THE MECHANISM OF INTRAMOLECULAR REARRANGEMENTS

A Thesis

by

Sydney H. J. Greenwood

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1940.

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The author wishes to take this opportunity
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CLAIM TO ORIGINAL RESEARCH

One method for the elucidation of the relationships between Intramolecular Rearrangements and Substitution Processes has been described and investigated. The basis of this method is the definite correlation of the configurations of the rearrangement product and the original compound, in this case 2 chloro-2,3-dimethyl hexane and n-propyl tert. butyl carbinol. Levo n-Propyl tert. butyl carbinol has been configurationally related to levo 2,3 dimethyl hexanol-2. An attempt to correlate the configurations of levo 2,3 dimethyl hexanol-2 and 2-chloro-2,3 dimethyl hexane however, led to the discovery of the occurrence of an intramolecular rearrangement, which had not previously been demonstrated in compounds of this type; thus invalidating the method for the conditions used in these experiments. This rearrangement has been shown to be of the "ionic" type, the "ionic mechanism" of intramolecular rearrangement processes being apparently applicable in this case. In this manner, the processes involved in the reactions of the isomeric octanols, n-propyl tert. butyl carbinol, 2,3 dimethyl hexanol-2 and 2,3 dimethyl hexanol-3 with aqueous hydrochloric acid have been determined.

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EXPERIMENTAL PART

The Mechanism of Intramolecular Rearrangements

The object of science is to systematize the changes which matter has been observed to undergo, to explain their cause, and to predict their occurrence. The investigations of the chemical reactions of the compounds of carbon have shown, in many cases, that rearrangements of the molecular structures concerned might occur either by the simple readjustment of the atoms already present, or as a result of an addition to, or a removal from the original molecule of certain atoms or groups of atoms. Since the molecular structure of an organic compound is its fundamental characteristic, the study of these rearrangement processes has become of prime importance. The organic chemist must be able to foresee when rearrangements may be expected to occur, and to know with certainty when and how they have taken place. The intimate mechanism involved in these transformations must therefore be understood.

The modern electronic concept of the mechanism of these reactions considers the prior formation of an atom deficient in electrons as the KEY to the processes of intramolecular rearrangements. This deficiency may be satisfied either by a new atom or radical entering the molecule in this position, or by an atom or radical migrating from within the molecule, that is, by an intramolecular substitution reaction, wherein the migrating radical has substituted on the carbon atom deficient in electrons. The investigations of substitution or replacement reactions, however, have shown that the new substituent need not always take up the position in space about the carbon atom which the group removed had occupied. That is, a Walden Inversion may occur. Recent studies have indicated that intramolecular rearrangements may involve a Walden Inversion at the carbon atom to which the migrating radical becomes attached.

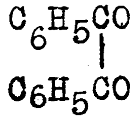
The present investigations were undertaken with the purpose of increasing our knowledge of intramolecular rearrangements in this direction. Prior to the description of these investigations and their results, a survey of our present knowledge of intramolecular rearrangement processes, together with a review of the various theories which have been proposed to explain these reactions, will be presented.

Historical Introduction

Organic chemistry began with the discovery of the first molecular rearrangement in 1828. In that year Friedrich Wohler synthesised urea, a typical product of the living or organic world, by simply heating ammonium cyanate (1), a typically inorganic material. This synthesis, being the first truly synthetic formation of an organic compound, is usually regarded as a turning point in the history of chemistry, for it directed attention to the possibility of synthesising other organic componnds artifically in the laboratory from inorganic materials. Previously, the laboratory or even the industrial preparation of those compounds which are built up in plant or animal organisms, by the combination of the elements or their derivatives, had been regarded as impossible of attainment. A mysterious vital force, which resided only in living matter, was thought necessary.

This classic synthesis is also of interest as the first recorded example of an isomeric change wherein one of a pair of isomeric compounds was converted into the other. Its great significance from the synthetic standpoint, drew attention to the possibility of molecules rearranging within themselves under the appropriate conditions. However, no great progress could be made in the study of intramolecular rearrangements until the development of the doctrine of valency, and the assignment to the molecules of organic compounds of definite molecular structures by Kekule, Couper, Butlerov and Erlenmeyer after 1860. Just as soon as the significance of the structural or space formulation of organic molecules, that is, of the actual arrangement of the atoms within the molecule in the sense of the order of their successive attachments to each other, was realised, molecular rearrangements were found to have occurred in a number of reactions. For example, the transformation of benzil to benzilic acid, discovered by Liebig in 1838 (2), and the transformation of pinacol to pinacolone by Fittig in 1860 (3), were not recognized as reactions involving a rearrangement within the molecule until 1874.

Prior to 1874, much speculation and discussion had taken place as to the formulae of benzil and benzilic acid. Two isomeric formulae had been proposed for benzil, I and II, the latter on the basis of the transformation to benzilic acid, III.



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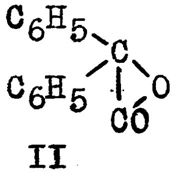

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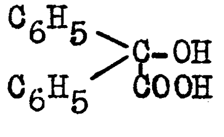
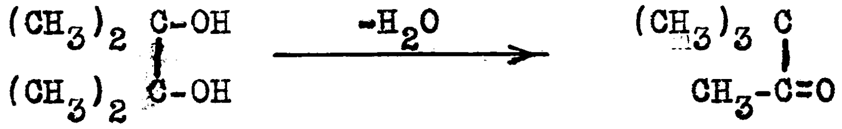


III

At this time, Symons and Zincke (4) reviewed the experimental evidence in favor of the formulae and concluded that benzil and benzilic acid could not belong to one and the same series, and, that in the formation of the latter, a migration of the phenyl group from one carbon to the other must be assumed. This transformation discovered as it was in 1838, becomes then, the oldest known molecular rearrangement wherein a migration of a carbon radical from one carbon atom to another has taken place.

In the same year, the pinacol-pinacolone transformation was shown by Butlerov (5) to involve an alkyl radical migration during the process of dehydration, after he had succeeded in synthesising the ketone from trimethyl acetyl chloride and zinc methyl.



$$\begin{matrix}(CH_3)_2\,C{-}OH\\ |\\ (CH_3)_2\,C{-}OH\end{matrix} \xrightarrow{-H_2O} \begin{matrix}(CH_3)_3\,C\\ |\\ CH_3{-}C{=}O\end{matrix}$$

Two years previously, in 1872, Linneman (6) had concluded, from his observations that the reaction of isobutyl iodide with silver acetate and iodine monochloride produced the corresponding tertiary butyl derivatives, that a transposition of a hydrogen atom might occur during typical double decomposition reactions.

Rearrangements of this type, wherein an atom or a radical migrates from one atom to an adjacent atom of the molecule, have been found to occur in avery large number of the reactions of organic chemistry. They may be classified as 1,2 - or α,β - or Vicinal Intramolecular Rearrangements.

Vicinal Intramolecular Rearrangements

Many different classes of compounds have been observed, sometimes unexpectedly. to undergo this type of rearrangement. A. Michael (7) visualized the reactions as occurring in two different chemical systems, -

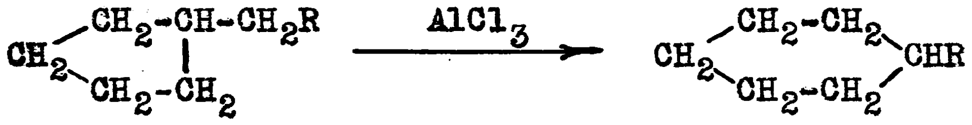
(a) "In a homogeneous chemical system, an intramolecular rearrangement takes place through a change in the positions of certain atoms or groups of atoms in the molecule and the new isomeric produce may belong to the same or to a different chemical type."

(b) "In a heterogeneous chemical system, the change in chemical structure may occur with the loss of a component part of the substance, through the catalytic effect or the chemical action of the energy in the reagent, with isomerization of the residual structure. Or, by the union of the substance with the reagent, where owing to the chemical energy thus added, an isomerization in the substance part of the "polymolecule" takes place with partial conversion of its free energy into bound energy, and is followed by the breaking down of the system into the isomerized substance and the reagent."

1. Rearrangements and Isomerization:-

A rearrangement may simply involve, a readjustment of the atoms present in the molecule, to form a product which is isomeric with the original compound. Intramolecular rearrangements occurring in this manner are referred to as isomerizations and are generally considered to occur in the direction producing a more stable substance.

Isomerizations involving an interchange of two radicals on adjacent atoms of the skeleton of the molecule have been found to occur in many of the different types of chemical compounds. Hydrocarbons, alcohols, aldehydes, ketones, ethylene oxides, isocyanides, etc., have all been found to isomerize under various conditions:-



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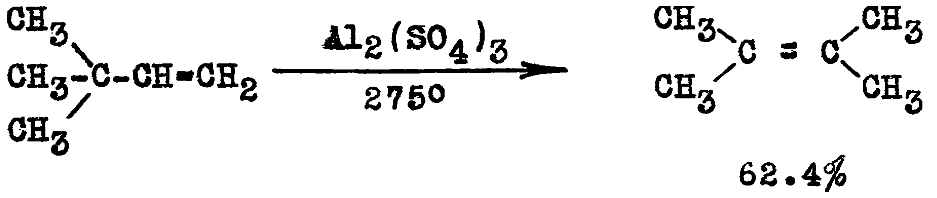

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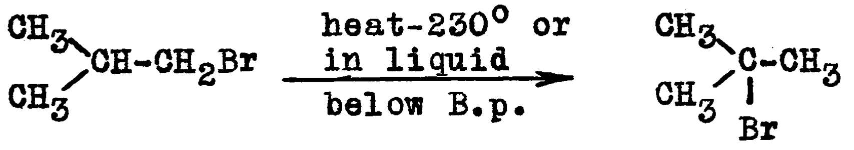

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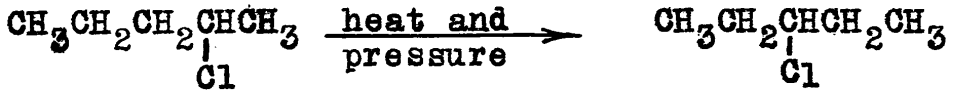
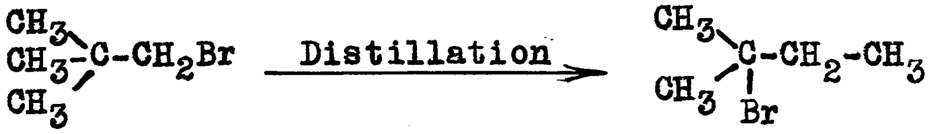


$$CH_3CH_2CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3 \xrightarrow[\text{pressure}]{\text{heat and}} CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_3$$

(11)



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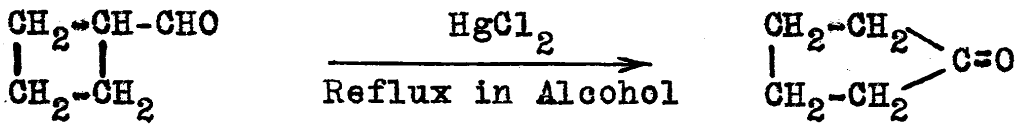

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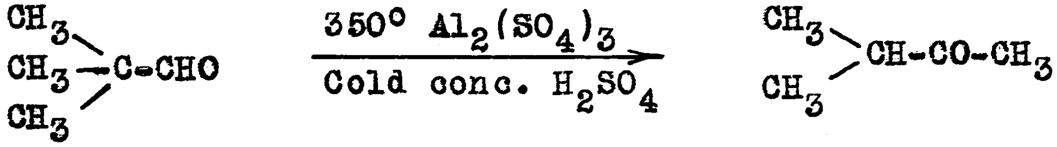

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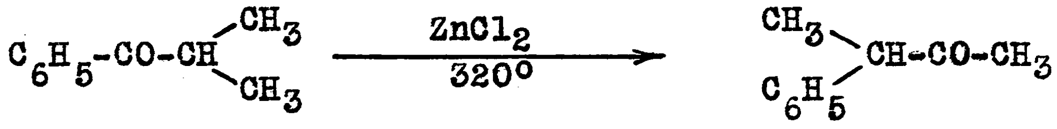

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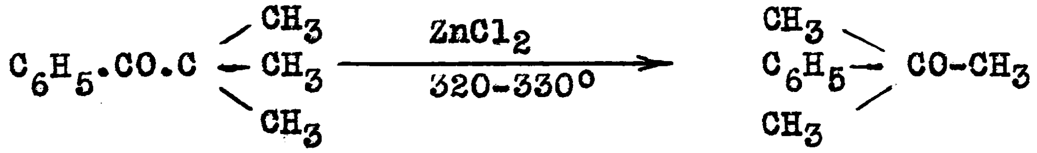

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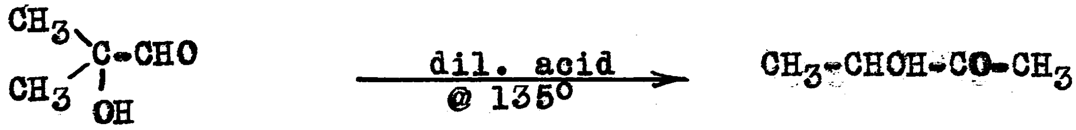

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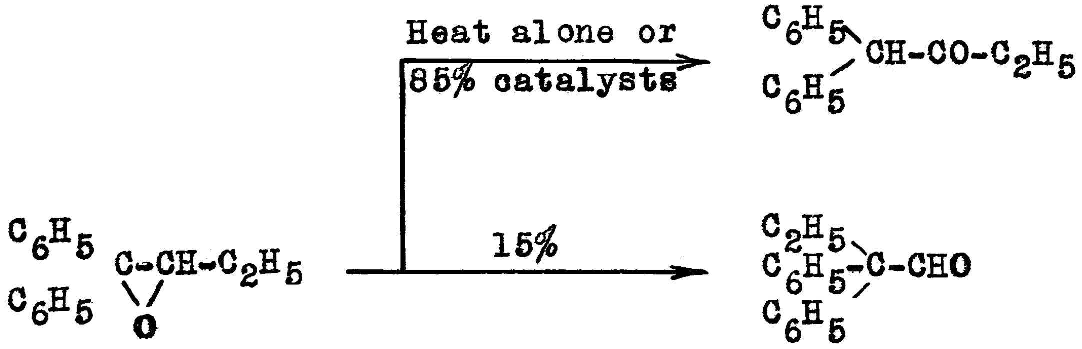

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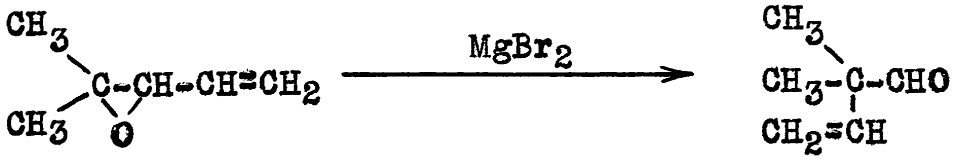
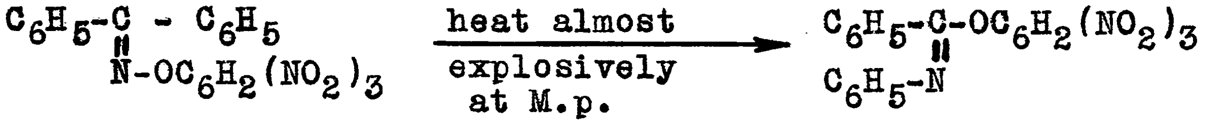


(19)

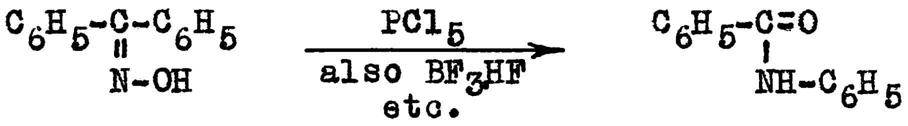
$$C_6H_5\text{-}N{\equiv}C \xrightarrow{200\text{-}220^\circ} C_6H_5\text{-}CN \qquad (20)$$

$$C_6H_5CO\text{-}CHOH\text{-}CO\text{-}C_6H_5 \xrightarrow[\text{at 4 m.m.}]{\text{distillation}} C_6H_5CO\text{-}CH_2O\text{-}CO\text{-}C_6H_5 \qquad (21)$$



$$\underset{\displaystyle N\text{-}OC_6H_2(NO_2)_3}{C_6H_5\text{-}\overset{}{C}\text{-}C_6H_5} \xrightarrow[\substack{\text{explosively}\\ \text{at M.p.}}]{\text{heat almost}} \underset{\displaystyle C_6H_5\text{-}N}{C_6H_5\text{-}C\text{-}OC_6H_2(NO_2)_3} \qquad (22)$$

This latter example is similar to the familar Beckmann rearrangement of ketoximes to acid amides (23) affected by a large number of reagents chiefly acidic in nature, and occasionally under the influence of heat alone. (24)



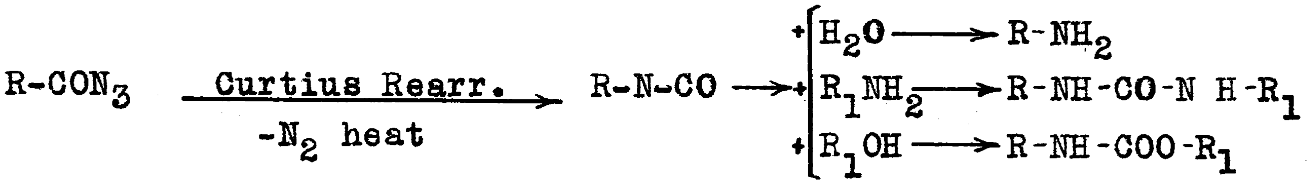
$$\underset{\displaystyle N\text{-}OH}{C_6H_5\text{-}C\text{-}C_6H_5} \xrightarrow[\substack{\text{also } BF_3HF\\ \text{etc.}}]{PCl_5} \underset{\displaystyle NH\text{-}C_6H_5}{C_6H_5\text{-}C{=}O}$$

The oxime and the corresponding amide are isomeric. Beckmann regarded the rearrangement as involving a simple catalyzed direct interchange of radicals between carbon and nitrogen.

2. <u>Rearrangements and Elimination Reactions:-</u>

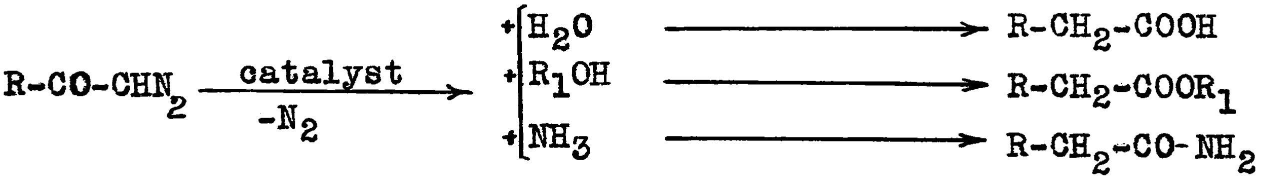
Changes in molecular structure, in which a group migrates from one position in a compound to an adjacent position also occur with the elimination of nitrogen, water, halogen acid or some other simple molecule.

Molecular rearrangements of great synthetic importance take place on the elimination of nitrogen from azides and related compounds, thus,-



$$R\text{-}CON_3 \xrightarrow[-N_2\ \text{heat}]{\text{Curtius Rearr.}} R\text{-}N\text{-}CO \rightarrow \left[\begin{array}{l} +H_2O \longrightarrow R\text{-}NH_2 \\ +R_1NH_2 \longrightarrow R\text{-}NH\text{-}CO\text{-}N\ H\text{-}R_1 \\ +R_1OH \longrightarrow R\text{-}NH\text{-}COO\text{-}R_1 \end{array}\right.$$

(25)



$$R\text{-}CO\text{-}CHN_2 \xrightarrow[-N_2]{\text{catalyst}} \left[\begin{array}{l} +H_2O \longrightarrow R\text{-}CH_2\text{-}COOH \\ +R_1OH \longrightarrow R\text{-}CH_2\text{-}COOR_1 \\ +NH_3 \longrightarrow R\text{-}CH_2\text{-}CO\text{-}NH_2 \end{array}\right.$$

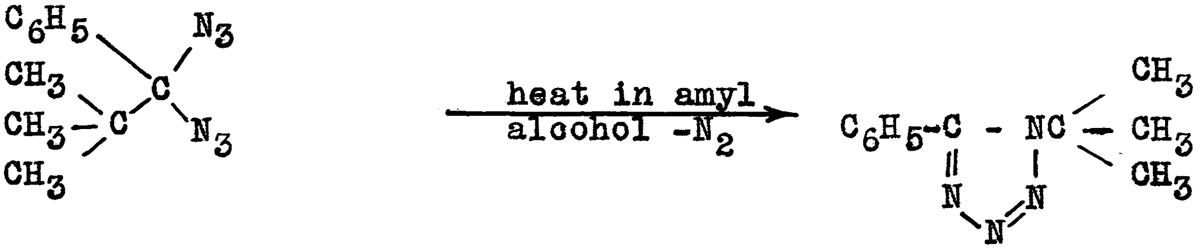
(26)

(Ardnt-Eistert Rearr.)

$$(C_6H_5)_3CN_3 \xrightarrow{\text{heat } -N_2} (C_6H_5)_2C{=}N\text{-}C_6H_5 \qquad (27)$$

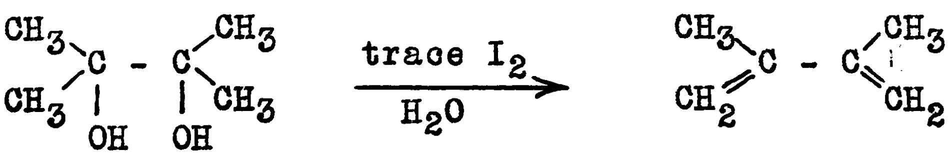
$$C_6H_5\text{-}CO\text{-}C(N_2)\text{-}C_6H_5 \xrightarrow{\text{heat } 60^\circ\ -N_2} (C_6H_5)_2C{=}C{=}O \qquad (28)$$

(Azibenzil) (diphenyl ketene)



(29)

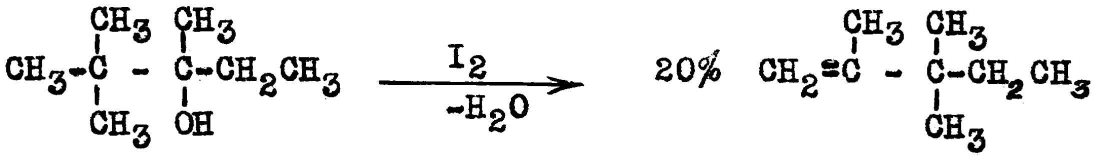
The elimination of water from tertiary aliphatic carbinols by Hibbert's Iodine method (30) may proceed with or without rearrangement. Thus pinacol when refluxed with a trace of iodine yields 82% 2,3 dimethyl butadiene 1,3.



and similarly

$$(CH_3)_3C\text{-}CHOH\text{-}CH_2COCH_3 \xrightarrow[-H_2O]{I_2} (CH_3)_3C\text{-}CH{=}CH\text{-}COCH_3 \qquad (31)$$

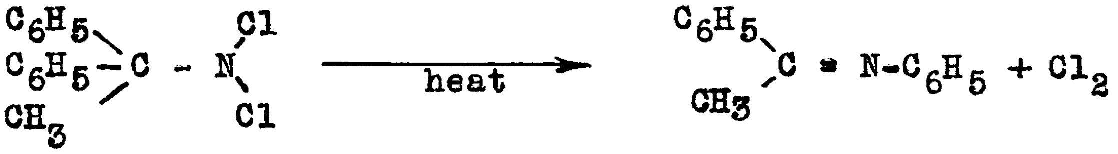
Rearrangement has been found to occur in other cases, although not completely:



$$CH_3\text{-}\overset{CH_3}{\underset{CH_3}{C}} - \overset{CH_3}{\underset{OH}{C}}\text{-}CH_2CH_3 \xrightarrow[-H_2O]{I_2} 20\%\ CH_2{=}\overset{CH_3}{C} - \overset{CH_3}{\underset{CH_3}{C}}\text{-}CH_2CH_3 \qquad (32)$$

The elimination of other simple molecules may also cause a skeletal rearrangement, thus,-

$$CH_3\text{-}CON\text{-}NaBr \xrightarrow[rapid]{80^o} NaBr + CH_3\text{-}NCO \qquad (33)$$



$$(C_6H_5)_2(CH_3)C - NCl_2 \xrightarrow{heat} (C_6H_5)(CH_3)C = N\text{-}C_6H_5 + Cl_2 \qquad (34)$$

$$(C_6H_5)_2CH\text{-}CH_2Cl \xrightarrow{Distillation} C_6H_5\text{-}CH{=}CH\text{-}C_6H_5 + HCl \qquad (35)$$

3. <u>Rearrangements and Addition Reactions</u>

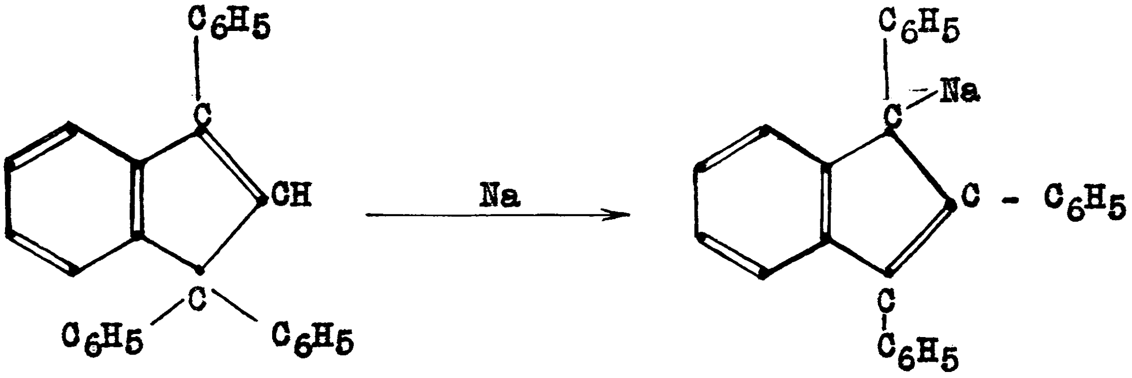
The wandering of an atom or radical from one atom to the adjacent atom is occasionally met with during addition reactions.

