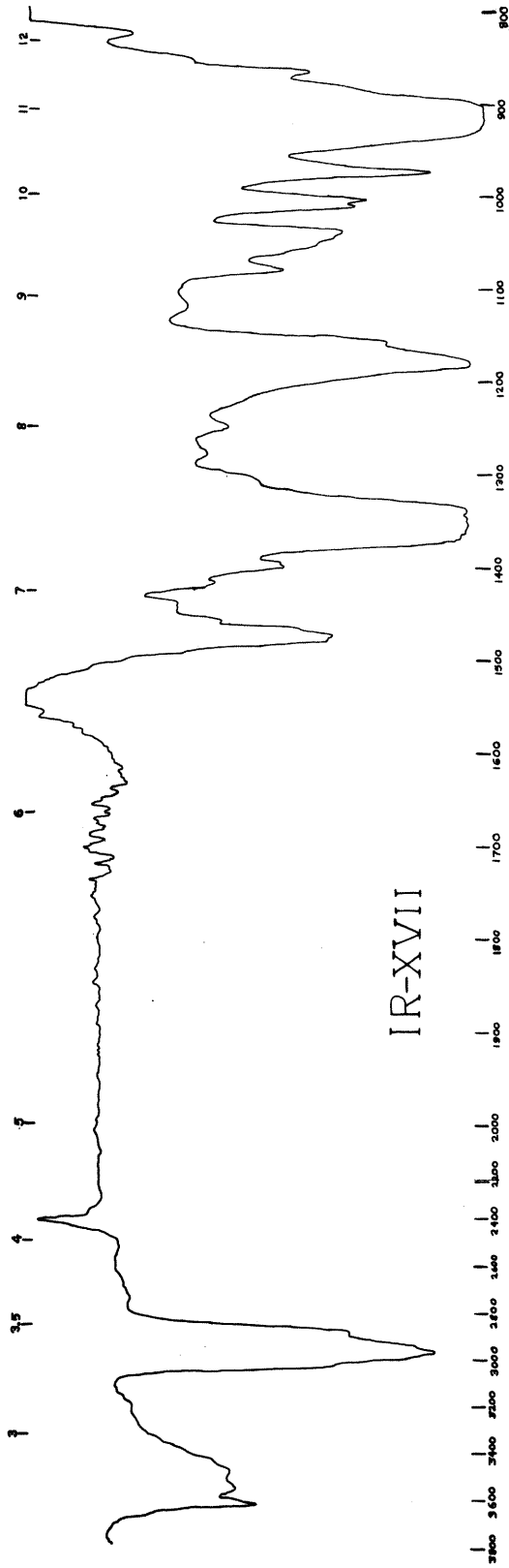


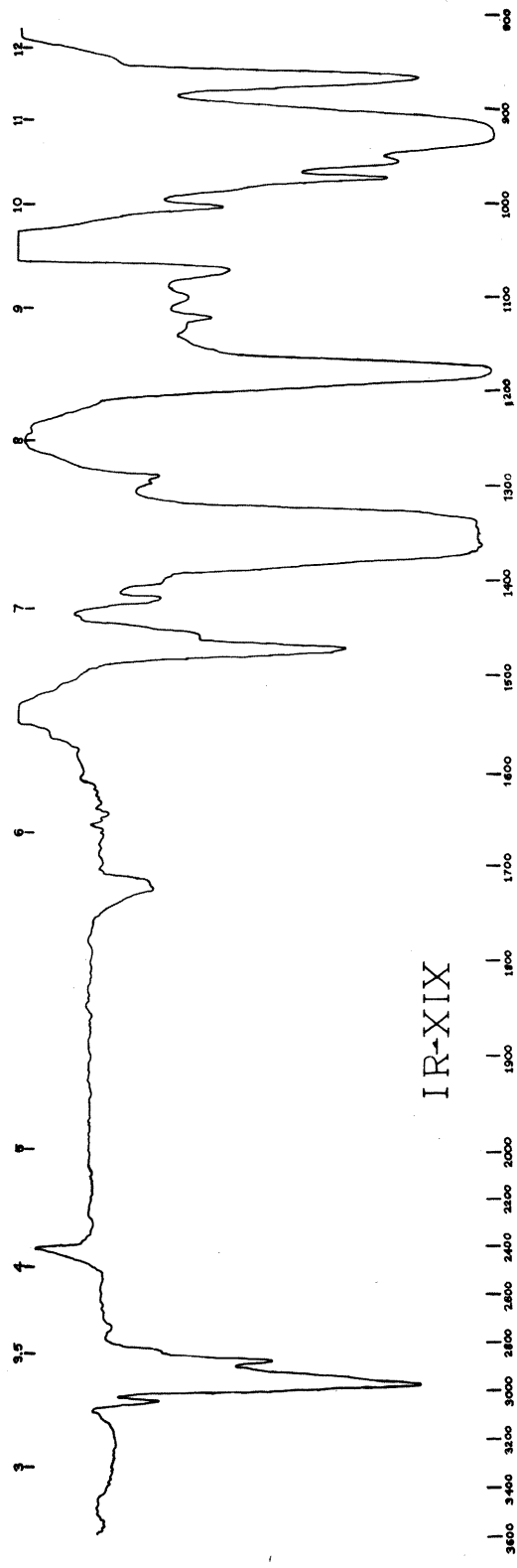


IR-XV



IR-XVI





IR-XIX