A rearrangement resulting from addition to the olefinic linkage was shown to occur during the addition of hydrogen halide to isopropyl ethylene.

$$(CH_3)_2CH-CH=CH_2 \xrightarrow[H]{HCl} (CH_3)_2\ CH-CHCl-CH_3+(CH_3)_2\ CCl-CH_2CH_3$$

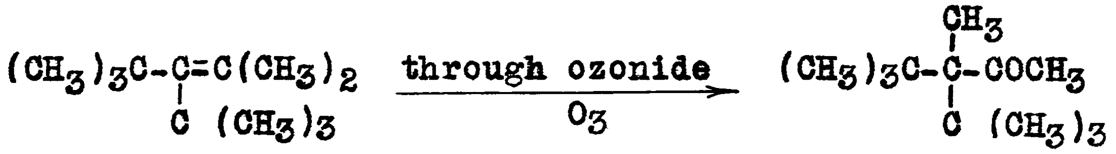
(equimolecular quantities)

Similarly, during the action of sodium on 1,1,3 triphenyl indene



(37)

and also during ozonization,



$$(CH_3)_3C-\underset{C(CH_3)_3}{C}=C(CH_3)_2 \xrightarrow[O_3]{\text{through ozonide}} (CH_3)_3C-\underset{C(CH_3)_3}{\overset{CH_3}{C}}-COCH_3$$

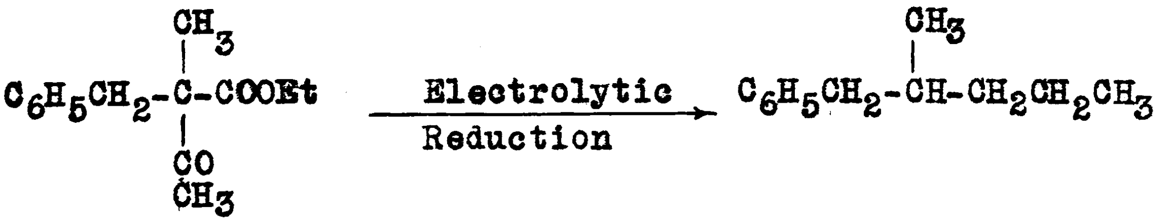
(38)

or oxidation by potassium permanganate in acetic acid solution,

$$(C_6H_5)_2\ C=C\ (C_6H_5)_2 \xrightarrow{[O]} (C_6H_5)_3\ C-CO-C_6H_5$$

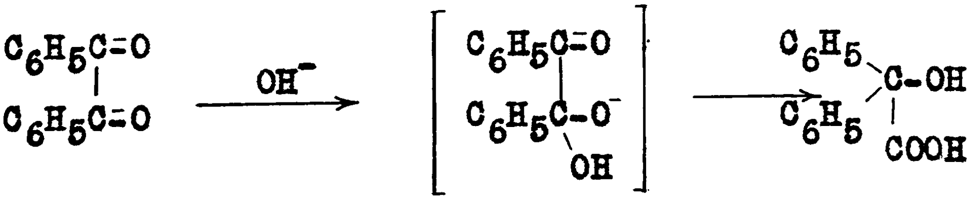
(39)

Reactions in which an addition to a carbonyl group takes place may also proceed with rearrangement,-



$$C_6H_5CH_2-\underset{\substack{CO\\CH_3}}{\overset{CH_3}{C}}-COOEt \xrightarrow[\text{Reduction}]{\text{Electrolytic}} C_6H_5CH_2-\overset{CH_3}{CH}-CH_2CH_2CH_3$$

(40)



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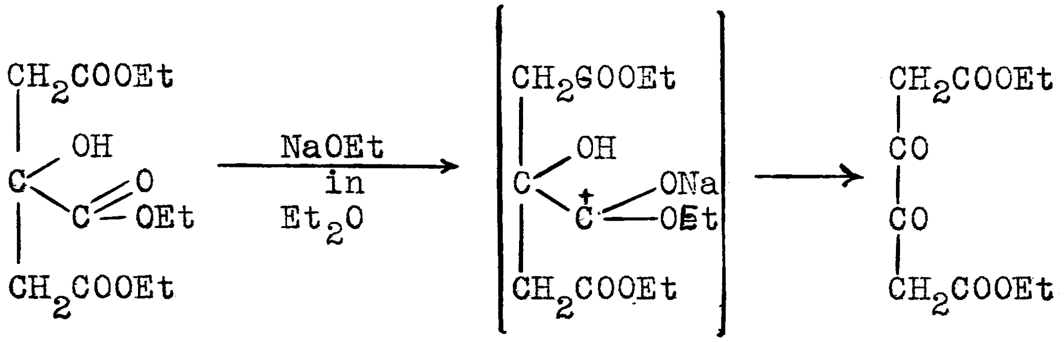


(42)

The latter two cases are respectively the historic benzil-benzilic acid rearrangement and its reversal.

4. Rearrangements During Removal Reactions.

The historical rearrangement of pinacol to pinacolone represents a vicinal rearrangement occurring on the removal of the elements of water. All pinacols on treatment with acids undergo the pinacol-pinacolone rearrangement. A considerable volume of work has appeared dealing with this change and the related rearrangements of α,β, amino-alcohols, α,β halohydrins and α,β glycols in general.

Essentially similar in character, the rearrangements in these types of compounds have been classified into three main groups, (43), where Y may be OH, NH_2, Halogen:-

(I) the pinacolinic change proper:-

$$RR_1C(Y)\text{-}CR_2R_3(OH) \longrightarrow RR_1R_2C\text{-}CO\text{-}R_3$$

(II) the semihydrobenzoinic change in which the tertiary group is lost:-

$$RR_1C(Y).CHR_2(OH) \longrightarrow \begin{cases} RR_1R_2C\text{-}CHO \\ RR_1CH\text{-}CO\text{-}R_2 \end{cases}$$

(III) the semipinocolinic change in which the secondary group is lost:-

$$RR_1C(OH).CHR_2(Y) \longrightarrow \begin{cases} R\text{-}CO\text{-}CHR_1R_2 \\ R_1\text{-}CO\text{-}CHRR_2 \end{cases}$$

that is, 1,2 glycols and related α,β compounds on appropriate treatment, in the case Y=OH by dehydrating agents, in the case Y=NH_2 by deaminating agents, and in the case Y=halogen by alkalies, undergo rearrangement to give either aldehydes or ketones depending on the conditions and the groups involved.

<u>Similarly in the case of $\alpha\beta$-dibromides</u>

$$(CH_3)_2CBr\text{-}CH_2Br \xrightarrow{H_2O} (CH_3)_2\,CH\text{-}CHO \qquad (44)$$

This reaction is used for the preparation of methyl isopropyl ketone from tertiary amyl alcohol.

$$\begin{tikzcd}(CH_3)_2C(OH).CH_2.CH_3 \arrow[r, "Br_2"] & (CH_3)_2CBr.CHBr.CH_3 \arrow[dl, "+H_2O"] \\ (CH_3)_2CH.CO.CH_3 + 2HBr & \end{tikzcd}$$

The pinacol-pinacolone types of rearrangements are in a sense reversible, since on reduction of the carbonyl group to the corresponding alcohols and dehydration of these, the original carbon skelton may be reformed (by a retropinacolone rearrangement).

$$(CH_3)_3C\text{-}CHOH\text{-}CH_3 \xrightarrow{\quad 61\% \quad} (CH_3)_2C{=}C(CH_3)_2 \qquad (46)$$

$$(C_6H_5)_3C\text{-}CHOH\text{-}C_6H_5 \xrightarrow{I_2HAc\,100\%} (C_6H_5)_2C{=}C(C_6H_5)_2 \qquad (47)$$

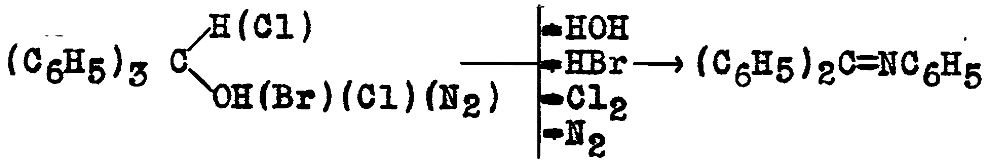
$$(C_6H_5)_2CH\text{-}CH_2OH \xrightarrow{P_2O_5} (C_6H_5)CH{=}CH\text{-}C_6H_5 \qquad (48)$$

A similar type of rearrangement takes place by the action of potassium amide in liquid ammonia on the 1,1 diaryl-2 chloro-ethenes and the 1,1, diaryl 2,2 dichloro ethanes.

$$(C_6H_5)_2C{=}CHCl \xrightarrow{KNH_2} C_6H_5{-}C{\equiv}C{-}C_6H_5 \qquad (49)$$

$$(C_6H_5)_2CH{-}CHCl_2 \xrightarrow{KNH_2} C_6H_5{-}C{\equiv}C{-}C_6H_5 \qquad (49)$$

Triphenyl hydroxylamine and its related derivatives have been found to undergo rearrangement to give the same product, the phenyl imide of benzophenone,



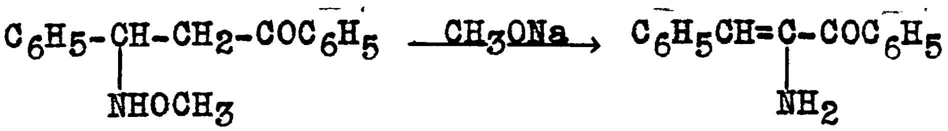
$$(C_6H_5)_3C\begin{matrix}H(Cl)\\OH(Br)(Cl)(N_2)\end{matrix} \xrightarrow{\begin{matrix}-HOH\\-HBr\\-Cl_2\\-N_2\end{matrix}} (C_6H_5)_2C{=}NC_6H_5 \qquad (50)$$

The Hofmann (A) and Lossen (B) rearrangements are also examples of rearrangements occurring during the removal type reaction,

A. $RCONH_2 \xrightarrow{Br_2} RCONHBr \xrightarrow{KOH} RNCO$ (51)

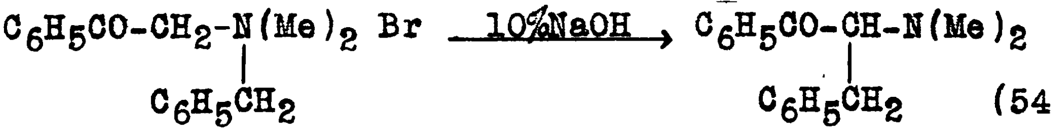
B. $RCONHOCOR \xrightarrow[-RCOOH]{alkali} RNCO$ (52)

The most characteristic and striking reaction of the β-methoxy amino propiophenones is the rearrangement which they undergo on treatment with strong bases to yield α-amino ketones.



$$C_6H_5{-}\underset{NHOCH_3}{\underset{|}{C}H}{-}CH_2{-}COC_6H_5 \xrightarrow{CH_3ONa} C_6H_5CH{=}\underset{NH_2}{\underset{|}{C}}{-}COC_6H_5 \qquad (53)$$

T.S. Stevens has discovered a similar rearrangement in the quaternary ammonium salts,-

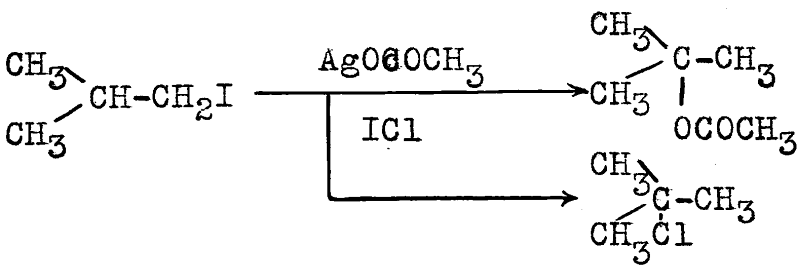


$$C_6H_5CO{-}CH_2{-}\underset{C_6H_5CH_2}{\underset{|}{N}}(Me)_2\ Br \xrightarrow{10\%NaOH} C_6H_5CO{-}\underset{C_6H_5CH_2}{\underset{|}{C}H}{-}N(Me)_2 \qquad (54)$$

5. Rearrangements During Substitution Reactions:-

The development of structural chemistry led chemists to regard the atoms that compose any given organic molecule as being arranged according to a definite architectural plan. Each atom in the molecule was assumed to occupy a definite position and when any other atoms or group was substituted, the entering group was supposed, always, to enter into the very position that had been occupied by the group displaced. That the atom or radical entering the molecule by double decomposition occasionally might fail to occupy the position of the out-going atom or radical was soon realised. Linnemann had come to this conclusion in 1872 (55) and pointed out that the structural formula of a substituted derivative, as a result, could not be assumed from the structural formula of the original substance.

Linnemann had found that the replacement of the iodine atom of isobutyl iodide by other groups might lead to the formation of the corresponding tertiary butyl derivatives:-



Six years previously, Butlerov had detected tertiary butyl alcohol as an impurity in commercial isobutyl alcohol after conversion into the chloride but had stated, "It is difficult to believe, that, in this case, trimethyl carbinol could be formed from its primary isomer (Isobutyl alcohol)". (56)

The preparation of halides from certain aliphatic straight and branched chain alcohols has been known for sometime to fail to yield the corresponding halide: a rearrangement occurring instead.

$$CH_3\text{-}CH_2\text{-}CHOH\text{-}CH_2\text{-}CH_3 \xrightarrow[\text{At RT}]{\text{HCl}\quad 75\%} \left\{\begin{array}{l} CH_3CH_2\text{-}CH\text{-}Cl\text{-}CH_2CH_3 \\ CH_3CH_2\text{-}CH_2\text{-}CHCl\text{-}CH_3 \end{array}\right. \quad 25\% \qquad (57)$$

$$(CH_3)_3\ C\text{-}CH_2OH \xrightarrow[65^oC,\ 20\%]{\text{HBr}\quad 72\%} \left\{\begin{array}{l} (CH_3)_2C(Br)\text{-}CH_2\text{-}CH_3 \\ (CH_3)_3C\text{-}CH_2Br \end{array}\right. \qquad (58)$$

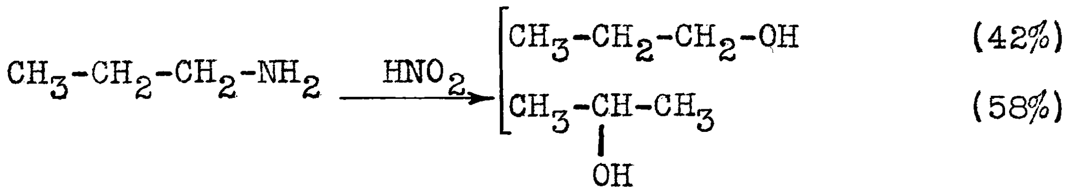
$$(CH_3)_2CH\text{-}CHOH\text{-}CH_3 \xrightarrow[\text{pyridine}]{SOCl_2\ 92\%} (CH_3)_2C(Cl)\text{-}CH_2\text{-}CH_3 \qquad (59)$$

$$(CH_3)_3C\text{-}CHOH\text{-}CH_3 \xrightarrow{\text{HBr}\ 91\text{-}92.5\%} (CH_3)_2C(Br)\text{-}CH(CH_3)_2 \qquad (60)$$

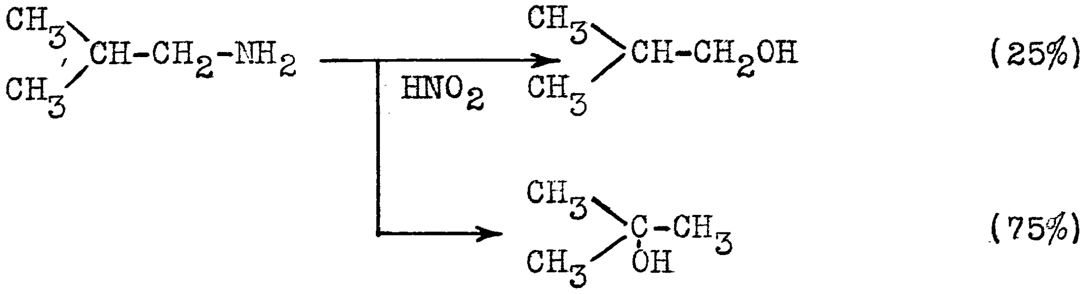
Similarly, Whitmore has observed the occurrence of a rearrangement during the preparation of n-amyl chloride from n-amyl alcohol by hydrochloric acid-zinc chloride reagent (61). A 57% yield of n-amyl chloride was produced in this manner accompanied by a 10% mixture of 2 and 3 chloropentanes. More extensive rearrangement was shown to occur during the preparation of the chloride of 2-Ethyl-butanol-1 (62) with this reagent. Thus, Whitmore reported the production of at least six different chlorohexanes; namely, 3-methyl 3-chloro-pentane, 3-methyl-2 chloro-pentane, 2-methyl-2-chloro-pentane, 4-methyl 2-chloro-pentane, 3-chlorohexane, 2-chloro hexane in addition to the direct substitution product 2-ethyl-1-chloro-butane.

Whitmore has also shown that the rearrangement occurs during, rather than after the replacement of the hydroxyl by the chlorine.

Similarly, Henry has found (63) in the decomposition of many primary aliphatic amines by nitrous acid, that the hydroxyl group fails to take the position previously occupied by the amino group, the tendency being to produce secondary and tertiary alcohols.

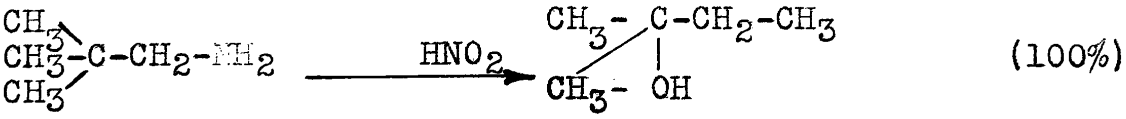


$$CH_3-CH_2-CH_2-NH_2 \xrightarrow{HNO_2} \left[\begin{array}{l} CH_3-CH_2-CH_2-OH \quad (42\%) \\ CH_3-CH(OH)-CH_3 \quad (58\%) \end{array}\right.$$



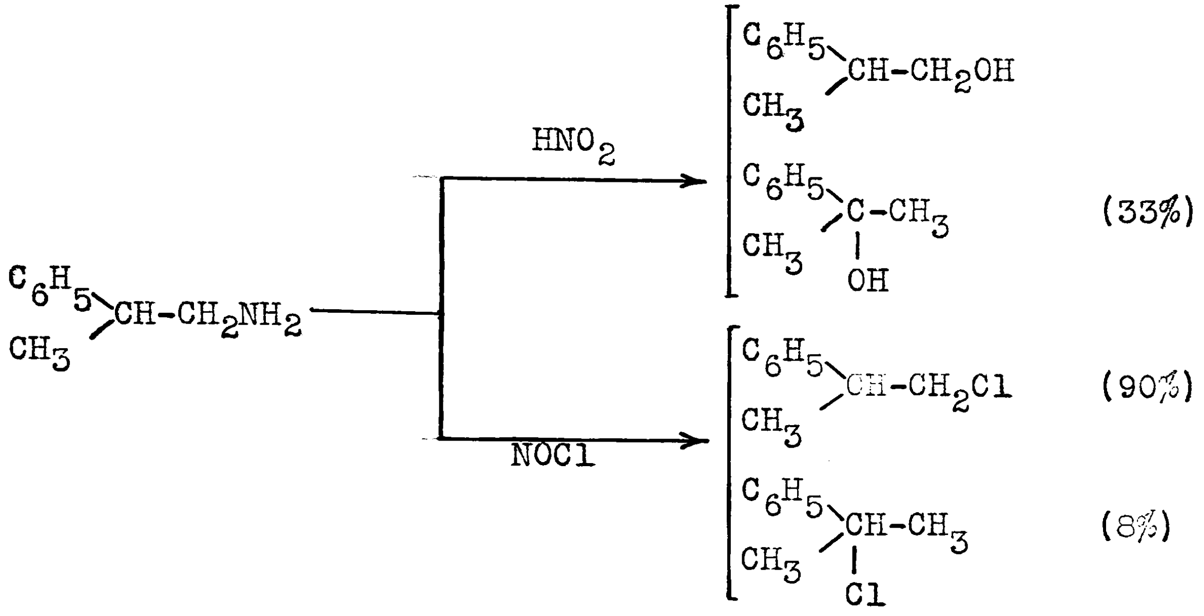
$$(CH_3)_2CH-CH_2-NH_2 \xrightarrow{HNO_2} (CH_3)_2CH-CH_2OH \quad (25\%)$$

$$ \longrightarrow (CH_3)_2C(OH)-CH_3 \quad (75\%)$$



$$(CH_3)_3C-CH_2-NH_2 \xrightarrow{HNO_2} (CH_3)_2C(OH)-CH_2-CH_3 \quad (100\%)$$

Levene and Marker have also reported (64) the partial occurrence of rearrangement by the action of nitrous acid and nitrosyl chloride on methyl phenyl ethyl amine



A recent attempt to prepare 1,1, diphenyl 2,2, dichloro-ethane, desired as an intermediate, by the action of phosphorus pentachloride on diphenyl acetaldehyde led not to the production of the expected 1,1, diphenyl 2,2, dichloroethane but to stilbene dichlorides, (65):

$$(C_6H_5)_2\ CHCHO \xrightarrow[\text{in benzene}]{PCl_5} C_6H_5\text{-CHCl-CHCl-}C_6H_5$$

The above rearrangements exemplify the various kinds of vicinal rearrangements which have been observed. Whether they occur through simple isomerisation or as a substitution reaction, it is to be noted that they are always associated with quite definite groups of atoms. Thus, a rearrangement of this type may occur, in general, regardless of the particular compound as long as it possesses these certain well defined groupings of atoms, in either open chain aliphatic or aromatic compounds as well as in those of cyclic structures.

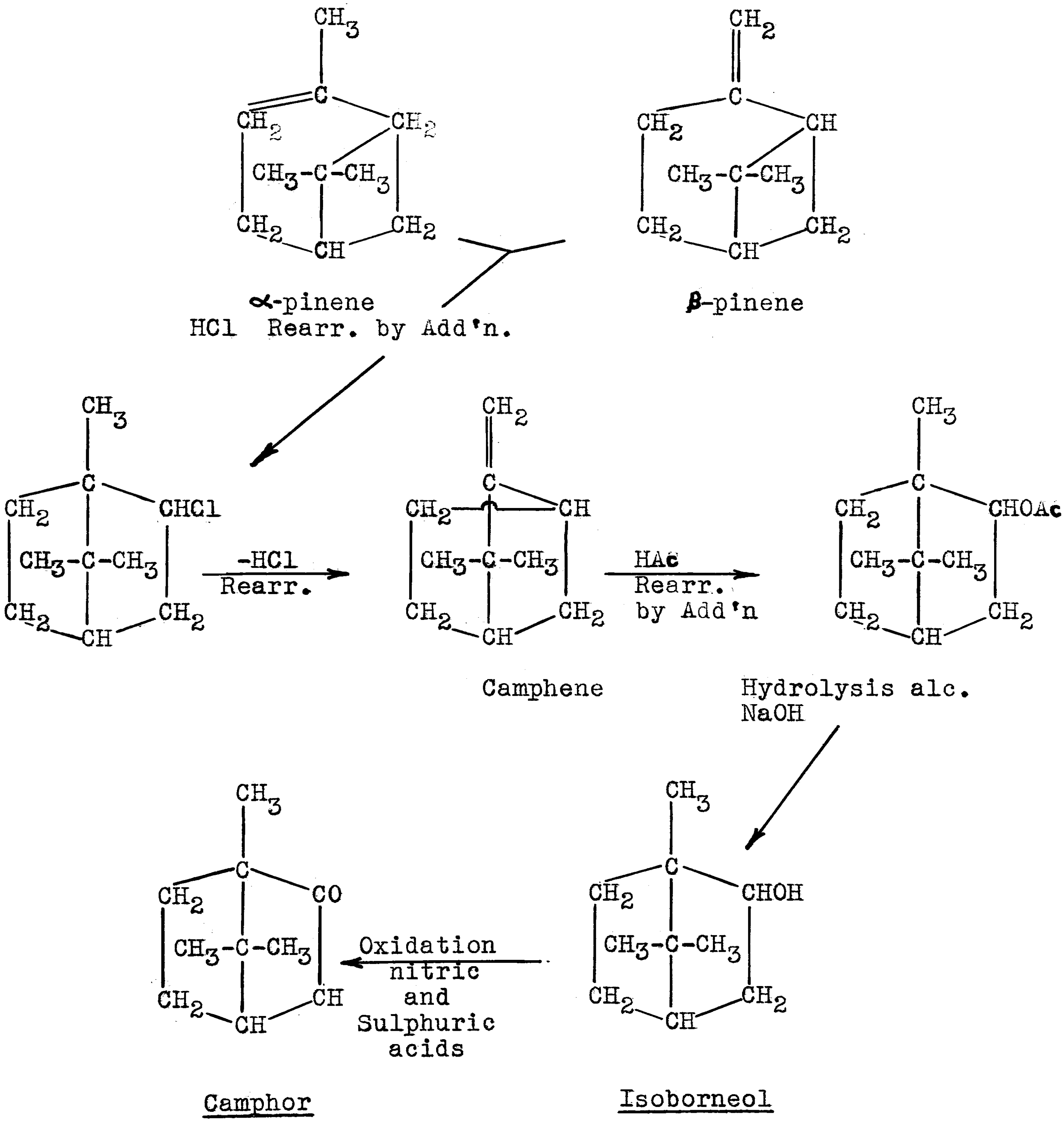
In many cases, vicinal molecular rearrangements have proven to be of great synthetic value, as well as of value in the proof of the structure of a compound, in spite of the occurrence of the rearrangement. The commercial synthesis of camphor involves the molecular rearrangement of the α and β-pinenes contained in the raw material, oil of turpentine. The classical and commonly accepted general process (66) is based on the transformations formulated in Scheme 1.*

The Curtius, Hofmann and Lossen rearrangements, wherein the isocyanate formed may loose carbon monoxide by hydrolysis to produce an amine are methods for the descent or a homologous series. The Curtius reaction is especially valuable in going down a series with compounds which might be sensitive to more violent degradative reactions. On the other hand, the Ardnt-Eistert rearrangement of Diazoketones represents a method for the ascent of a homologous series.

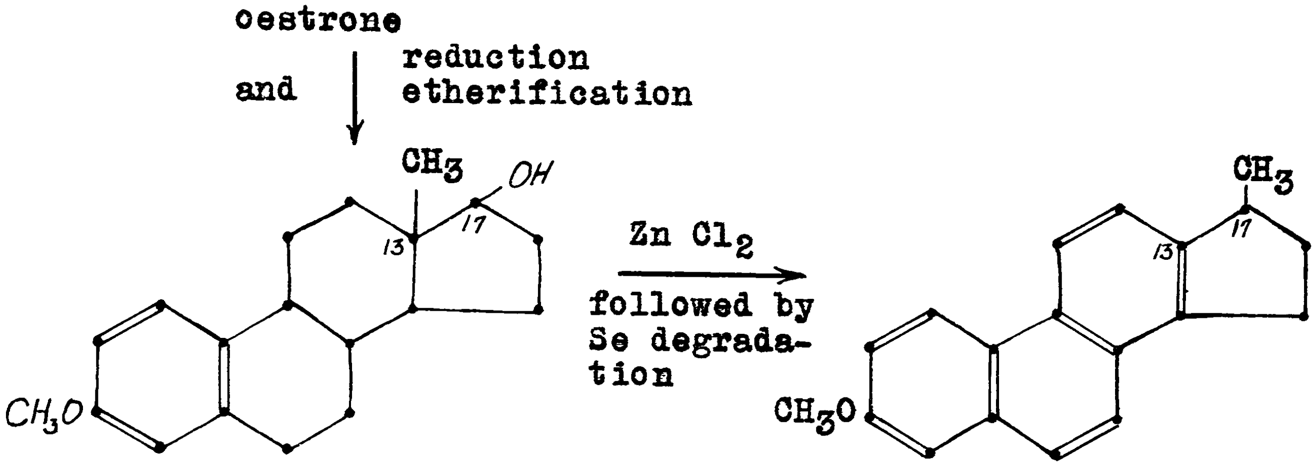
The Hofmann transformation has become a standard method for the preparation of primary amines and is applied, through the action of sodium hypochlorite and alkali on phthalimide to the synthesis of anthranilic acid, the starting point in the synthesis of indigo using naphthalene as the ultimate raw material.

* See Page 21

Scheme 1



Cohen, Cook, and Hewett, applied the retropinacolone rearrangement to the location of the quaternary methyl groups of the hormones, oestrin, equilen, and equilenin, (67), in the following manner,-



7-Methoxy, 3^1-Methyl
1: 2-cyclopenteno-phenanthrene

These authors consider the methyl group which appears in the final product as the quaternary methyl group of the original oestrone molecule, and regard these transformations as supplying indisputable proof of position 13 for the methyl group. The Beckmann rearrangement of ketoximes has often been used as a method of degrading ketoximes to simpler products for identification purposes.(68)

Theories of Intramolecular Rearrangements

The various theoretical interpretations of the processes involved in intramolecular rearrangements have assumed as intermediates, cyclopropane rings, ethylene oxide rings, olefins, univalent nitrogen, bivalent carbon, partial valencies, free valencies, ionic fragments, chelate compounds, and "open sextet" atoms.

These mechanisms may be classified into the following groups,-

A. Mechanisms which assume the formation in one form or another of intermediate products, capable of independent existence and isolatable under appropriate conditions.

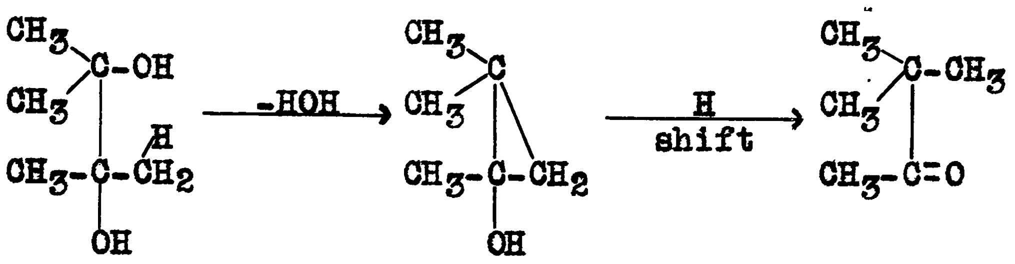
B. Mechanisms which assume the prior formation of "activated intermediates" or "unsaturated radicals" which possess for example free or latent valencies and are not capable of an independent existence, but of necessity reorganize themselves to form stable chemical compounds.

C. Mechanisms which explain all rearrangements on a common basis of an electronic mechanism and considers the processes involved as occurring simultaneously and thus involving no real formation of intermediate compounds.

A. Formation of Isolatable Intermediates:-

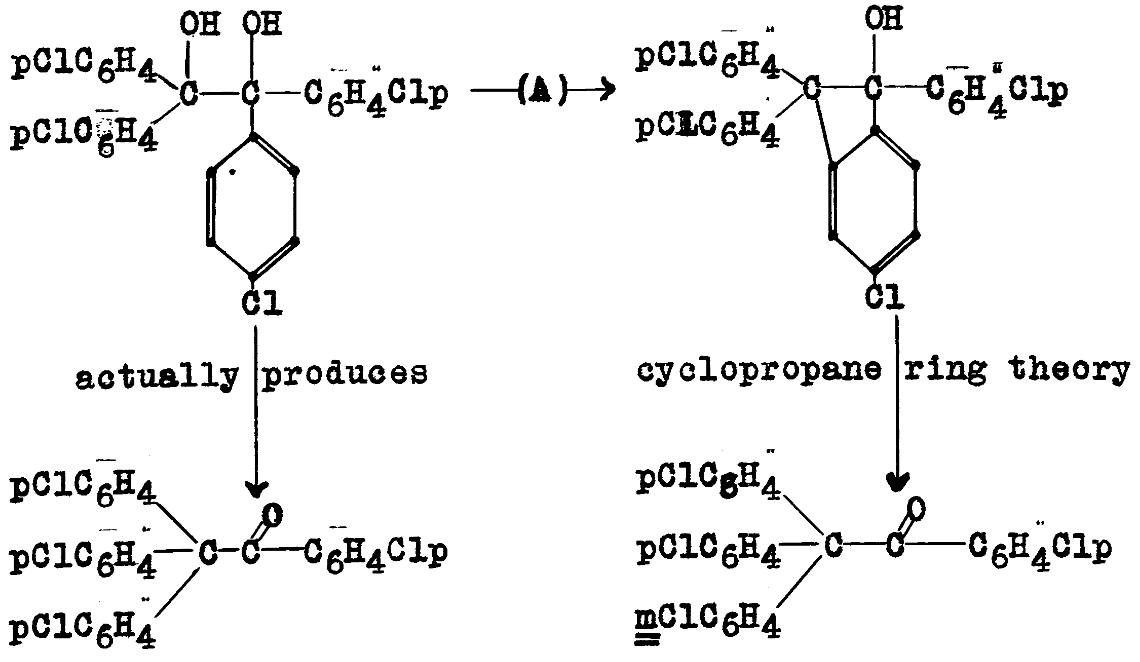
The basic idea underlying the proposal of hypotheses of this kind is the attempt to avoid the assumption of sudden and direct interchanges of atoms or groups within the molecule taking place in a continuous manner as distinct from a step by step process.

Erlenmeyer (68) introduced the concept of the formation of an intermediate cyclopropane derivative and formulated the pinacol-pinacolone rearrangement as ,-



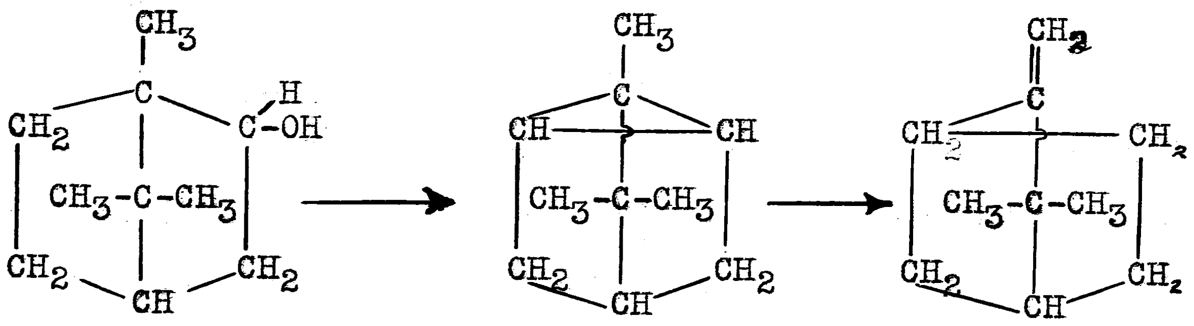
Under the conditions of the experiment, the cyclopropane ring was considered incapable of existence, so that at the moment of its formation, it was ruptured in a different position from where it was formed by the migration of the hydroxyl hydrogen to form the ketone.

Montagne disproved this mechanism for aromatic pinacols (69) by a consideration of the rearrangement of sym-tetra-parachloro benzopinacol to the corresponding pinacolone. On the basis of the cyclopropane ring theory, the product to be expected would have one of the chlorine atoms in the meta position (equation A), thus ,-



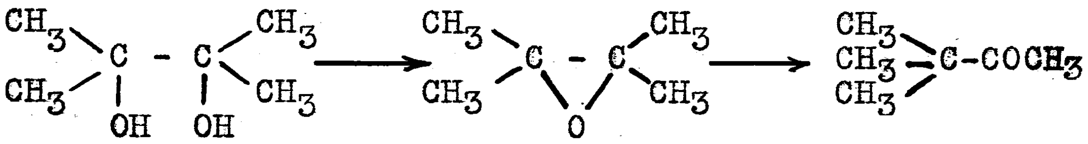
Montagne found that the resulting pinacolone had all four chlorine atoms in the para positions, and thus the point of attachment of groups during the rearrangement was not altered.

Ruzicka applied Erlenmeyer's scheme to the explanation of the Wagner rearrangement of isoborneol to camphene, (70). Thus, he postulated the intermediate formation of a tricyclene, with fision of the cyclopropane ring in a different direction to that of the closure:-



The intermediate tricyclene (71) was prepared by Lipp and later by Meerwein and Von Emster, and found to be far too stable to react under the mild conditions which are used during the isoborneol-camphene conversion. For example, the later authors reported that the tricyclene was practically unaltered by treatment with 33% sulphuric acid at 100°, conditions under which isoborneol is almost completely converted to camphene. At the same time, Meerwein and Von Emster recalled the work of Lafont, wherein optically active camphene was converted to optically active isoborneol, and concluded that the tricyclene could not be the intermediate in the isoborneol-camphene, since the tricyclene is structurally symmetrical and could thus possess no optical activity.

Breuer and Zincke formulated the intermediate formation of an ethylene oxide during the pinacol-pinacolone rearrangement, (72). The subsequent rupture of the ethylene oxide



ring causing the migration of the group. Meerburg, (73) has shown that the rate of reaction is slower in the case of the ethylene oxide reaction than in the actual rearrangement. Similarly, Tiffeneau and co-workers, (74) found that these oxide derivatives did not undergo the rearrangement under conditions similar to the actual conversion. In many cases, they could find no evidence for their existence, their formation requiring more vigorous conditions than those of the pinacol-pinacolone change proper. It was thus concluded that these characteristic ring intermediate products were not formed.

The intermediate formation of olefins was assumed for the conversion of iso- into tert- butyl bromide*. Eltekoff (75) and Favorsky (76) considered the isomerisation as proceeding through the dissociation of the alkyl halide into hydrogen bromide and isobutylene followed by recombination to form either the original or the isomeric bromide.

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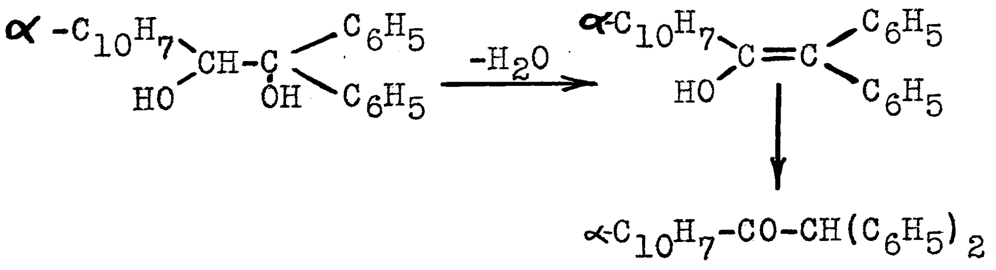
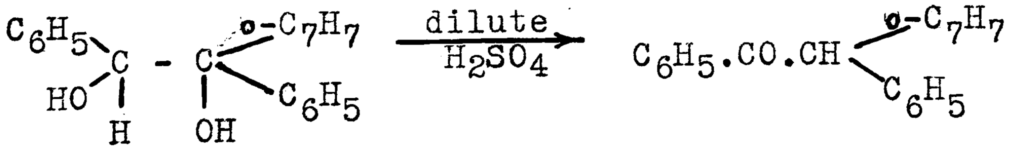
*See page 2.

Michael and Leopold (10) found that the rearrangement occurred readily at relatively low temperatures and could find no evidence of the production of hydrogen bromide under such conditions. In addition, these authors established that the rearrangement proceeded faster in the liquid phase than in the gaseous phase where the dissociation would be the greater. Thus, Michael and Leopold considered the reaction as proceeding through a direct interchange between hydrogen and bromine within a single molecule rather than by a dissociation mechanism.

In certain rearrangements of α, β, glycols to ketones, there is no change in the actual carbon skeleton of the molecule; that is, there is no alteration in the relative positions of the carbon radicals. Thus, McKenzie and Dennler, (77) considered the conversion of 1-α naphthyl 2:2- diphenyl ethylene glycol to diphenyl aceto-naphthone as best depicted through the intermediate formation of an olefin by vinyl dehydration, involving no transposition of radicals.



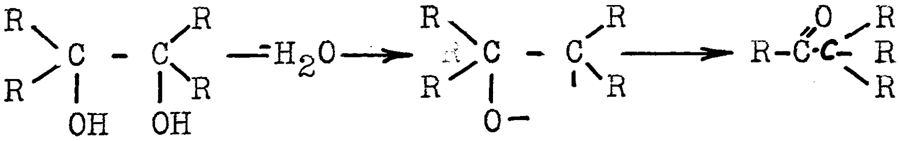
However, Roger and McKay later (78) were able to show that the product of the same type of rearrangement of dextro o-tolyl hydrobenzoin was a highly dextrorotatory o-tolyl deoxybenzoin.



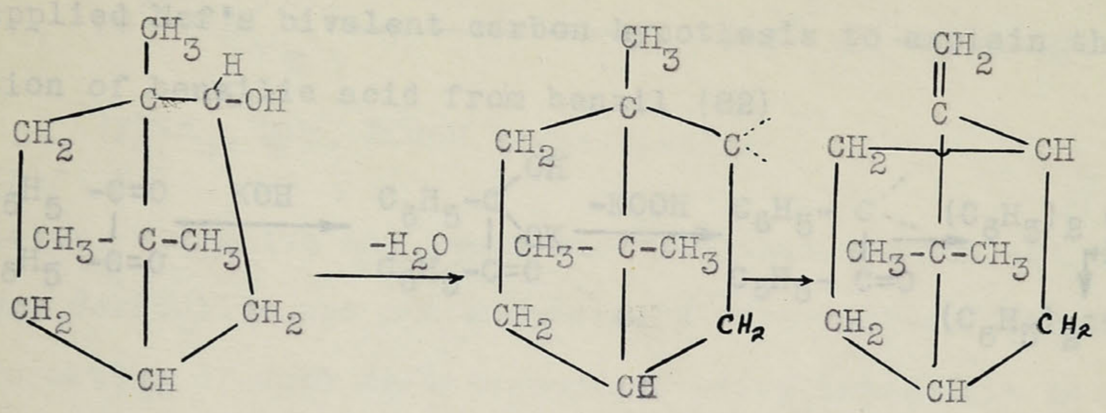
Since the proposed olefin intermediate could possess no optical activity, the formation of optically active o-tolyl deoxybenzoin from optically active o-tolyl hydrobenzoin by this mechanism was considered inadmissable.

(B) Formation of "Activated Intermediates" or Unsaturated Radicals.

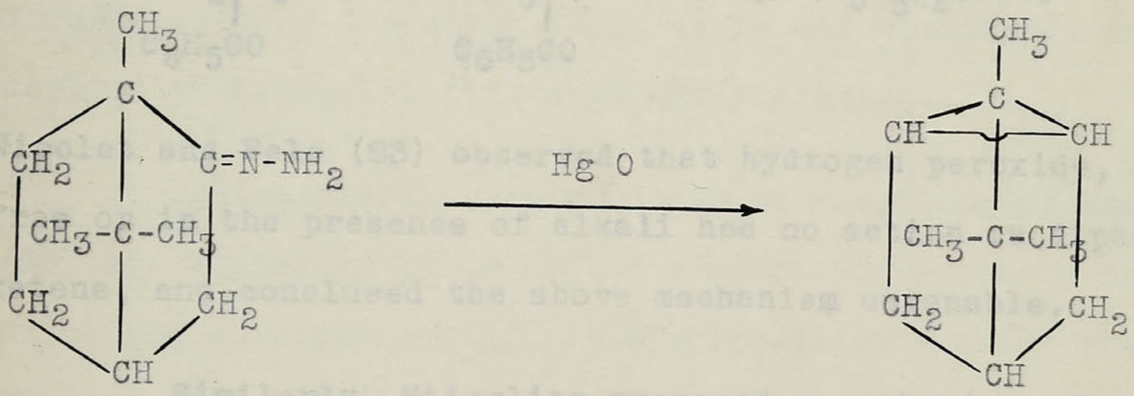
The investigation of the ethylene oxide derivatives as intermediates have shown that they are somewhat less reactive than the "intermediate" formed during the pinacol-pinacolone rearrangement. Tiffeneau, (79) then formulated a mechanism based on the formation of active molecules with free valencies, an actual linkage between the oxygen atom and the carbon atom not being formed, so that the intermediate would be more reactive than the oxide.



He then extended this mechanism to propose that all rearrangements wherein an elimination of simple molecules such as water, nitrogen etc., is involved, proceed through an intermediate which possesses "free valencies", the migration being determined by the instability caused by the unsaturated atoms. The rearrangement of isoborneol into camphene was accordingly formulated as follows:

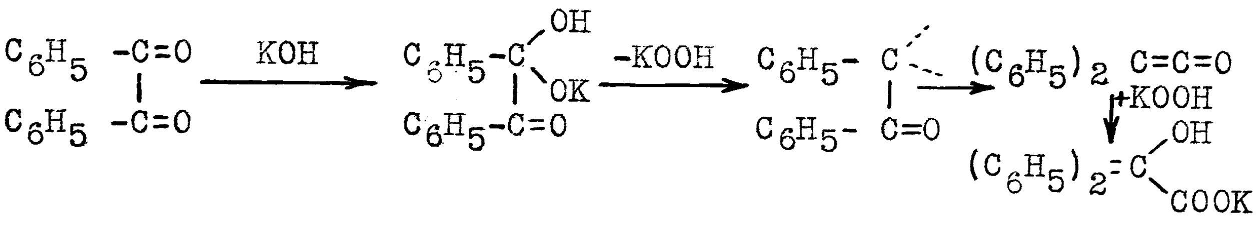


To obtain experimental proof of this assumption, Meerwein studied the decomposition of camphor hydrazone (80), a reaction considered to proceed by formation of the above hypothetical intermediate. The product, however, was tricyclene.

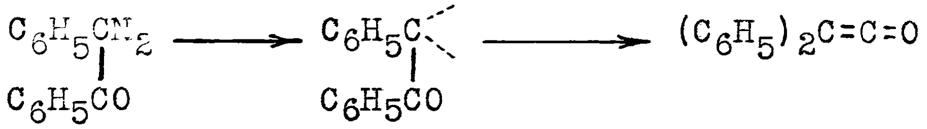


Meerwein concluded that the intermediate formation of the compound with a bivalent carbon atom during the isoborneol-camphene rearrangement could no longer be assumed.

Previous to this time, Nef had considered the rearrangement of isonitriles-nitriles at 230° as best explained on the basis that the bivalent carbon possesses sufficient energy to pull off an alkyl or aryl from the nitrogen and thus, give rise to the formation of the nitrile (81) Schroeter applied Nef's bivalent carbon hypothesis to explain the formation of benzilic acid from benzil (82)

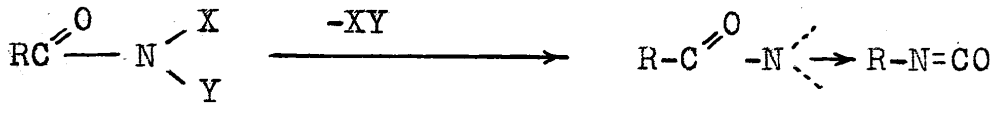


In order to test this view, he prepared azibenzil and found, as he had predicted, that on heating in benzene solution it lost nitrogen to form diphenyl ketene, whilst in methyl alcohol, benzilic acid is formed.



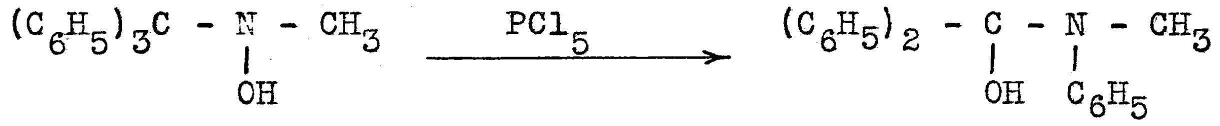
Nicolet and Pele (83) observed that hydrogen peroxide, either free or in the presence of alkali had no action on diphenyl ketene, and conclused the above mechanism untenable.

Similarly, Stieglitz proposed a mechanism of the Curtius, Hofmann and Lossen rearrangements (84) wherein the intermediate formation of molecules with univalent nitrogen atoms was assumed. Furthermore, the free valencies of the univalent nitrogen were assumed to be powerful enough to detach the radical R from carbon and bring about a rearrangement to a stable molecule. Stieglitz proposed that the mechanism be formulated as follows:-



(XY=N_2, HBr, RCOOH respectively)

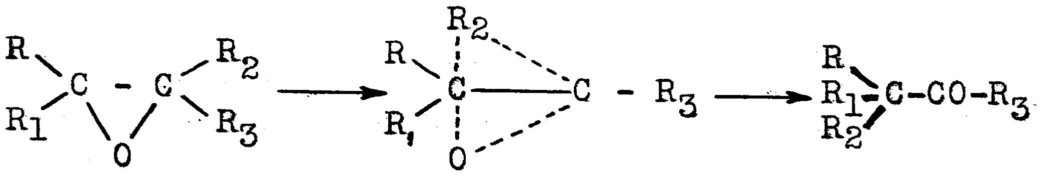
Later, Stieglitz and Leech observed that a univalent nitrogen derivative was not a necessary intermediate (85); the formation of such an intermediate being impossible in the rearrangement of triphenyl methyl hydroxylamine.



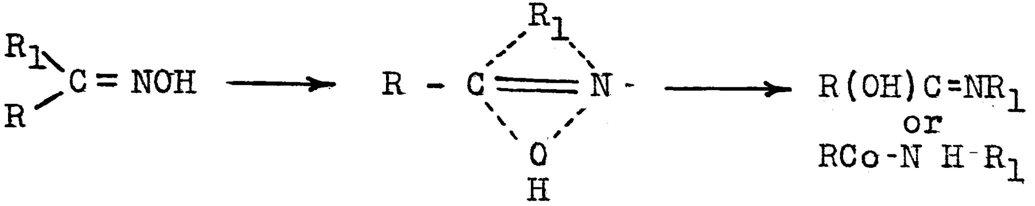
$$(C_6H_5)_3C - \underset{OH}{N} - CH_3 \xrightarrow{PCl_5} (C_6H_5)_2 - \underset{OH}{C} - \underset{C_6H_5}{N} - CH_3$$

This forced new speculations regarding the mechanism of these transformations and ultimately led to the electronic conception of molecular rearrangement processes.

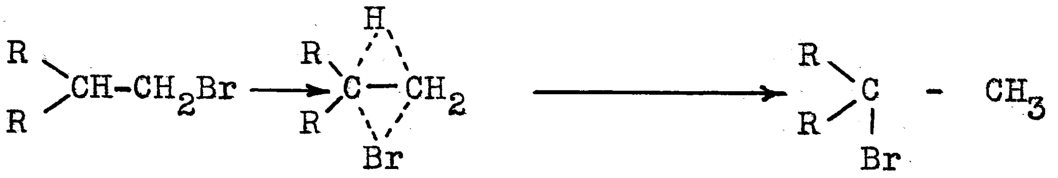
Intramolecular rearrangements according to Ramart-Lucas (86) are explained by using the concept of Perrin of semivalence or single electron bonds. A stable molecule under the influence of a catalyst or heat is converted to a labile form which in turn may rearrange either to give the original product or a rearrangement product. The isomerisation of ethylene oxides was formulated through the unstable form, which by a simple migration of valence electrons between adjacent atoms gave the ketone:-



similarly, the Beckmann Rearrangement,



and the isobutyl-tertiary butyl bromide isomerisation,



(C) The Modern Electronic Concept of Intramolecular Rearrangements

The modern electronic concept of intramolecular rearrangements has been formulated during the development of the modern electronic theories of valency. Whitmore has presented a general application of these concepts in his paper (87) entitled, "The Common Basis of Intramolecular Rearrangements", wherein he states, "The purpose of this paper is to show that rearrangements and the pecularities of organic 'methathetical' reactions have a common mechanism based on the very nature of the 'bonds' in organic molecules. All the essentials of the mechanism proposed in this paper are old and are implicit in conceptions of atoms and molecules introduced during the last twenty years by G. N. Lewis, Arthur Michael, Julius Stieglitz, Lauder W. Jones, W. A. Noyes, Hans Meerwein, H. J. Lucas and Charles Prèvost............ In recent years, Meerwein and his co-workers have added materially to our knowledge of rearrangements and have shown that conditions which favor ionization also favor rearrangement in many cases ... The present study is an extension of this work, but is not limited to cases in which ordinary ionization is possible. The English school of organic chemists, including Robinson, Ingold, Shoppee and their students has long emphasized the dependence of various types of rearrangements on electron transfer within the molecule. The present study involves, then, a fusion and a simplification as well as a more general application of much that has gone before."

Whitmore then formulated all vicinal rearrangements electronically by expressing that portion of the molecule involved in these processes in the general form,-

System (1) $:\overset{\cdot\cdot}{\underset{\cdot\cdot}{A}}:\ \overset{\cdot\cdot}{\underset{\cdot\cdot}{B}}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{X}}:$

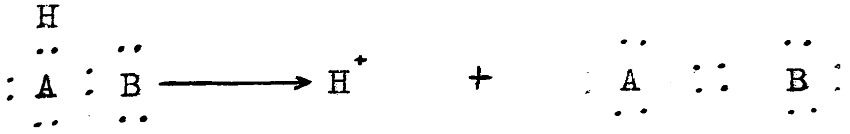
where X us usually oxygen or halogen or other strongly electronegative atom and A and B are atoms like carbon and nitrogen which are neither strongly electronegative nor strongly electropositive, and where each atom has a completed octet of electrons, the linkages being due to a sharing of these electrons. "When a molecule containing system (1) is brought into a reaction which results in the removal of X from its attachment to atom B, then, regardless of the mechanism, of the process, X keeps a complete octet of electrons and leaves B with only a sextet of electrons, an "open sextet". Thus, at some instant system (1) becomes

Three different changes may take place:

1. The positice organic fragment, depending on the chemical nature and environment of A and B, may have a life long enough to allow it to combine with a negative ion Y in the reaction mixture.

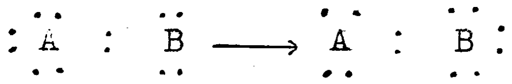
In such a case, the reaction is "normal", no rearrangement takes place, and the process resembles the simple metathetical reactions of inorganic chemistry. It is not usual for an organic reaction to follow this course entirely.

2. If the atom A has a hydrogen attached to it, the fragment can be stabilized by loss of a proton.



The product is an olefin or other unsaturated molecule. This process is very common in organic reactions and has led many to believe that the olefin is an intermediate product in such reaction instead of merely a by-product.

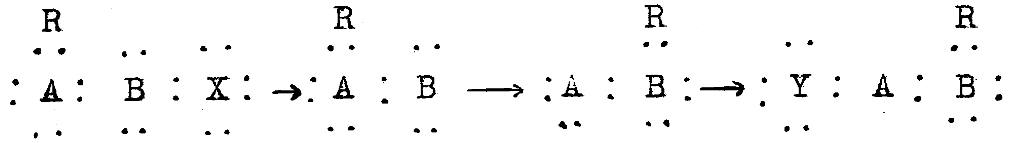
3. The nature and environment of A and B may be such that B has the greater attraction for electrons or that A can more readily dispense with a pair of its electrons. In either case, a change in the fragment will leave A with an open sextet.



$$:\overset{..}{\underset{..}{A}} : \overset{..}{\underset{..}{B}} \longrightarrow \overset{..}{\underset{..}{A}} : \overset{..}{\underset{..}{B}}:$$

The shift of the electron pair includes the atom or group which it holds"

"The new fragment can then recombine with the ion X or with a new negative ion Y from the reaction mixture. The result is an "abnormal" or rearranged product, the series of changes being



$$:\overset{R}{\overset{..}{\underset{..}{A}}}: \overset{..}{\underset{..}{B}} : \overset{..}{\underset{..}{X}}: \rightarrow :\overset{R}{\overset{..}{\underset{..}{A}}} : \overset{..}{\underset{..}{B}} \longrightarrow :\overset{..}{\underset{..}{A}} : \overset{R}{\overset{..}{\underset{..}{B}}}: \longrightarrow :\overset{..}{\underset{..}{Y}} : A : \overset{R}{\overset{..}{\underset{..}{B}}}:$$

If atom B in the rearranged positive fragment has a hydrogen attached to it, the system may lose a proton. Depending on the other groups attached to A and B, the resulting unsaturated compound may or may not be identical with that obtained by the loss of a proton from the original fragment. It is important to note that the shift of electrons within the positive fragment, and the stabilization by loss of a proton are monomolecular processes which may effectively compete with the bimolecular union of the original or the rearranged fragment with an ion from the reaction mixture."

Whitmore stressed that this hypothesis does not assume that a group leaves one part of a molecule and later attaches itself to a different part, the important process being the intramolecular transfer of an electron pair with the attached group from an adjacent atom. The KEY to molecular rearrangements on this basis is the formation of an atom with an "open sextet", a deficiency of an electron pair, to act as a centre of instability.

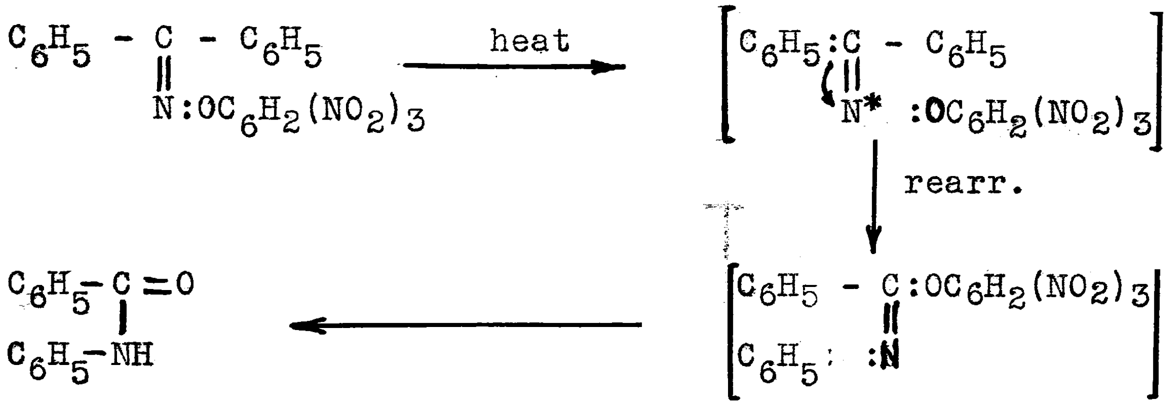
The hypothesis in the above form has since beem modified by the consideration that the processes involved may take place simultaneously, so that an atom with a true 'open sextet' may probably not actually be formed as an intermediate. That is to say, a simultaneous addition and dissociation of reactants, a simultaneous formation and breaking of linkages is considered as taking place.

Various authors have applied the electronic concept to the explanation of the different vicinal rearrangements, in the following manner (the asterisk* indicating the atom with the "open sextet");

A. Rearrangements and Isomerisation

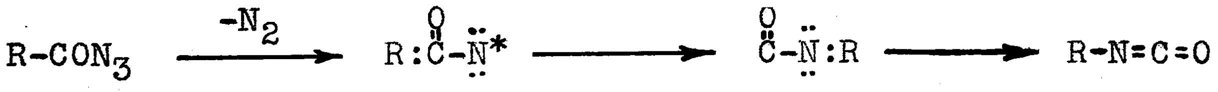
The Beckman Rearrangement -

The spontaneous Beckmann rearrangement which the picryl and related ethers of ketoximes undergo was regarded by Chapman and Howis (88) as proceeding by an intramolecular exchange of positions of the hydrocarbon radical and the picrate group, through perhaps a preliminary dissociation taking place within the molecule; this dissociation never reaching the stage of true ionisation



B. Rearrangements and Elimination

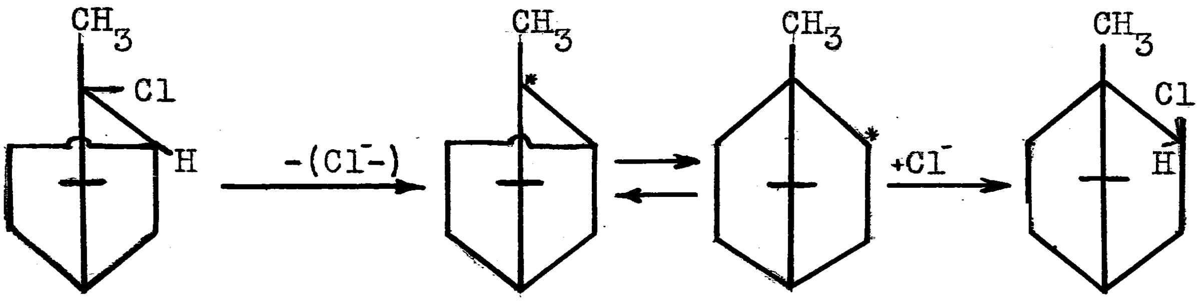
The Curtius Rearrangement - The elimination of the nitrogen leaves an "open sextet".



$$R\text{-}CON_3 \xrightarrow{-N_2} R:\overset{O}{\ddot{C}}\text{-}\ddot{\underset{..}{N}}^{*} \longrightarrow \overset{O}{\ddot{C}}\text{-}\ddot{\underset{..}{N}}:R \longrightarrow R\text{-}N{=}C{=}O$$

The Wagner Meerwein Rearrangement-

Ingold (89) considered that "there may be special structures in which the natural distribution of affinity (apart from any tendency to elimination) is such as to loosen one of the attached groups, and give rise, under suitable conditions, to isomeric change dependent on the formation of an ion." An ionic mechanism was put forward in explanation of the Wagner rearrangement by Meerwein (90). The evidence in support of this mechanism is provided by the observation that the ease of the transformation increased with increasing anionic stability of X and with increasing dielectric constant of the medium. Bartlett and Pockel (91) formulated the arrangement in the following manner



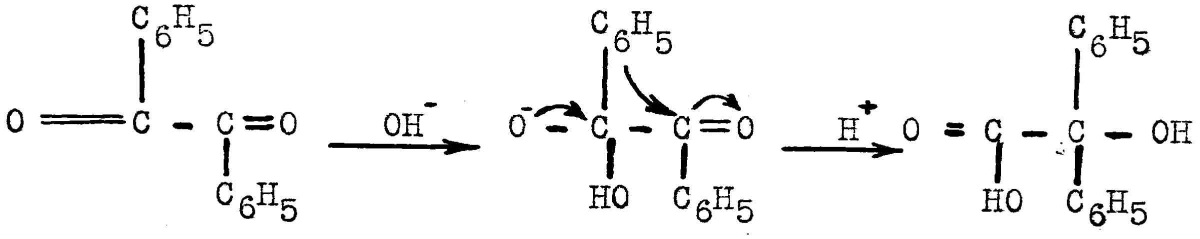
C. <u>Rearrangements and Addition Reactions</u>-

The "positive fragment" which undergoes rearrangement may not only be formed by the removal of an atom or group with a complete octet of electrons but may also be formed by the addition of a proton to one carbon of an ethylenic linkage leaving the other carbon atom with only six electrons.*(92)

$$\begin{tikzcd}
(CH_3)_2CH\text{-}CH{=}CH_2 \arrow[r, "H^+"] & (CH_3)_2CH\text{-}\overset{*}{C}H\text{-}CH_3 \arrow[r, "Cl^-"] \arrow[d, "H:"', "rearr."] & (CH_3)_2CH\text{-}CHCl\text{-}CH_3 \\
& (CH_3)_2C^{*}\text{-}CH_2CH_3 \arrow[r, "Cl^-"] & (CH_3)_2C(Cl)\text{-}C_2H_5
\end{tikzcd}$$

<u>The Benzil-Benzilic Acid Rearrangement</u>-

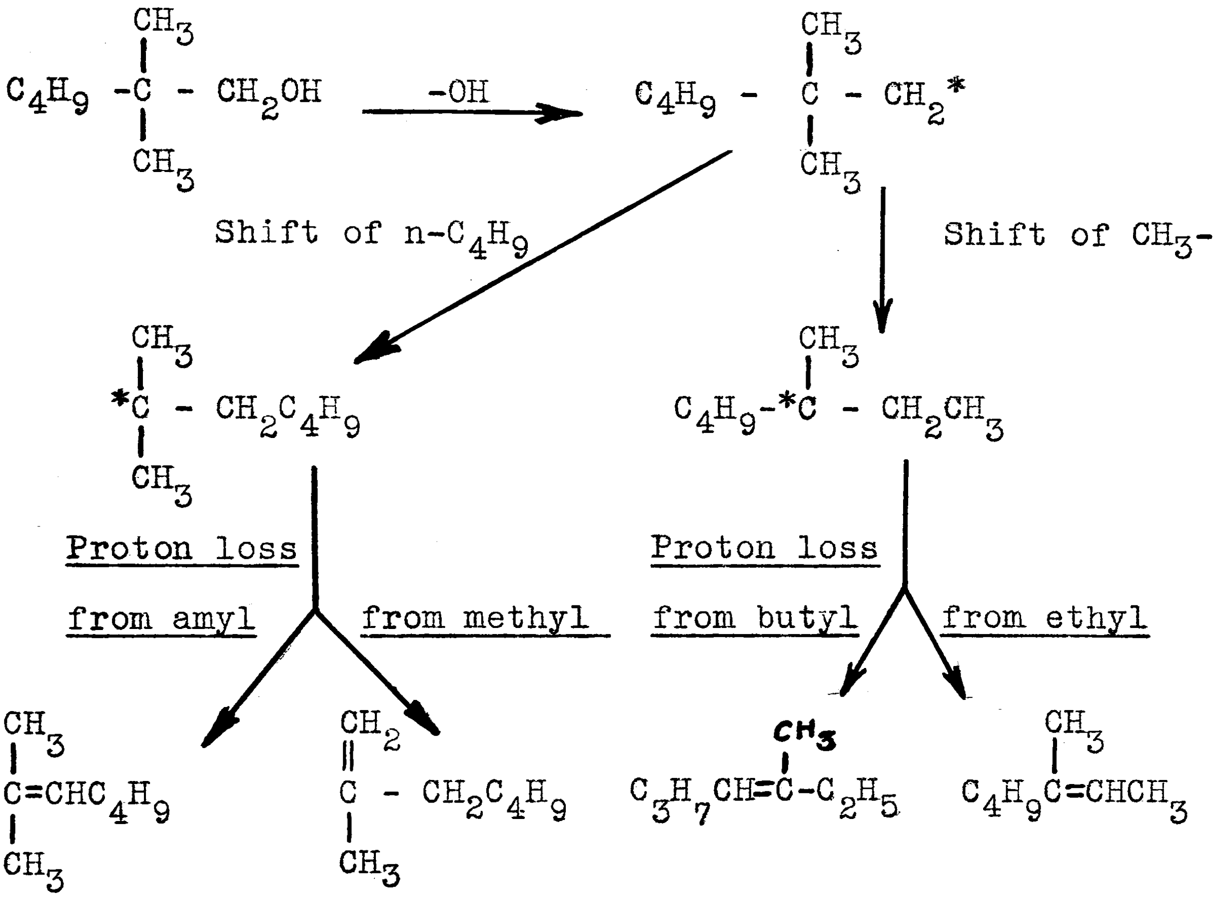
The benzil-benzilic acid change has been formulated by Ingold (92) and Shoppee (93):



Robinson had considered that the driving force of the rearrangement lies in the strong tendency of the ion $\overset{\ \ O^-}{C{-}OH}$ "to stabilize itself by becoming a true ion of a carboxylic acid" (by the loss of an electron pair.) (94). According to Ingold and Shoppee this excess of electrons stabilizes itself by a "pinacolic electron displacement" towards the other carbonyl group which acts as an "electron sink". These authors considered that both an electron source and an electron-sink must be present in a molecule for pinacolic electron displacement to occur.

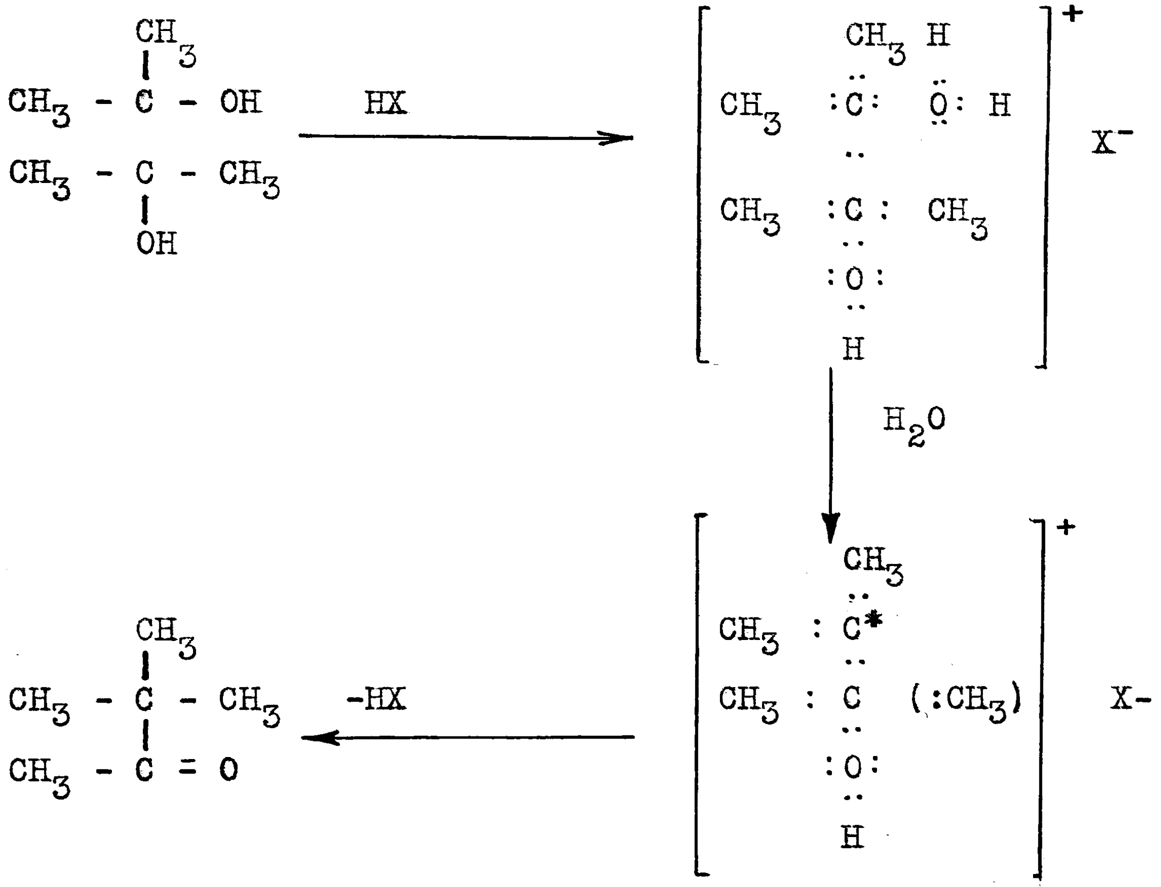
D. Rearrangements and Removal Reactions-

Whitmore and Church (95) have reported the formation of four different octylenes on the dehydration of 2,2-dimethyl hexanol-1, by heating with concentrated sulphuric acid, and have formulated their formation as follows:-



The Pinacol-pinacolone Rearrangement-

"The Stieglitz mechanism of the pinacolone rearrangement assumes that an intermediate oxonium salt (I) loses water to leave a nucleus (II) in which one of the carbon atoms possesses only three pairs of electrons. This "fault" in the molecule is then repaired by the migration of a negative methyl group, with its full complement of electrons, from the adjacent carbon atom to the electron deficient carbon atom." (96)



Hofmann and Lossen Rearrangements-

Bright and Hauser have represented (97) the general course for the Hofmann and Lossen rearrangements of compounds of the type R-CO-NH-X (where X is halogen, benzoate, etc.,) in the presence of alkali, as follows,

$$\begin{tikzcd}
\text{R-CO-NHX} + \text{KOH} \arrow[r] & (\text{R-CO-NX})^{-}\text{K}^{+} + \text{HOH} \arrow[d] \\
\text{RNCO} & (\text{R-CON*}) + \overset{+}{\text{K}}\text{X}^{-} \arrow[l]
\end{tikzcd}$$

"First, an acid-base reaction occurs forming the salt (I): many salts of this type can be isolated. Second, the anion of the salt releases X with a complete octet of electrons (i.e. as an anion) leaving the nitrogen atom with only a sextet of electrons. Third, the molecule is stabilized by rearrangement to an isocyanate. The stabilization by rearrangement is considered to involve a shift of an electron pair with the group R attached from C to N".

E. Rearrangements and Substitution Reactions

The extensive rearrangement which Whitmore has reported (98) in the preparation of the chloride of 2 ethylbutanol-1 by the action of hydrochloric acid-zinc chloride reagent, wherein six different chlorohexanes, namely 3-methyl-3-chloropentane (B), 3-methyl-2-chloropentane (C),2-methyl-2-chloro pentane (F), 4-methyl-2 chloro pentane (C), 2-methyl-2-chloro pentane (F), 4-methyl - 2-chloro pentane (G), 3-chlorohexane D, 2-chlorohexane E, in addition to the direct substitution product 2-ethyl 1-chloro butane (A) are produced, has been formulated as in scheme 2.*

The Migrating Radical

Wallis and Moyer have studied the Hofmann rearrangement of dextro 3,5-dinitro 6,α-naphthyl benzamide. (99) In this molecule optical activity is conditioned by the restriction of free rotation about the diphenyl linkage. On rearrangement, an optically active amine, 3,5-dinitro,6, α-naphthylamine was obtained with no change of sign in the

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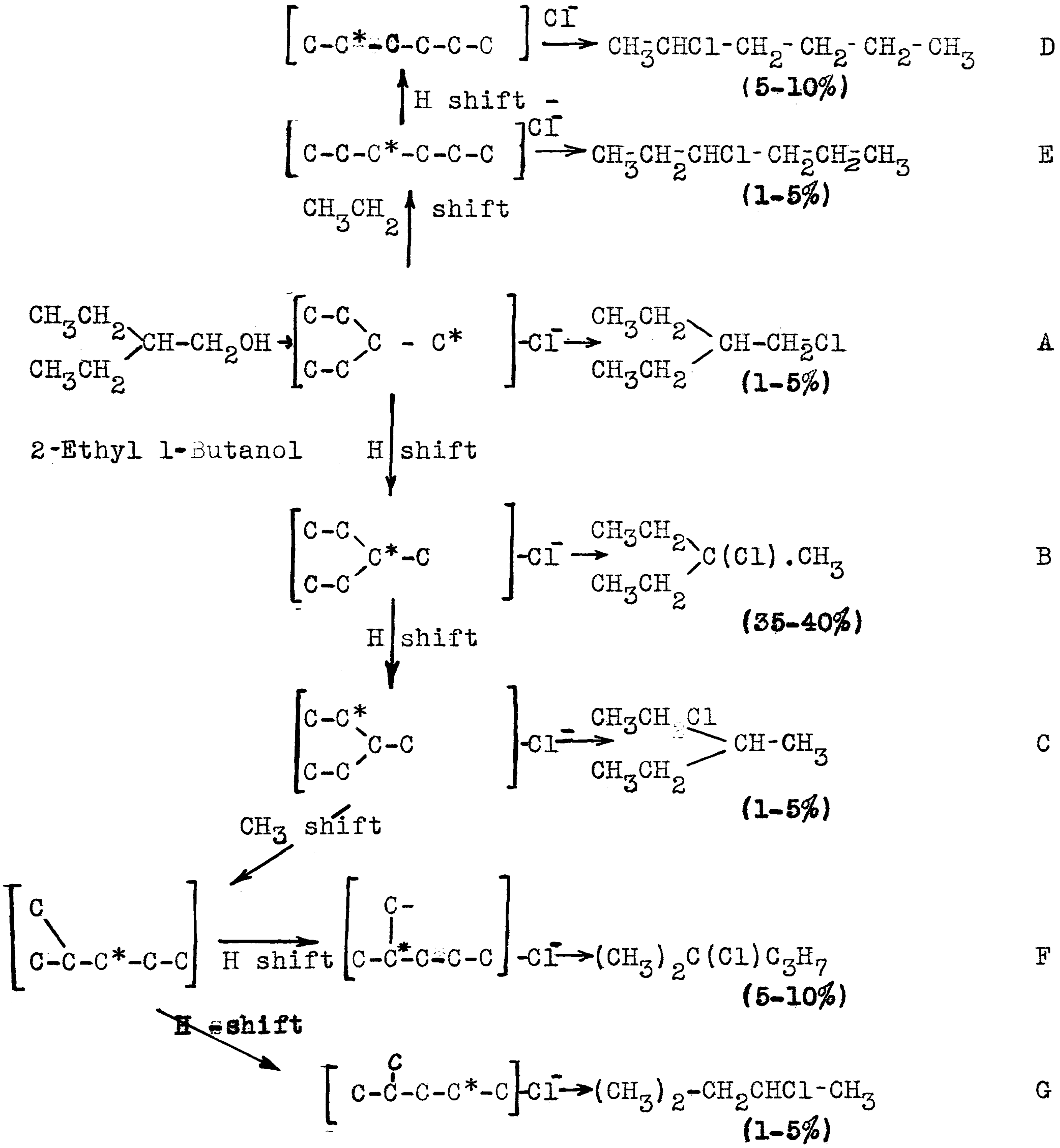
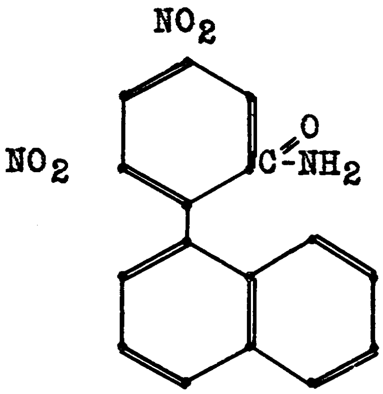
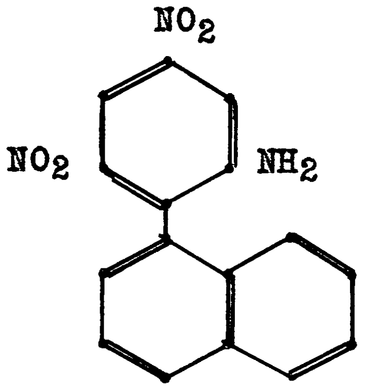
* See Page 43


C-C*-C-C-C-C
Cl⁻
CH3CHCl-CH2-CH2-CH2-CH3
(5-10%)
D
H shift -
C-C-C*-C-C-C
Cl⁻
CH3CH2CHCl-CH2CH2CH3
(1-5%)
E
CH3CH2 shift
CH3CH2 CH3CH2 >CH-CH2OH
C-C C-C C - C*
-Cl⁻
CH3CH2 CH3CH2 >CH-CH2Cl
(1-5%)
A
2-Ethyl 1-Butanol
H shift
C-C C-C C*-C
-Cl⁻
CH3CH2 CH3CH2 >C(Cl).CH3
(35-40%)
B
H shift
C-C* C-C C-C
-Cl⁻
CH3CH Cl CH3CH2 >CH-CH3
(1-5%)
C
CH3 shift
C C-C-C*-C-C
H shift
C- C-C*-C-C-C
-Cl⁻
(CH3)2C(Cl)C3H7
(5-10%)
F
H shift
C C-C-C-C*-C
-Cl⁻
(CH3)2-CH2CHCl-CH3
(1-5%)
G

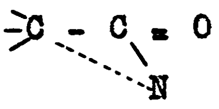
Scheme 2.

rotatory power and no appreciable racemisation



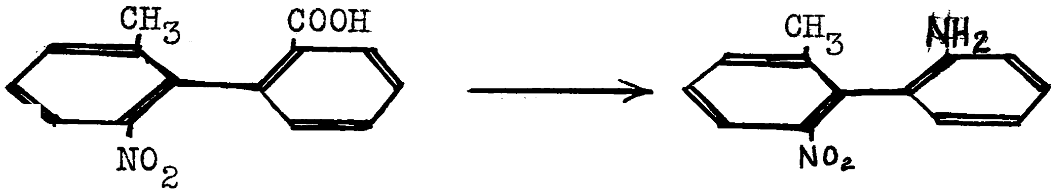


These results were interpreted as showing that at no time is the blocking effect of the -CON group removed, that is, in rearrangements of this sort the radical R is never free even momentarily. This change is therefore truly intramolecular, the migrating group being never completely free, either as a negative, positive or neutral fragment. "The process therefore seems clear enough. After the hydrogen bromide has been removed from the nitrogen atom the appropriate picture of the system must be much like that indicated in the following diagram:

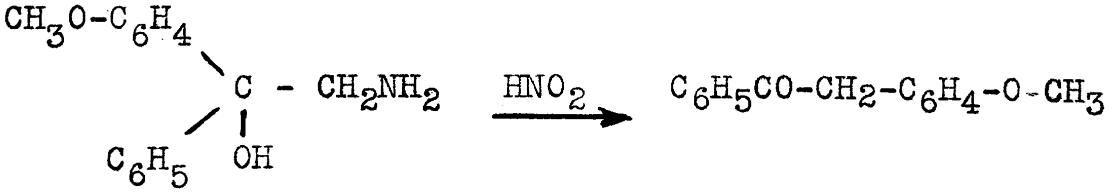


with dotted lines indicating partial valencies which are beginning to form......... With subsequent motion of the nitrogen atom the bond between the two carbon atoms will grow continuously weaker, and this will be accompanied by a strengthening of the dotted bonds and the appearance of an additional bond between the nitrogen and carbon atoms..... One could predict that no free radical, positive or negative, would appear. Therefore, an asymmetric configuration is maintained."

A similar observation has been made by Bell, (100) optically active 6-nitro - 2 methyl diphenyl - 2 carboxylic acid when submitted to the Hofmann or Curtius reactions producing an amine of the same sign of rotation

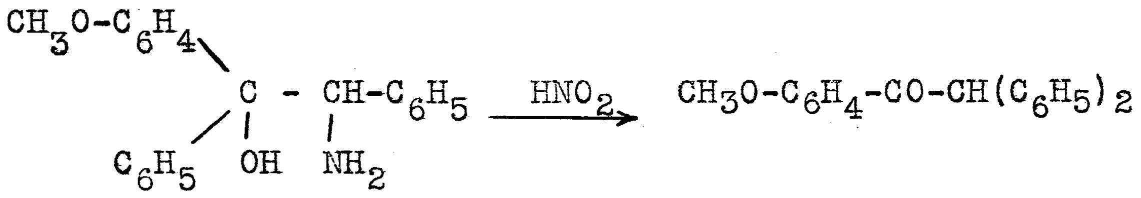


The aspect of the problem of molecular rearrangements which considers the relative ease with which groups migrate is not as yet fully understood, the study of the relative migrating aptitudes of groups having led to many anomalous results. Thus, Orekov and Roger, (101), observed in 1-phenyl 2-amino - 1 anisyl ethanol, that the anisyl group migrated, there being no evidence that the phenyl had migrated at all:-



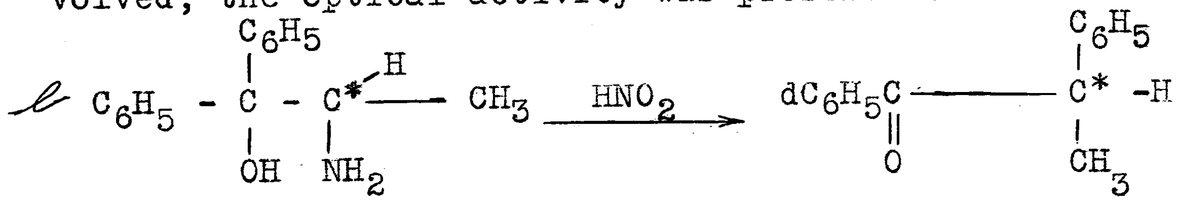
$$\mathrm{(CH_3O{-}C_6H_4)(C_6H_5)C(OH) - CH_2NH_2} \xrightarrow{HNO_2} \mathrm{C_6H_5CO{-}CH_2{-}C_6H_4{-}O{-}CH_3}$$

whereas, with 2-amino-1:2-diphenyl, 1-anisyl ethanol-1,McKenzie and Mills found that the phenyl group migrated, (102):



Molecular Rearrangements and Substitution Processes

A new chapter in the study of Intramolecular Rearrangements was begun with the discovery by McKenzie, Roger and Wills in 1926, of the transformation without loss of optical activity of an optically active amino alcohol to an optically active ketone, wherein a hydrocarbon radical had migrated from the adjacent carbon atom to the asymmetric carbon atom, (103). In spite of the intramolecular rearrangement involved, the optical activity was preserved.



$$C_6H_5-\underset{OH}{\overset{C_6H_5}{C}}-\underset{NH_2}{\overset{H}{C^*}}-CH_3 \xrightarrow{HNO_2} dC_6H_5\underset{\overset{\|}{O}}{C}-\underset{CH_3}{\overset{C_6H_5}{C^*}}-H$$

A reaction of substitution at the optically active centre is involved during the transposition of the phenyl group, the phenyl group replacing the eliminated amino group.

Simple Substitution Processes:-

The surprising discovery that a new substitutent need not always enter the exact spatial position occupied by the atom or radical being replaced, but may enter another valence position on the same carbon atom was reported by Walden in 1895. (104).

Walden had established the following transformations:

$$\begin{tikzcd}
\text{l-COOH-CH}_2\text{-CH(NH}_2\text{)-COOH} \arrow[r, "HNO_2"] \arrow[d, "NOCl"] & \text{l-COOH-CH}_2\text{CHOH-COOH} \arrow[d, "PCl_5"] \\
\text{l-COOH-CH}_2\text{-CHCl.COOH} & \text{d-COOH-CH}_2\text{-CHCl-COOH}
\end{tikzcd}$$

Scheme 3

That is, Walden had found it possible to obtain from an optically active substance containing a single asymmetric carbon atom, the substitution product in either of its optically active forms. In one of these transformations, Walden realized a change of configuration or an optical inversion must have occurred. That is to say, the relative spatial positions of the atoms or radicals in union with the asymmetric carbon atom had been altered.

Optical inversion had not been anticipated as a corollary to the Van't Hoff-LeBel theory of the stereochemistry of carbon compounds and thus was considered the result of an abnormal substitution. It was however, soon observed to occur so frequently and so regularly that Fischer was led to regard the process as normal rather than abnormal and as representing a very general phenomenon (105) which he designated " The Walden Inversion."

The question at once arose as to whether a theoretical explanation of "The Walden Inversion" could be formulated.

W. Ostwald in his review of Walden's paper comments, somewhat sarcastically, "One may indeed be highly expectant of efforts which will be made to explain this contradiction," (106).

Modern Theories of Walden Inversion:-

The modern theory of the typical substitution reaction of organic chemistry was suggested by London's quantum mechanical interpretation of the process and was developed and applied by Meer and Polanyi, by Olson, and by Hughes and Ingold.

London has shown (107) from quantum mechanical considerations that the energy of activation for reactions of the type: $Y + XZ \longrightarrow YX + Z$, is smallest if the atom approaches (the molecule) along the line joining the nucleii of the molecule. It also follows from his theory that the activation energy (under this condition) would be, in general, as little as one-seventh of the dissocation energy of the dissociating molecule (XZ).

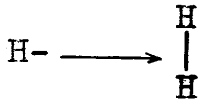
Eyring and Polanyi (108) applied London's theory to the simplest substitution reaction, the atomic exchange conversion of para hydrogen to ortho hydrogen by hydrogen atoms.

$$H- + p\text{-}H_2 \longrightarrow o\text{-}H_2 + H-$$

The designated ideal simplicity of this transformation involving a single process and only one reactant permits of a theoretical treatment as well as an experimental study. Application of London's theory showed that the energy of activation of reactions of this type is a minimum if the hydrogen atom approaches the hydrogen molecule along the molecular axis, (Fig.1) and is so large that under ordinary circumstances the transformation would not occur if the attacking atom were to approach the molecule symmetrically, (Fig.2); that is, perpendicularly to the molecular axis.

$$H- \longrightarrow H\overset{*}{-}H$$

Fig. 1.



$$H- \longrightarrow \begin{array}{c} H \\ | \\ H \end{array}$$

Fig. 2.

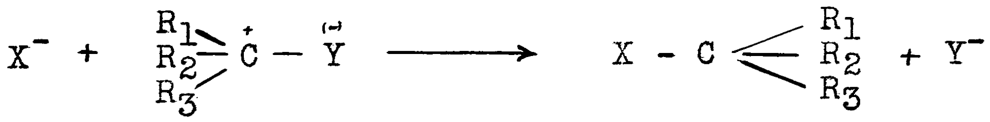
Theoretical calculations, (109), show that the activation energy of the process as in Fig.2 is about 100Kg. cal., whereas for the process as shown in Fig.1, is only about 13-15 kg. cal. Experimentally, the activation energy was found by Farkas (110) to be 4,300 -11,000 calories and by Geib and Harteck (111) to be 7250 ± 250 calories. Pelzer and Wigner (112) have extended the calculations for a molecular axis approach to obtain a value for the reaction velocity which is in excellent agreement with experimental results. The general agreement between theory and experiement in this case as well as in other similar cases, that have been reported, indicates that the processes involved in the reactions of the type; $Y + XZ \longrightarrow YX + Z$, may be considered to take place as follows: -

(1) The attacking atom Y approaches the molecule XZ along the molecular axis. Since the activation energy required in these reactions is only a fraction of the energy required to break either bond outright, the approach of the attacking atom Y, must weaken the bond XZ.

(2) The energy of activation of the reaction allows Y to form with XZ an activated state,-the state where X is attracted equally to both Y and Z. This activated state represented by a linear configuration of the three atoms then breaks down to either Y+ XZ or YX + Z.

Indirect Substitutions:-

In 1932, Meer and Polanyi formulated a stereo-chemical corollary to the interpretation; namely, that all bimolecular substitution reactions of the type,-

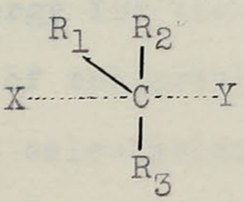


took place with inversion and classified them as "Negative Mechanism" reactions, (113). These authors pointed out that when a substitutent of the negative type is exchanged for a negative ion (anion), the driving force of the reaction must lie in the interaction of the negative ion with the carbon atom to which it becomes attached, (the effect of the positive ion being restricted to a "salt effect"), and that the negative ion will necessarily approach the carbon atom from the side opposite to the group to be substituted, since the electrostatic forces of the dipole attacked by the ion will cause this to be the position of minimum energy. Thus, the new substitutent X^-, will always react with the carbon atom at the face of the tetrahedron which is opposite to the position of the original substitutent, Y. A Walden s inversion will accordingly always occur.

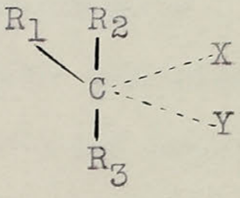
Olsen extended this theory to postulate inversion in every substitution, (114). Substitution reactions, $Y + XZ \longrightarrow YX + Z$, taking place by mechanism in which either dissociation of XZ is the primary step or the formation of the complex YXZ is the primary step, were considered as limiting cases of an inclusive group in which dissociation and association may be simultaneous phenomena. Olson referred to the quantum mechanical considerations of Pauling and Slater (115) which have indicated that the carbon eigenfunction which is involved in the carbon chlorine bond extends beyond the carbon atom on the side away from the chlorine. That is, the carbon atom has a tendency to form a bond at each face of the tetrahedron. Furthermore, the weaker the bond is to the apex, the stronger the bond is to the opposite face. Therefore, "The group which is to be displaced determines a unique path for the entering group, such that the system requires less energy than it would for any other path*. Olson considered it immaterial whether there is first addition to the face-centered bond or whether there is a dissociation which strengthening this bond attracts the entering group, causing a similtaneous addition. This then leads to complete inversion of configuration for the reaction which takes place in one step. .

H. Menke (116) had given experimental support to the existence of this face-centered bond, since his interpretation of the X-ray diffraction pattern of liquid carbon tetrachloride required the assumption that the chlorine from one molecule of carbon tetrachloride in the liquid state was face-centered on the adjoining carbon tetrachloride tetrahedion.

The relative energies of the two possible transition states (I,II) which could be involved in this transformation were assessed by Hughes and Ingold (117) by application of the exclusion principle; that is, by consideration of the conditions which would minimize the replusive exchange energy integrals. They conclude that state I will correspond to a smaller state of activation then state II.



I



II

Hughes and Ingold considered the effect arising from the exclusion principle to be more important, and in all ordinary eases determinative, than the effect of the dipole field in the line C-Y, previously considered by Meer and Polanyi to be the force which preferentially directs the anionic reagent to the position leading to inversion. Such a view is confirmed by Read and Walker's observation (118) of inversion occurring in the replacement by OH^- of $\overset{+}{N}-Me_3$ in l-piperityl trimenthyl ammonium hydroxide to give a piperitol. In this case, the bond to be ruptured is $C - \overset{+}{N}\ R_3$ and the electrostatic forces alone would direct the attacking anion to the position giving a retained configuration, whereas, the exclusion principle still favors transition state I. The experimental results indicate that inversion of configuration occurs and thus the exclusion principle is determinative. That is to say, the most favorable method of attack still remains along the line of the linking involved in substitution.

Confirmation of the theoretical views was given By Ogg and Polanyi who were able to arrive at a theoretical activation energy for the "Negative Mechanism" reaction, by an extension of the previous quantum mechanical considerations. (119). The calculation of the activation energy was based on the approach of the negative ion toward the positive end of the carbon halogen dipole along the line joining the carbon and halogen nucleui. The theoretically established values were in general agreement with the experimentally observed activation energies.

Various other experimental observations were cited by these authors in support of their theoretical considerations. The investigations of Phillips and Kenyon (120) on the reactions of the toluene sulfonates, in which the conclusion was reached that substitution by a negative ion resulted in a Walden inversion, support these considerations. The kinetic studies of the racemisation of optically active halides by the corresponding halogen ion wherein the velocity constants of the racemisation have been found similar to the velocity of substitution by halogen ions, has brought additional evidence (120a). The thermodynamical indices, for example, the activation energies and collision numbers, have also been found similar whether substitution or racemisation was considered, and regardless of ion or structure of the compound.(120b)

For a particular case of the reaction of an organic halide with halide ion, the validity of the theory has been conclusively demonstrated by the work with radioactive iodine isotopes (121). The rate of exchange, that is, substitution between dl sec. octyl iodide and sodium iodide containing the radioactive isotope of the halogen obtained by exposure to the action of neutrons, was determined by measurement of the radioactivity of the products. In another series of experiments, the rate of racimisation of dextro sec. octyl iodide by sodium iodide in acetone was determined polarimetrically. When reduced to the same units, the two processes were found to have velocity constants agreeing to within 10%. This reaction clearly involves exchange between the iodine atom of the sec octyl iodide and the iodine ions of the solution.

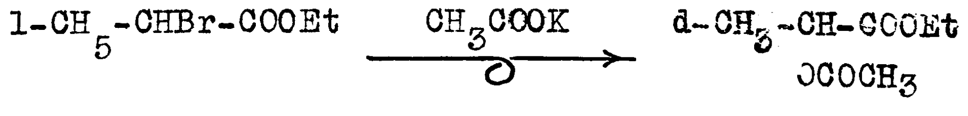
The "Negative Mechanism" group of substitution reactions includes the following transformations,-

(A) The conversions of optically active halides with salts of inorganic or organic acids, for example, lithium chloride, silver acetate, sodium benzoate belong to this class of substitution and are accordingly accompanied by Walden Inversion.

Levorotatory bromides and iodides all lead on the action of lithium chloride to dextrotatory chlorides (122).

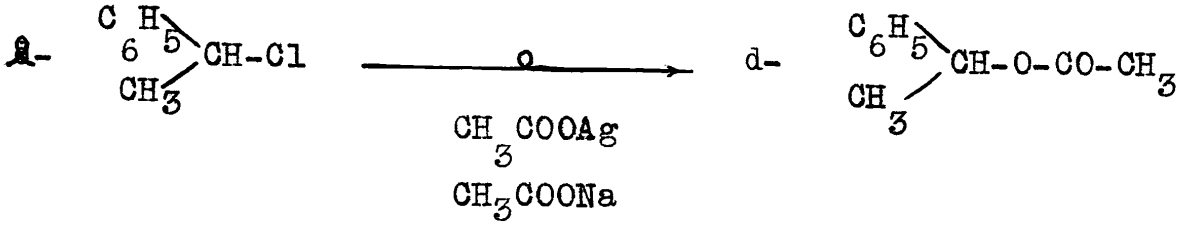
$$\text{levo } CH_3\text{-}CHI\text{-}C_6H_9 \xrightarrow[LiCl]{\circlearrowleft} CH_3\text{-}CHCl\text{-}C_4H_9$$

The action of potassium acetate on levo ethyl bromo propionate in absolute ethyl alcohol under reflux for 6 hours yields dextro ethyl α-acetoxy propionate (123)



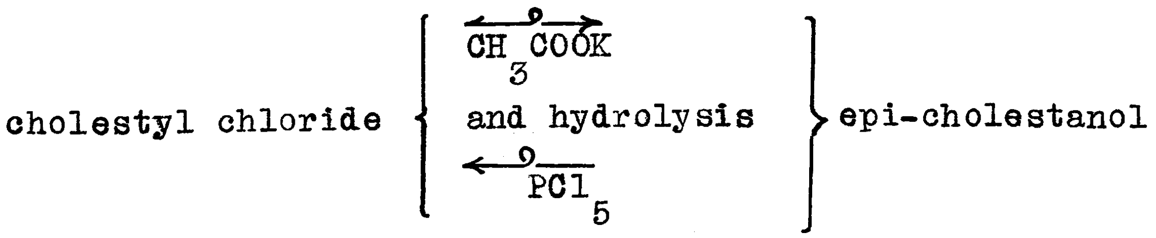
$$1\text{-}CH_5\text{-}CHBr\text{-}COOEt \xrightarrow[\circlearrowleft]{CH_3COOK} d\text{-}CH_3\text{-}\underset{OCOCH_3}{CH}\text{-}COOEt$$

Levo rotatory phenyl methyl chlormethane produces by gentle warming with silver acetate the dextro rotatory acetate of phenyl methyl carbinol


(120b)

The reaction with silver acetate is accompanied by considerable partial racemisation. The acetate obtained in this manner has a smaller rotation than the one obtained through direct acetylation of the carbinols, and also than the one obtained by analogous means using the sodium acetate. Bergmann considered this to be an indication that the silver acetate tends to react by a "positive mechanism" and pointed out that the favoured formation of the silver chloride must play an important role.

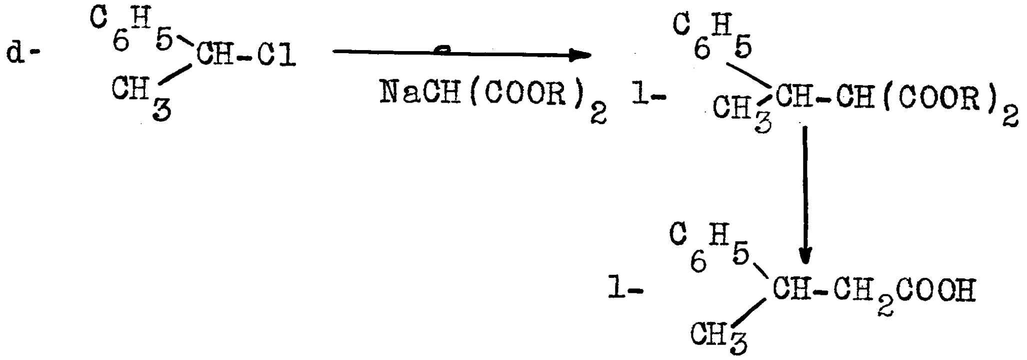
Marker, Whitmore and Kamm (124) have established the following transformations in sterol chemistry



$$\text{cholestyl chloride}\left\{\begin{matrix} \xleftrightarrow{\circ} \\ CH_3COOK \\ \text{and hydrolysis} \\ \xleftarrow{\circ} \\ PCl_5 \end{matrix}\right\}\text{epi-cholestanol}$$

Potassium acetate was considered to have produced inversion

(B) The reaction of an optically active halide with sodium malonic ester, that is with malonic ester ion, leads to an alkyl malonic ester with opposite configuration.(120b)

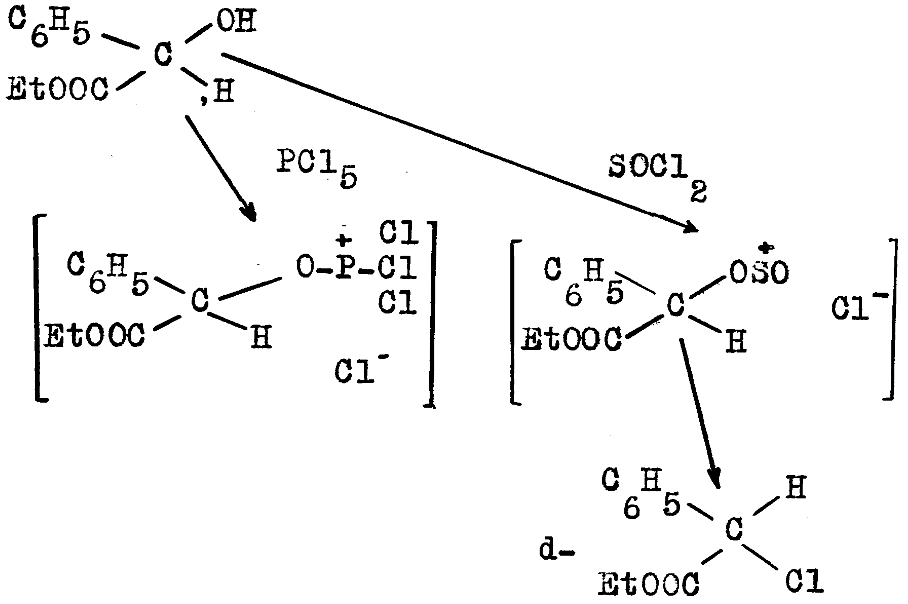


Similarly d-2-bromo butane by the malonic ester synthesis yields 1-β-methyl valeric acid.

(C) The reactions of the sulfonic esters of optically active hydroxy compounds with the alkali salts of inorganic and organic acids (125), such as potassium acetate, potassium benzoate, lithium chloride, sodium bromide, potassium iodide etc., have been shown to produce products with a change of configuration.

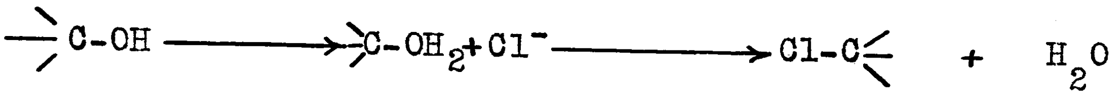
Ammonia and primary and secondary amines have also been found to react with such esters to produce optically active animes. The stereochemical nature of the reaction is not definite but there are indications that these derivatives have the same configuration as the original sulphonate (126).

(D) Replacement by means of halides of Phosphorus and Sulphur are assumed to proceed through the prior formation of an ester-halide. These ester halides are considered to ionise to form a halide ion (127), especially in the presence of pyridine or other tertiary base owing to the production of pyridinium halides;-



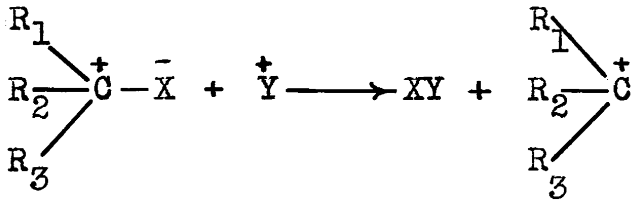
The decomposition of the alkyl chloroformates in the presence of a tertiary base may be regarded similarly. (128)

(E) Replacement by means of hydrogen halides under conditions favoringionisation are considered to proceed by a mechanism quite similar to the mechanisms in the case of the halides of phosphorus and sulfur (129), an oxonium ion being formed as on intermediate.



Direct Substitution

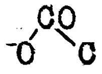
Meer and Polanyi distinguished between these replacements by an anion, the "negative mechanism" substitution, and those in which the attack is by a cation, a positive mechanism" substitution. There are very few cases of true "positive mechanism" substitutions, wherein a positive ion may be considered to attack the negative end of the polar bond, thus taking the negative substituent to form a neutral molecule, leaving as the remainder, a positive carbon radical;



This latter is stabilized in a secondary reaction, whereby the optical result of the substitution depends on the stability of the configuration in the positively charged radicle. Substitution through the "positive mechanism" then need not be accompanied by Walden Inversion nor by racemization.

Displacements of the halogens of organic halides with silver oxide or silver salts involve a heterogeneous attack by silver ions on the organic halide absorbed on the surface of the insoluble silver salt. Hughes and Ingold, et al (130), assume that the absorption of the halide stretches the carbon-halogen bond, and an absorbed silver ion takes advantage of the disturbance in order to extract the halogen as an ion. The final step involves the heterogeneous reaction of the carbon cation with an absorbed nucleophilic reagent or solvent molecule. The substitution process then depends on an assisted positive mechanism.

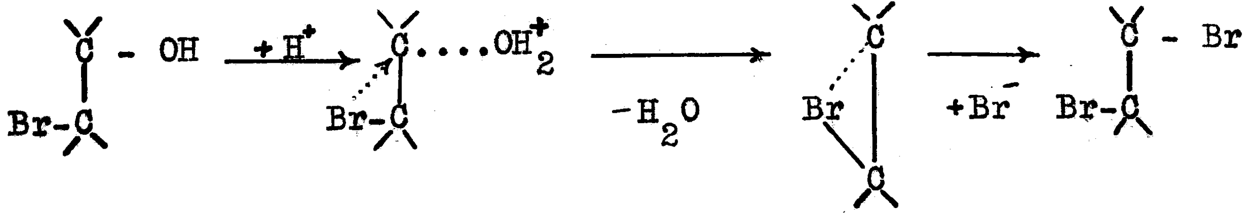
Olson extended his face-centred bond theory to explain substitutions in which an apparent direct substitution without Walden inversion occurs. "Thus, if the face of the asymmetric carbon atom opposite to the chlorine were absorbed on some surface, the carbon-chlorine bond would be weakened causing the dissociation of chloride ion and inversion to form a wall complex. Hydroxide ion would now add, again causing inversion and releasing the molecule from the surface" The net result would be the production of the product with same configuration. The action of silica on the hydrolysis of optically active phenyl bromoacetic acid to produce the mandelic acid with the same configuration was explained with this mechanism. The function of silver salts was interpreted similarly. The action of the silica, silver oxide and silver salts might thus be regarded as a " face-centre shielding " effect blocking the "negative mechanism" as well as a catalytic effect wherein the bond of the group to be displaced is weakened, facilitating the occurrence of the "positive mechanism".

"Face-centre shielding" effects have also been postulated within the molecule. The presence of a charged group of the appropriate sign (negative for the organic cation and positive for the anion) was considered by Hughes and Ingold (129) as tending to stabilise and to preserve the ion. Since the ion is a betaine  $\overset{CO}{{}^{-}O\quad C}$ this structure is likely to remain until a new group enters the position vacated by the one expelled; the result being a considerable retention of configuration. If the reagent intervenes before the intramolecular stablising structure is formed, only partial retention of form will be observed.

Winstein and Lucas (131) also postulated a "face-centre shielding" in a mechanism developed to account for the retention of configuration in the conversion by hydrogen bromide of dl-threo 3-bromo butanol to dl-2,3-dibromobutane

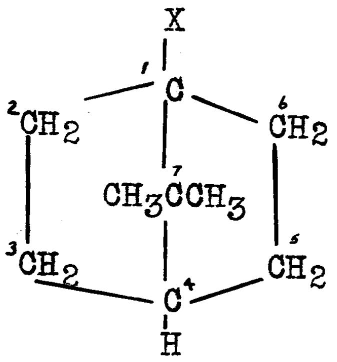
$$\underset{\text{threo-}}{\text{dl-}}\ CH_3\text{-}CHOH\text{-}CHB_r\text{-}CH_3 \xrightarrow[\text{No W.I.}]{\text{HBr}} \text{dl- } CH_3\text{-}CHBr\text{-}CHB_r\text{-}CH_3$$

The unusual behavior of the bromobutanols was ascribed to the presence of the bromine atom in the following mechanism,



wherein the bromine atom is considered as being attracted to the back face of the carbon atom holding the hydroxium group in the same way that an independent bromine ion may.

Substitution by negative ions is accompanied by a steric hindrance effect when large substituents are attached to the carbon atom at which substitution takes place. The effects of complete steric hindrance were studied by Bartlett and Knox. (132) "A derivative of bicyclo 2,2,1 heptane with a substituent on the bridge head is incapable of reacting by the currently favoured mechanism of negative substitution with Walden Inversion. In the first place, no negative ion or other nucleophilic reagent can approach carbon atom 1 from the side opposite to the substituent and get within bond-forming distance, because carbon atoms 3,4,5 and 7 or 8 form a cage around it. In the second place, the three carbon atoms directly bound to the bridgehead (carbons 2,6 and 7) are not free to alter their positions as required for an inversion of configuration. Both these restrictions apply whether there is optical activity present in the system or not. Hence we may work with an optically inactive series of compounds and still be sure that the mechanism of reaction which, in optically active compounds, underlies the Walden inversion is excluded."

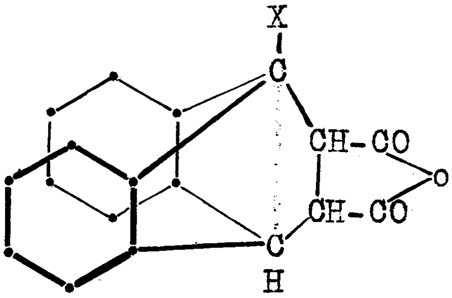


(X =NH_2:- 1 apocamphylamine

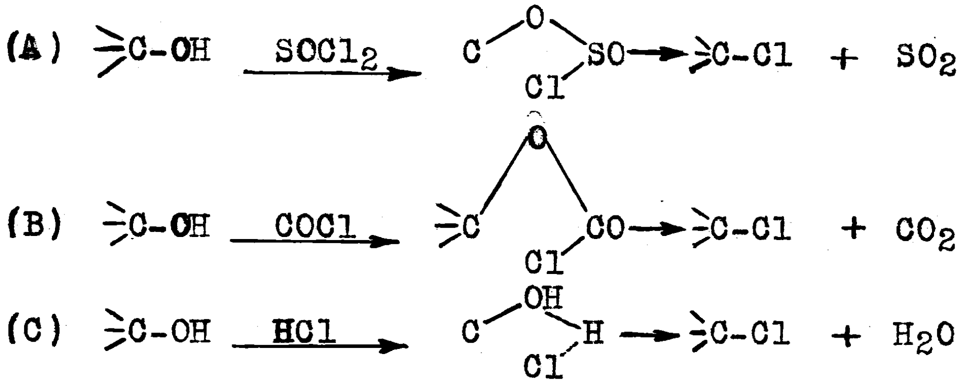
=OH :- apocamphanol-1

1-Apocamphylamine was found to react with nitrous acid to form apocamphanol-1 (X=OH), with nitrosyl chloride to form 1-chloro apocamphanol (X=Cl). The hydroxyl group of apocamphanol-1 could not be replaced by the action of thionyl chloride, phosphorus pentachloride or gaseous hydrogen bromide. The chlorine group of 1-chloro apocamphane could not be replaced by the action of 30% alcoholic potassium hydroxide. "We can now say quite definitely that no inversion, or series of inversions, need be involved, in the reaction of an amine with nitrous acid or nitrosyl chloride. These reactions proceed as smoothly and rapidly when the Walden Inversion is prohibited as when it is possible".

Recently Bartlett with Cohen has continued his studies of structures which prohibit the Walden Inversion. The addition product of maleic anhydride to 9-bromoanthracene, a derivative of dibenzobicyclo-octadiene, is structurally incapable of a Walden Inversion in the replacement of the bromine, and as these authors have found, shows no replacement of this bromine on boiling for 18 hours with 30% KOH in 50% aqueous ethyl alcohol (133). The bromine however can be replaced by hydrogen with reduction using sodium and alcohol. It is to be noted, that, although the bridge head carbon is directly bound to two phenyl groups which in the acyclic analogues means an enhanced activity of the group X, again no replacement occurs through a negative mechanism.



"Face-centre shielding" has been shown to facilitate direct substitution. Replacement reactions involving intermediate compound formation, in which the entering atom and the atom which it replaces are held on the same side of the asymmetric carbon atom have been shown to be equally effective in facilitating direct substitution. Transformations by means of thionyl chloride, carbonyl chloride, and by hydrogen halides may take place in this manner, under conditions inhibitory to ionisation.



(A) $$\geq C{-}OH \xrightarrow{SOCl_2} C\overset{O}{\underset{Cl}{\quad}}SO \rightarrow\ \geq C{-}Cl + SO_2$$ (134)

(B) $$\geq C{-}OH \xrightarrow{COCl} \geq C\overset{O}{\underset{Cl}{\quad}}CO \rightarrow\ \geq C{-}Cl + CO_2$$ (135)

(C) $$\geq C{-}OH \xrightarrow{HCl} C\overset{OH}{\underset{Cl}{\quad}}H \rightarrow\ \geq C{-}Cl + H_2O$$ (136)

Under suitable conditions, low temperatures in the case C, and in the absence of substances causing ionisation, the intermediates may decompose to yield the respective products with no change in configuration. Catalysts for reaction (B) are magnesium and mercuric chlorides. (135) A possible catalyst for reaction (A) is zinc oxide. (137)

Dissociation Mechanisms

Reactions of the two previous classes are complicated. in some cases by primary dissociation into ions of the substance under consideration. For example, Ward has observed that phenyl ethyl carbinyl chloride when dissolved in an alcohol water mixture, liberates hydrochloric acid at a rate which is independent of the hydroxyl ion concentration. (138) That is to say, the halide does not react directly with the hydroxyl ion but undergoes a primary dissociation into ions.

Bimolecular substitutions in which the bond is exchanged in one act, (Sn_2), are distinguished by Hughes and Ingold (139) from substitutions in which the bond is broken and then reconstructed in separate acts (Sn_1). Which of these mechanisms will operate in a given example depends, inter alia, on structure, i.e. on the groups attached to the seat of substitution. Groups which withdraw electrons thereby facilitate approach of the nucleophilic reagent, the presence of which is necessary for reaction by mechanism. (Sn_2) Groups which supply electrons favor the dissociation which is the rate determining step of mechanism Sn_1.

Hughes and Ingold's views on the effect of groups may be summarised as follows,- Replacements in methyl halides are exclusively bimolecular.

(1) Alkyl groups release electrons more strongly than hydrogen, and hence the progressive replacement of the hydrogen atom in a methyl chloride by alkyl groups will tend to replace mechanism Sn_2 by mechanism Sn_1.

(2) Aryl substituents at the seat of substitution facilitate mechanism Sn_1 much more strongly than do alkyl groups.

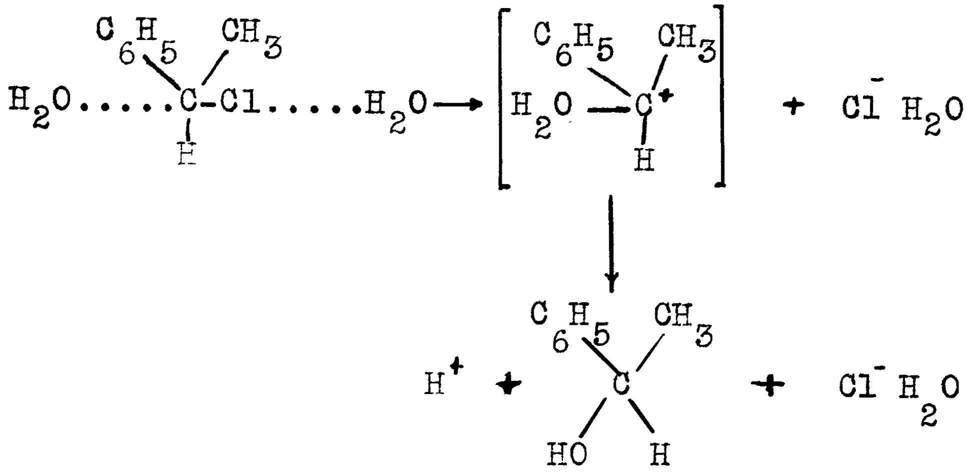
(3) Groups of the form, COOR, being electron attractors will serve to establish mechanism Sn_2 to the exclusion of Sn_1.

(4) The carboxylate ion group, - COO^-, repels electrons and thus a transition from mechanism Sn_2 to Sn_1 is expected.

Mechanism Sn_1 may involve inversion, racemisation, or retention of form depending on the circumstances which have to be considered in detail. The presence of an unsaturated group, such as phenyl, at the seat of substitution introduces mesomerism, a factor which tends to stabilise and at the same time to flatten the ion. The result will be enhanced racemisation.

A number of investigators have emphasised that the solvent must play an especially important part in the ionic fission, since in all spontaneous ionisations it is solvation which reduces the activation energy to accessible values. The hydrolysis and solvolysis of optically-active alkyl halides have been found to occur with Walden inversion. (140). Ogg and Polanyi (141) consider the process to take place as follows, - "The transition to the ionic state can only take place if both ions are formed as hydrates, otherwise the activation heat would be unaccessibly high. At the moment of its formation the carbonium ion can add a water molecule only on its side opposite to the halogen link. It is to this side, therefore, that the hydroxyl group formed on decomposition of the carbonium hydrate, will become linked to".

The picture of the process is:-

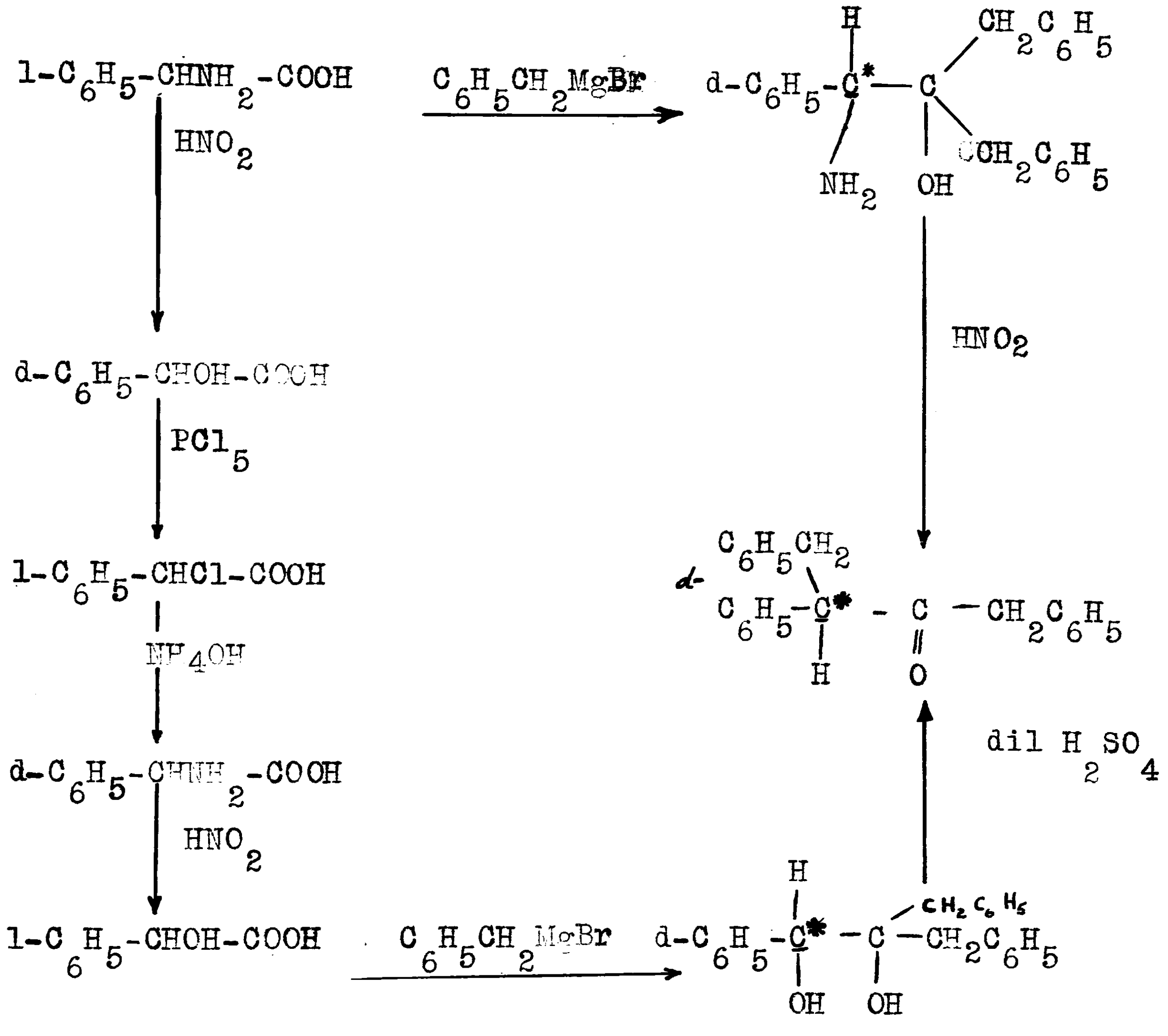


Stiegman and Hammett (140) also suggest that another solvent molecule removes the proton. Olson and Voge consider the first step to be hydrogen bond formation with the bromide ion in the case of hydroxylic solvents (142)

Bartlett has recently observed that the composition of the product obtained from a solvolytic reaction exhibits a dependence on the solvent composition, (143) and concluded that the rate determining step in this case was ionization, the solvent serving to solvate the anion and that the solvent components than compete for the cation in rough proportion to their mole fractions.

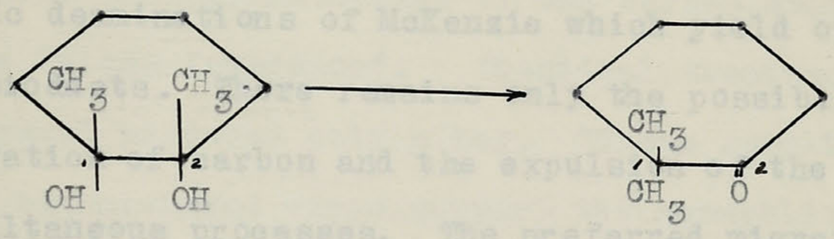
Molecular Rearrangements and Substitution Processes

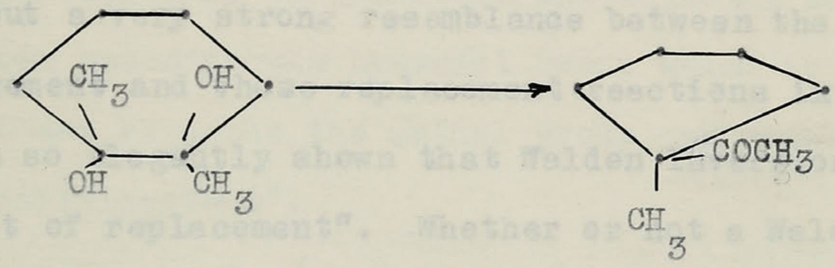
Roger and McKenzie (144) formulated the following experimental scheme in 1929;



The processes of intramolecular rearrangement and Walden inversion were thus definitely linked one to the other.

Later Bartlett and Pockel studied the pinacol rearrangement of cis and trans 1,2 dimethyl cyclohexandiol-1,2, (145) The trans glycol was found to yield on rearrangement 78% 1-methyl 1-acetyl cyclopentane. The cis glycol however produced 2,2-dimethyl cyclohexanone in 74% yield using the same procedure.



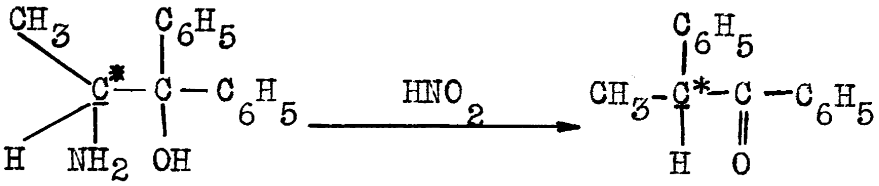


These authors considered their observations as follows,- "In the cis pinacol, the ring carbon atom and the methyl group which migrates are about equally remote (on a time average) from the OH group which is eliminated in the reaction. In the trans pinacol, the ring carbon atom which migrates is much more remote from the replaced hydroxyl group than the methyl. In other words, a group migrates by preference which is located in space near the opposite side of carbon atom No.1, to that occupied by the hydroxyl group which is replaced. This is inconsistent with the idea that the hydroxyl group is actually removed before the migration occurs, for then the radical most accessible to the open spot on carbon No. 1 would surely be the one to migrate. The fact that different products result from the two stereoisomers also excludes the formation of a racemisable "open sextet" as do the pinacolic and semipinacolic deaminations of McKenzie which yield optically active products. There remains only the possibility that the migration of carbon and the expulsion of the hydroxyl are simultaneous processes. The preferred migration of the radical situated near the back side of the carbon No. 1 brings out a very strong resemblance between the pinacol rearrangement and those replacement reactions in which it has been so elegantly shown that Walden Inversion attends every act of replacement". Whether or not a Walden Inversion mechanism is the only one by which a pinacol rearrangement occurs, Bartlett and Pockel have established a case in which the inversion mechanism is the preferred one.

Bartlett and Bavey (146) pointed out that the above studies had left something to be desired in exactness of interpretation due to the non-planar structure of the cyclohexane ring, which property allows of many different orientations of adjacent substituents with respect to each other. Thus, they extended the investigation to the pinacol rearrangement of cis and trans 1,2-dimethyl cyclopentane diol-1,2 wherein the planar nature of the five membered ring makes the relative positions of the groups in space much more certain. Refluxing the cis glycol with 30% aqueous sulphuric acid produced in 87% yield 2,2 dimethyl cyclopentanone-1. "Thus the methyl group has migrated in that pinacol in which it is in a position to displace the adjacent hydroxyl group by attacking the opposite side of the carbon atom holding it, as in the Walden Inversion". Identical treatment of the trans pinacol produced only a tar. "These results with the five and six membered rings support the generalization that a group cannot migrate in the pinacol rearrangement unless by a simple movement it can reach the adjacent carbon atom on the face opposite the hydroxyl group which it is replacing. Thus in these pinacols the methyl group can migrate only in the cis modifications".

However Criegee and Plate have observed, contrary to expectations that both the cis and the trans isomers of diphenylacenaphthendiol produce the same product on rearrangement, diphenylacenaphthenone, and that the difference in the rates of isomerisation of the two isomers was not particularly great (cis / trans = 7/23). (147) The relatively large differences in the rearrangement products which were expected due to the difference in spatial structures of the pinacols was not observed. Similarly Hans Meerwein (148) by modifying Bartlett and Bayley's experimental conditions observed that the trans glycol of 1,2 dimethyl cyclopentane 1,2 diol produced, on treatment with concentrated sulphuric acid at -10°, 22%

2,2 dimethyl cyclopentanone and concluded that the difference in behavior of the two isomers is thus one of degree and not of kind. Bernstein and Whitmore have recently investigated the rearrangement by semipinacolic deamination of levo 1,1-diphenyl 2-amino proponol -1 to dextro methyl phenyl acetophenone in order to ascertain whether the shifting phenyl group actually takes the place of the removed amino group or takes part in a Walden Inversion by approaching the back of the adjacent carbon atom, the front being considered as the corner holding the amino group.

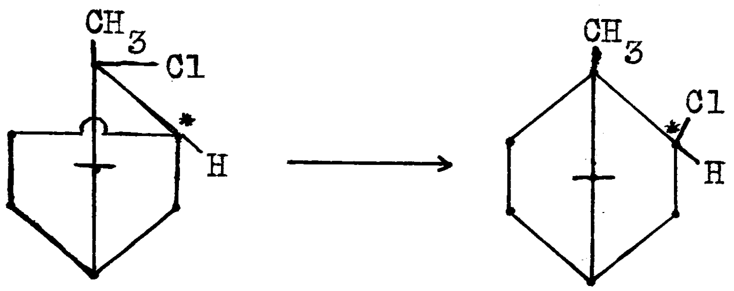


99% yield

They were able to establish that the levo amino alcohol and the dextro ketone were of opposite configuration and thus concluded that the transformation involved a Walden Inversion. This gives additional evidence for the 'rearward' attack on a carbon atom during the replacement of a group".

Bartlett and Pöckel also considered the relationship of the Walden Inversion to the mechanism of the Wagner-Meerween rearrangement of camphene hydrochloride to isobornyl chloride and concluded that here too a complete Walden

Inversion is involved at the starred carbon atom (15)



camphene hydrochloride isobornyl chloride

Similarly the conversion of isobornyl chloride into camphene must involve a Walden Inversion, isobornyl chloride eliminating hydrochloric acid quite readily with the formation of camphene on simply boiling with water. On the other hand, the conversion of the stereoisomeric chloride, bornyl chloride to camphene, a step upon which the synthesis of camphor depends, cannot involve a Walden Inversion. This latter transformation however, requires the action of bases for the elimination of the hydrochloric acid. That is, there is a considerable difference in the facility with which these reactions proceed, the loss of the hydrochloric acid occurring with much greater facility from isobornyl chloride, the transformation which involves a Walden Inversion. A similar behavior was observed by Huckel and Nerdel (151) for the isobornyl and bornyl amines ($Cl-NH_2$). Isobornyl amine reacting with nitrous acid produced only pure camphene and camphene hydrate. Bornyl amine produced the same two bicyclic products, camphene and camphene hydrate and in addition considerable amounts of α-terpineol, a monocyclic end-product, wherein the gem-dimethyl bridge has not been reformed. That is to say, intramolecular rearrangements need not always involve a Walden Inversion, these cases, however, seemingly proceeding less readily.

It was thus highly desirable to investigate a case wherein steric factors could have no possible dominating influence, in order to establish the natural stereochemical course of the migrating group and if possible the extent of the rale played by the two mechanisms, namely that proceeding with and that proceeding without Walden Inversion. We therefore turned to a study of simple alephatic compounds whose stereochemical relationships could be ascertained.

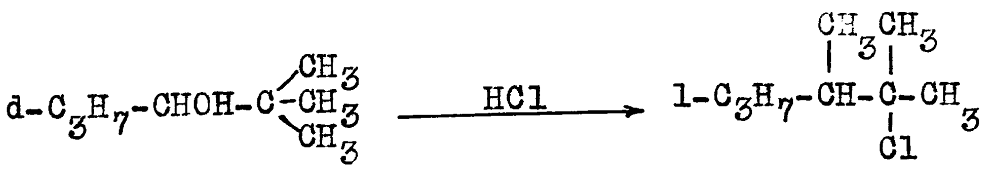
The Present Investigation

A survey of our present knowledge of substitution processes and intramolecular rearrangements has indicated an apparently natural tendency for one group to replace another by a Walden Inversion mechanism. The question arises as to whether a Walden Inversion mechanism is the only one by which an intramolecular rearrangement occurs, in the absence of steric or other possible directing influences. A few cases have been established wherein the inversion mechanism is seemingly the one preferred. On the other hand, there are certain special cases wherein a Walden inversion could not have been involved in the transformation. However these latter rearrangements are all of the type in which a rearrangement occurs as a consequence of a removal reaction. No simple aliphatic case of a rearrangement occurring during the replacement of one group in a molecule by another has heretofore been investigated from this point of view.

The basis of any such study is the definite correlation of the configuration of the original compound and the rearrangement product. In only a few cases have the relative configurations of the two compounds concerned been established.

P. G. Stevens and coworkers (152) have shown that dextro n-propyl tert.-butyl carbinol on treatment with saturated aqueous hydrochloric acid yields a levorotatory chloride, containing 94.2% tertiary chlorine. That is a rearrangement from a secondary carbinol to a tertiary chloride had occurred accompanied by a change in the sign of rotation. It has long been recognized that a change of sign of rotation does not represent a change of configuration, for there are numerous cases where such a change of sign occurs in which no change of configuration could be involved. That is, the relative configurations must be known in order to be able to draw conclusions regarding the mechanism.

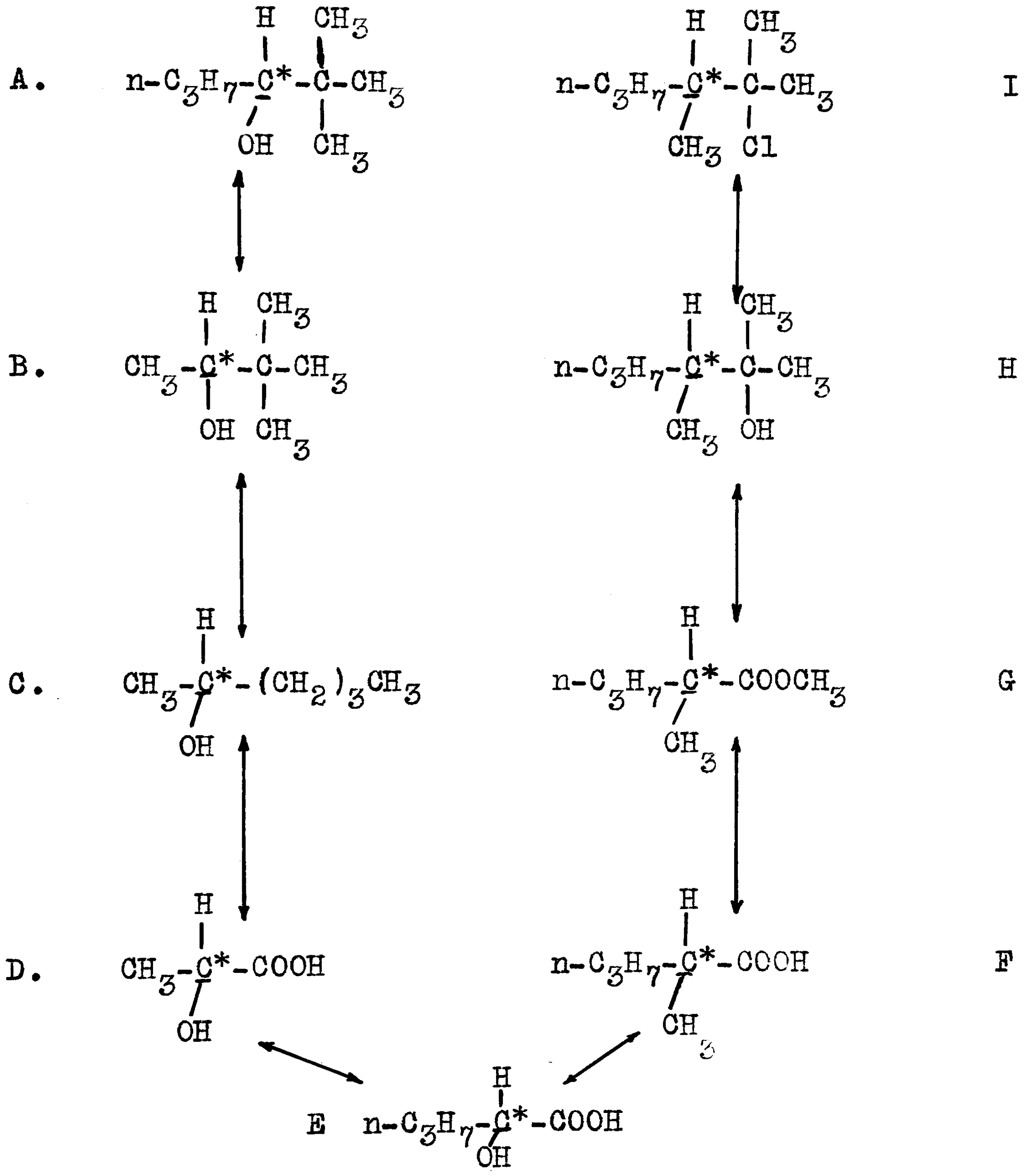
This rearrangement could be considered an example of a retropinacolone rearrangement, the tertiary chloride being assigned the structure of 2-chloro,2,3-dimethyl hexane.



$$d\text{-}C_3H_7\text{-}CHOH\text{-}C\begin{matrix}CH_3\\CH_3\\CH_3\end{matrix} \xrightarrow{\quad HCl \quad} l\text{-}C_3H_7\text{-}\overset{\overset{CH_3}{|}}{C}H\text{-}\underset{\underset{Cl}{|}}{\overset{\overset{CH_3}{|}}{C}}\text{-}CH_3$$

Equation 1.

This tertiary halide may be configurationally related to the original carbinal through the following series of relationships,-



Herein, lies a possible method for the elucidation of the relationships between Substitution Processes and Intramolecular

Rearrangements. Should the two configurationally related carbinols, n-propyl tert. butyl carbinol (A) and 2,3 dimethyl hexanol-2 (H) produce under identical conditions the same chloride with the same sign of rotation, the transformation of A to I according to Equation L. must have proceeded without Walden Inversion. On the other hand, should the carbinol A produce a chloride, identical in structure but differing in the sign of rotation from the chloride obtained from carbinol H, the transformation must have proceeded with Walden Inversion. Furthermore, should it be possible to ascertain the maximum rotations of the carbinol A and the chloride I, the extent to which this rearrangement involves a Walden Inversion mechanism may be found.

The occurrence of a retropinacolone type of rearrangement during the preparation of the chlorides of secondary carbinals containing the grouping $R_3C\text{-}CHOH\text{-}$ has long been known. (153) Thus pinacolyl alcohol gives a tertiary chloride in at least 90% yield, the tertiary bromide being produced similarly in 92.5% yield.

$$(CH_3)_3C\text{-}CHCH\text{-}CH_3 \begin{array}{l} \xrightarrow{HCl} 90\% \; (CH_3)_2C(Cl)\text{-}CH(CH_3)_2 \qquad (154) \\ \xrightarrow{HBr} 92.5\% \; (CH_3)_2C(Br)\text{-}CH(CH_3)_2 \qquad (155) \end{array}$$

This transformation has not been studied from the point of view of establishing the stereochemical mechanism involved.

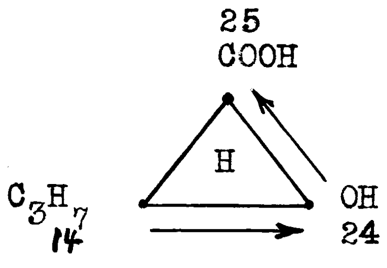
On the other hand, the preparation of the tertiary chloride (I) from the corresponding tertiary alcohol, 2,3 dimethyl hexonal-2 (H) represents a type of transformation which has as yet not been investigated throughly. Whitmore (156) has assumed however the production of the corresponding chloride from tertiary alcohols of the general type $R_2CH-C(OH)-R_2$ wherein two adjacent carbon atoms hold tertiary hydroxyl and tertiary hydrogen, respectively. There have been several cases reported where no rearrangement occurs during the replacement of a tertiary hydroxyl group.

For example, benzpinacol dissolved in a cold benzene solution is readily converted by hydrogen chloride into the corresponding dichloride in 75.8% yields. (157) Similarly Huckel (158) has reported the preparation of the menthyl chlorides in nearly pure form from 1-menthol.
By the use of thionyl chloride, hydrobenzoin has been converted to the corresponding stilbene dichloride (159a) and diphenyl tertiary butyl carbinol to the corresponding chloride. (159b) The chloride of αnaphthyl nopinol has been prepared using phosphorus pentachloride in ligroin (160) Conant and Blatt produced phenyl tertiary butyl carbinyl bromide from phenyl tert. butyl carbinol by passing dry hydrogen bromide into the cold carbinol. (161) Nevertheless, the possibility of a rearrangement should not be overlooked.

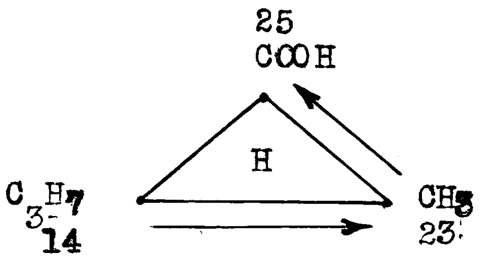
Perhaps the most satisfactory method of detecting the occurrence of a rearrangement during the preparation of substituted derivatives of carbinols of this type, $R_2CH-C(OH)-R_2$, would be to prepare this type of compound optically active with the carbon atom alpha to that with the hydroxyl group the optically active centre, for reactions which involve this centre would certainly effect the optical activity in a characteristic manner.

The starting material for such a study as outlined above thus becomes α-methyl valeric acid (F). α-methyl valeric acid (F) can be configurationally related to n-propyl tertiary butyl carbinol (A) as well as to the tertiary alcohol, 2,3-dimethyl hexanol-2 (H). A correlation of the configurations of α-methyl valeric acid (H), alternatively referred to as n-propyl methyl acetic acid, and α-hydroxy valeric acid (E) may be made by the application of Marker's Rule (162), an empirical rule proposed by Marker in 1936 for predicting the relative configurations of optically active compounds. From a correlation of the molecular rotations of a series of configurationally related compounds, an empirical table of ordinal numbers was developed for twenty-nine of the common groups which occur in many optically compounds. By means of these ordinal numbers, some three hundred known configurations were successfully checked. Marker's Rule may be stated :- If the arrangement of the ordinal numbers of the substituents of the two molecules at the corners of the face of the carbon tetrahedron diammetrically opposite to the hydrogen atom are both clockwise or both counterclockwise, when considered in the same sense, the two compounds have the same configuration for the same sign of rotation.

The ordinal numbers assigned to the groups with which we are concerned are,- n-C_3H_7:14; CH_3:23;OH:24;COOH:25. Applying the rule we have



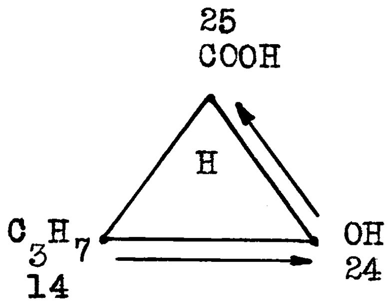
E.



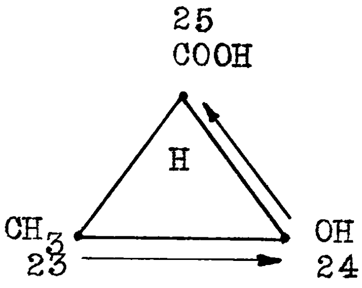
F.

The above corresponding faces of the tetrahedrons using the ordinal numbers for the groups are shown. All these numbers increase counterclockwise. Therefore the compounds E and F have the same configuration for the same sign of rotation. Levene and Harris (163) have also considered these acids to be configurationally related by the application of the postulates of Boys to their results.

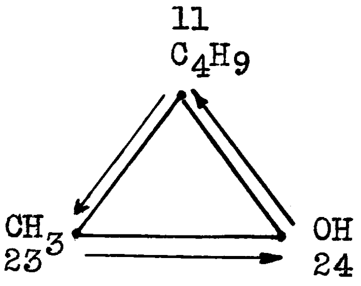
Marker's rule may also be applied to the correlation of the configurations of α-hydroxy valeric acid (E), lactic acid (D) and methyl n-butyl carbinol (C), the ordinal number for C_4H_9 being 11.



E.



D.



C.

The **ordinal** numbers are seen here to be in a counterclockwise sequence also, so that these substances all have the same configuration for the same sign of rotation. However, these three substances have been definitely configurationally related by Levene, Haller and Marker(164) employing a chemical method of correlation of configuration, which is based on the axiom of stereochemistry that no change of configuration of the carbon atom under consideration will occur if the valencies of said carbon atom are not involved in the reactions employed.

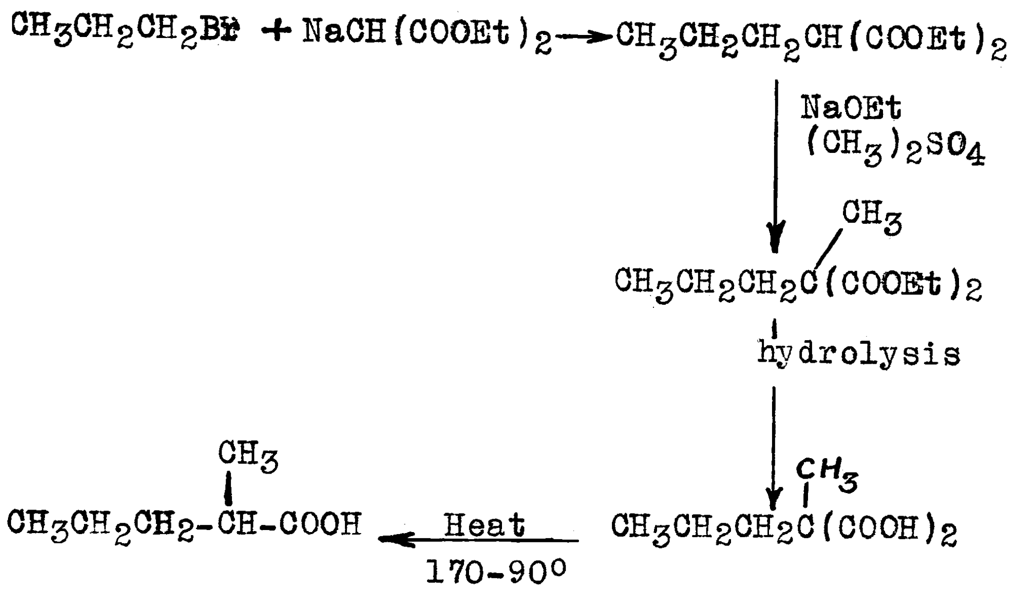
No direct chemical method has been found for correlating the configuration of methyl tert butyl carbinol (B). P. G. Stevens (165) has applied Freudenberg's Displacement Rule or Optical Displacement Principle (Verschiebungsgesatz). This principle (166) postulates that in similar configurationally related substances, an identical substitution on identical groups produces a shift of the rotation in the same direction.

The correlation of methyl tert. butyl carbinol was accomplished by comparing the rotation of its acetate, benzoate and phthalate and those of the closely related carbinol, methyl n-butyl carbinol, and dextro shift from the acetates through the benzoates to the phthalates being observed. According to the Displacement Rule thus, methyl. tert. butyl carbinol (B) and methyl n-butyl carbinol (C) are configurationally related when they have the same sign of rotation.

Stevens and coworkers (167) similarly applied Freudenberg's Rule to the determination of the configurations of propyl t-butyl carbinol (A) and concluded that levo propyl t-butyl carbinol has the same configuration as dextro methyl t-butyl carbinol (B).

Thus according to the above series of correlative studies of configurations levo n-propyl tert-butyl carbinol (A) possesses the same configuration as dextro n-propyl methyl acetic acid (F), that is, α methyl valeric acid.

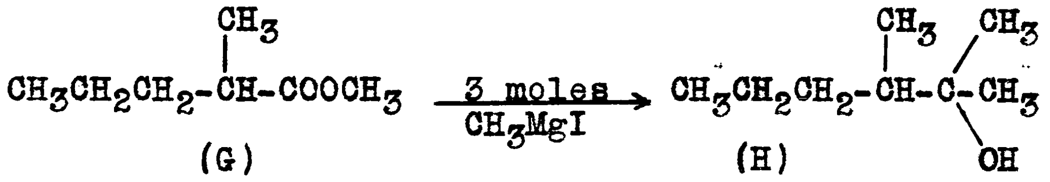
In the present investigation, α-methyl valeric acid (F) was configurationally related by direct chemical means to 2,3-dimethyl hexanol-2 (I). The α-methyl valeric acid was prepared through the malonic ester synthesis, in a manner similar to that employed by Levene and Bass (168)



the product of each step being purified by fractional distillation. The resulting acid was characterised by the preparation of the anilide, M.P. 95°, that reported being M.P. 95.2°. (169) A partial resolution was finally carried out using the alkaloid cinchonidine, through the salt of which was obtained a dextro-methyl valeric acid with a molecular rotation $[M]^{25}_{D} = 8.27°$. The α-methyl valeric acid also possessed the following characteristic, B.P. 84.5°C @ 9 mm., 97.5° C @ 16½ mm; $n^{25}_{D} = 1.4121$; $d^{25}_{4} = 0.920$; M.R. $^{2}_{n}$: Found - 31.38; Calc - 31.25. Levene and Marker had previously assigned to this acid the maximum rotation $M^{25}_{D} = 21.4$, B.P.; 96°C @ 15 mm, $n^{25}_{D} = 1.4117$, $d^{25}_{4} = 0.920$.

By treatment of this acid with diazomethane in ethereal solution, the methyl ester of α-methyl valeric acid (G) was obtained, B.P. 77°C @ 98½mm., $n_D^{25} = 1.4004$, $d_4^{25} = 0.875$, M.R. - Found;-36.03, Calc.- 36.19, $[M]_D^{25} = +11.85$. Thus, dextro α-methyl valeric acid and its dextro ester have been configurationally related through a sure reaction for the preparation of an ester in a very pure state, the only by-product being a gas.

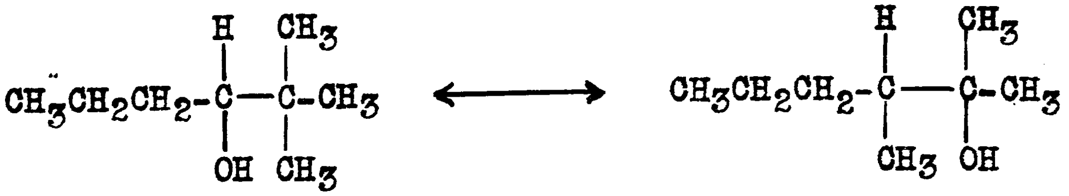
The methyl α-methyl valerate was next converted by the Grignard reaction using 3 moles of methyl magnesium iodide to 2,3-dimethyl hexanol-2 (H).



$$CH_3CH_2CH_2\text{-}CH(CH_3)\text{-}COOCH_3 \xrightarrow[CH_3MgI]{3\ moles} CH_3CH_2CH_2\text{-}CH(CH_3)\text{-}C(CH_3)_2OH$$

(G) (H)

The following physical constants were observed; $[M]_D^{25} = -15.35^\circ$ B.P. 75°C @ 29 mm., $n_D^{25} = 1.4288$, $d_4^{25} = 0.8314$. The asymmetric carbon atom was not involved in this transformation, so that dextro methyl α-methyl valerate and levo 2,3-dimethyl hexanol-2 possess the same configuration. That is to say, levo 2,3-dimethyl hexanol-2 has been directly correlated to dextro α-methyl valeric acid which had been related configurationally to n-propyl tert. butyl carbinol. In this manner, the carbinols A and H have been shown to be configurationally related when both have the same sign of rotation.

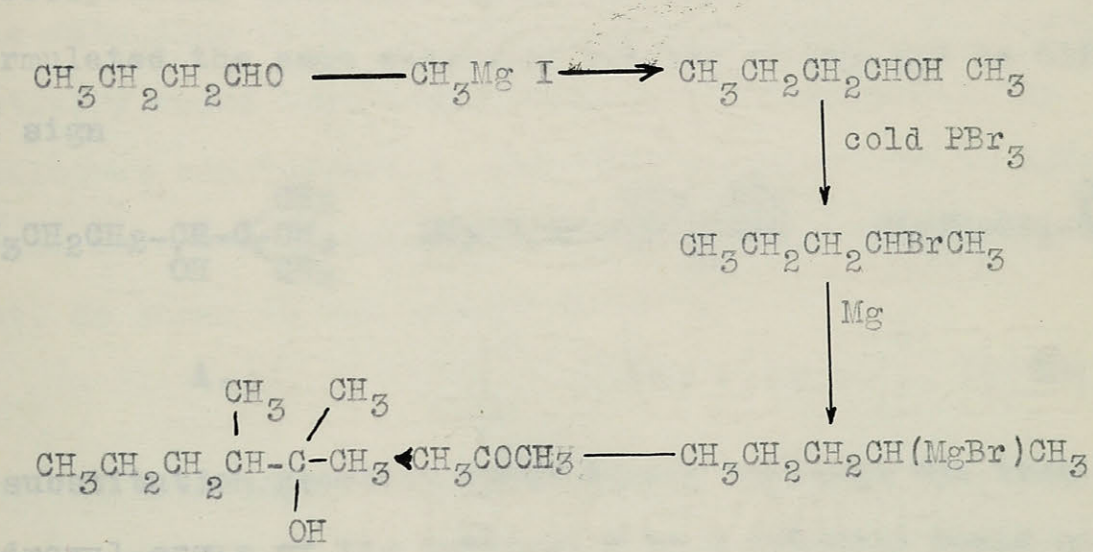


$$CH_3CH_2CH_2\text{-}C(H)(OH)\text{—}C(CH_3)_2\text{-}CH_3 \longleftrightarrow CH_3CH_2CH_2\text{-}C(H)(CH_3)\text{—}C(CH_3)(OH)\text{-}CH_3$$

(A) (H)

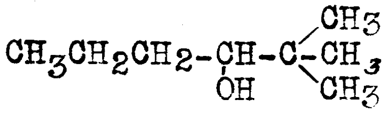
It may be noted here that the interchange of the hydroxyl group (OH) and the methyl group (CH_3) in the two configurationally related carbinols (A and H), does not change the sign of rotation.

Inactive 2,3-dimethyl hexanol-2 was also synthesised by the following procedure:-

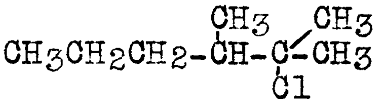


The various steps in this synthesis were carried out very carefully to avoid the occurrence of molecular rearrangements, the possibility of which, not encountered in the previous synthesis, must be considered in this procedure. The resulting 2,3 dimethyl hexanol-2 was purified by fractional distillation through a total condensation variable take-off column with an efficiency of 15 theoretical plates; B.P. 75° C @ 29 mm n_D^{25}= 1.4290

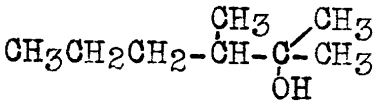
Having established the configurational relationships of levo n-propyl t-butyl carbinol to levo 2,3 dimethyl hexanol-2, the remaining steps which comprise this method for the elucidation of the spatial processes of intramolecular rearrangements are the transformation of the two carbinols to the chlorides, levo n-propyl t-butyl carbinol to the isomeric chloride,* and levo 2,3-dimethyl hexanol-2 to its corresponding chloride, which products would possess as formulated the same structure but may or may not be different in sign



A.



I.



H.

A substitution reaction which simply replaces the tertiary hydroxyl group of the carbinol H by a chlorine would not involve the asymmetric centre, so that the corresponding chloride would be configurationally related to the original carbinol H. and thus to the carbinol A. However when the carbinol H, -2,3-dimethyl hexanol-2 $[M]^{25}_{D} = -15.35$, was treated with saturated aqueous hydrochloric acid, the reagent employed by Stevens, the product was an optically inactive chloride, B.P. :43.5-44 $n^{25}_{D} = 1.4330$. Hydrolysis of the chloride yielded an optically inactive carbinol, B.P. 71.5-73°C, $n^{25}_{D} = 1.4294$. The chloride was completely hydrolysed by water, as no test

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* See Page 78

for chlorides was obtained on the hydrolysis product with either aqueous or alcoholic silver nitrates, thus showing the chloride to be tertiary.

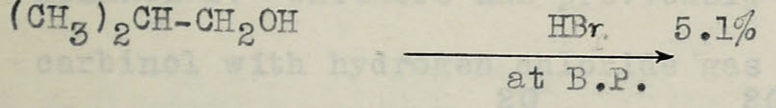
Should the conversion of the tertiary carbinol, 2,3-dimethyl hexanol-2 to the tertiary chloride have been a simple substitution reaction, the tertiary hydroxyl group being directly replaced by chlorine, and thus not involving the valencies of the optically active carbon, the optical activity would have been maintained. Furthermore, by analogous consideration, the carbinol recovered by hydrolysis would have been identical with the initial carbinol, it was not, as shown in the following table.

	$\left[M\right]^{25}_{D}$	B.P. @ 29 mm	n^{25}_{D}	Phenyl Urethane
INITIAL CARBINOL	-15.35	75°C	1,4288	M.P. 74°*
RECOVERED "	0	71.5-73°C	1,4294	M.P. 52.62.5°

*Prepared from inative carbinol

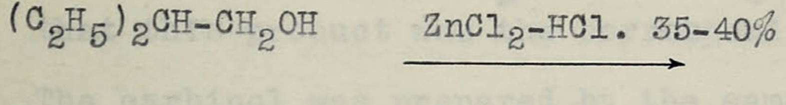
The optically active carbon atom must therefore have been involved in these transformations. That is to say, an intramolecular rearrangement has taken place.

2,3-dimethyl hexanol-2 may be considered as possessing a structure analogous to isobutyl alcohol, 2-ethyl 1-butanol, methyl isopropyl carbinol, diisopropyl carbinol, etc., all containing the common grouping $R_2CH\text{-}C(OH)$, with the distinction that the hydroxyl group is either primary or secondary in these latter carbinols. Alcohols of this general structure as well as those containing the grouping $R_3C\text{-}C\text{-}OH$, are known to be capable of undergoing rearrangement, showing this tendency in some cases to a very high degree, thus,-



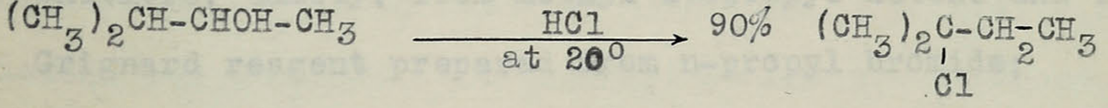
$$(CH_3)_2CH\text{-}CH_2OH \xrightarrow[\text{at B.P.}]{\text{HBr}} 5.1\%\ (CH_3)_3\underset{\underset{Br}{|}}{C}\text{-}CH_3$$

(171)



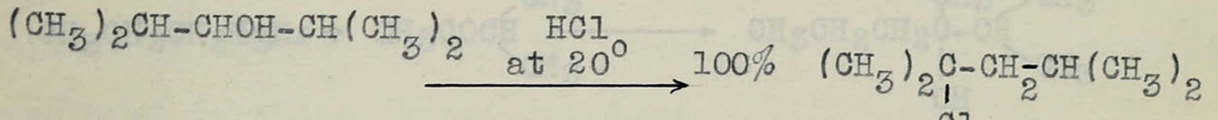
$$(C_2H_5)_2CH\text{-}CH_2OH \xrightarrow{ZnCl_2\text{-}HCl.\ 35\text{-}40\%} (C_2H_5)_2\underset{\underset{Cl}{|}}{C}\text{-}CH_3$$

(98)



$$(CH_3)_2CH\text{-}CHOH\text{-}CH_3 \xrightarrow[\text{at }20^{\circ}]{\text{HCl}} 90\%\ (CH_3)_2\underset{\underset{Cl}{|}}{C}\text{-}CH_2\text{-}CH_3$$

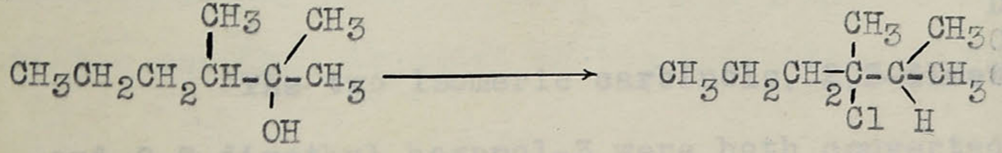
(172)



$$(CH_3)_2CH\text{-}CHOH\text{-}CH(CH_3)_2 \xrightarrow[\text{at }20^{\circ}]{\text{HCl}} 100\%\ (CH_3)_2\underset{\underset{Cl}{|}}{C}\text{-}CH_2\text{-}CH(CH_3)_2$$

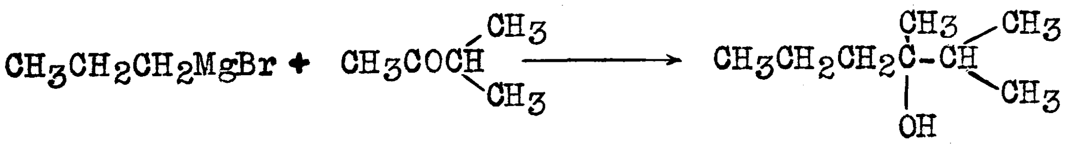
(172)

By anology then, the rearrangement which we have shown to occur in the transformation of 2,3 dimethyl hexanol-2 to the tertiary chloride may be formulated;



Considering the easy replacement of the tertiary hydroxyl, a mixture of the corresponding chloride and the isomeric rearranged chloride might be expected.

The question now arises as to how the tertiary carbinol, corresponding to the chloride obtained by rearrangement, namely 2,3 dimethyl hexanol-3, behaved when treated under similar conditions to the isomeric 2,3-dimethyl hexanol-2. Whitmore has previously treated the former carbinol with hydrogen chloride gas to produce a chloride B. P. 41-43 @ 12 mm, $n_D^{20} = 1.4350$ $d_4^{20} = 0.8869$ and has assumed that this product was the corresponding chloride (156). The carbinol was prepared by the same procedure as used by Whitmore, namely, from methyl isopropyl ketone and the Grignard reagent prepared from n-propyl bromide;



$$CH_3CH_2CH_2MgBr + CH_3COCH\begin{matrix}\nearrow CH_3\\ \searrow CH_3\end{matrix} \longrightarrow CH_3CH_2CH_2\underset{OH}{\overset{CH_3}{C}}-CH\begin{matrix}\nearrow CH_3\\ \searrow CH_3\end{matrix}$$

The 2,3 dimethyl hexanol-3 synthesised in this investigation was fractionally distilled through the 15-plate total condensation variable take-off column; the fractions employed in this work having a B. P. 72.5°C @ 29 mm, $n_D^{25} = 1{,}4301$.

The two isomeric carbinols, 2,3-dimethyl hexanol-2 and 2,3-dimethyl hexanol-3 were both converted to the chlorides by shaking with a large excess of concentrated hydrochloric acid for 12 hrs, a procedure essentially similar to that recommended in Organic Syntheses (173) for the preparation of tertiary butyl chloride from tertiary butyl alcohol. The following table shows the constants of the various chlorides obtained in these transformations

Carbinol	Reagent	B.P. @ 12mm.	Refract. n_D^{20}	Indices n_D^{25}	
2,3-dimethyl hexanol-2	sat.aq. HCl	43.5-44°C	1.4352	1.4330	
" "	conc. HCl		1,4351	1.4330	
2,3-dimethyl hexanol-3	conc. HCl		1.4353	1.4333	
	HCl gas	41-43°C @ 12 mm	1.4350	-	(156)

These observations may be reconciled satisfactorily on the assumption that both possible chlorides, 2 chloro, 2,3-dimethyl hexane and 3 chloro, 2,3-dimethyl hexane are produced, the same equilibrium mixture of the two always being formed from either of the two carbinols, under the experimental conditions employed in these transformations.

The comparatively small difference in the refractive indices of the tertiary carbinols (2,3-dimethyl hexanol-2, $n_D^{25} = 1.4288$ and 2,3-dimethyl hexanol-3, $n_D^{25} = 1.4301$) may be used in order to arrive at a rough estimate of the composition of the carbinol produced by the hydrolysis of the optically inactive chloride previously described. The Mixture Rule of the physical properties of binary mixtures of organic liquids which postulates the change of refractive index of a binary mixture as being a linear function of the composition may be applied. These carbinols are members of a closely related aliphatic series so would be expected to show very small deviations from this rule, these deviations being considered due to a certain degree of co-ordination between the molecules of the two substances concerned, a number of possibilities for co-ordination complexes arising on mixing of two alcohols, and secondly, to alterations in the degree of association of each pure constitment by addition of molecules of the ether (174). Application of the Mixture Rule in this case indicates a 50-50 mixture of the two tertiary carbinols in the hydrolysis product (1.4294 being the mean of 1.4288 and 1.4301). The refractive index of a mixture made up of equal amounts of the two pure carbinols was found to be 1,4295 which checks with 1.4294, the refractive index of the hydrolysis product, as well as with the calculated mean.

The success of the use of the refractive index determination depends upon the absence of small amounts of unsuspected substances which could easily lead to erroneous conclusions. Another method of analysis was found in the fact that the carbinols as well as the mixture of carbinols may be converted into the phenyl urethanes and that the composition of a mixture of urethanes may be determined using the method of thermal analyses of Rheinboldt and his coworkers (175), Shriner and Fuson have stated (176) that urethanes can be obtained from tertiary alcohols only with great difficulty, the difficulties in obtaining derivations of tertiary alcohols being due not only to the slowness with which they react, but also to the ease with which replacement of the hydroxyl or elimination of water takes place. In this investigation, it was found that phenyl urethanes of the tertiary carbinols could be obtained quite easily, albeit quite slowly, in spite of the fact that tertiary alcohols of the type $R_2CH-C(OH)R_2$ undergo dehydration very readily. The carbinol and the phenyl isocyanate were simply mixed at 0° C in a dry test-tube, allowed to warm up to room temperature, and stand (1 week or more) until the mixture had turned solid. A mixture consisting of equal amounts of the two urethanes, that from 2,3-dimethyl hexanol-2 melting at 74°, and that from 2,3-dimethyl hexanol-3, M.P. 90.5°. was found to melt at 56-63°. The phenyl urethane of the carbinol, obtained by hydrolysis of the chloride prepared from optically active 2,3-dimethyl hexanol-2, melted at 52-62.5°. Furthermore a mixture of these two samples melted in the same range, 53°-62°C. That is no significant difference in melting points was observed. As a result of the application of this method of analysis, nearly equivalent amounts of the two carbinols are found to be present in the carbinol from the hydrolysis, a result which is in agreement with the results obtained from a study of the refractive indices. In this manner, the hydrolysis of the inactive chloride to the inactive chloride and thus in all probability the formation of the inactive chloride from the optically active carbinol has been shown to yield a mixture consisting of approximately equal amounts of the two isomeric tertiary compounds. That is to say, 50% of the product obtained from a reaction involving the replacement of the hydroxyl group in 2,3-dimethyl hexanol-2 and apparently also in 2,3-dimethyl hexanol-3 is the rearrangement product.

A molecular rearrangement which involves the optically active centre has therefore been shown to occur during the replacement of the hydroxyl group in the optically active carbinol, levo 2,3-dimethyl hexanol-2 (H) by a chlorine atom. That is, one of the necessary steps for the establishment of the configurational relationship of n-propyl t-butyl carbinol (A) and the product of rearrangement, formulated as 2-chloro-2,3-dimethyl hexanol-2 involves in itself a molecular rearrangement. It can thus be stated that regardless of the mechanism by which the rearrangements takes place, the method just described for discovering the relationship of substitution processes and molecular rearrangements is invalid under the

the conditions used in these experiments. Furthermore any future application of this method must first establish the conditions necessary for the non-occurrence of this type of rearrangement.

Theoretical Discussion

The processes involved in the particular transformation under discussion may be considered in the light of the mechanisms proposed for the Wagner-Meerwein rearrangement, to which the rearrangement just described is essentially as closely allied as to the pinacol transformation. It will be recalled that Meerwein explained the Wagner rearrangement by an ionic hypothesis, after he had found that dissociation, or ionisation, occurred in camphene hydrochloride and isobornyl chloride, analogously to triphenyl methyl-chloride, the rearrangement of camphene hydrochloride being preceded by its ionisation and therefore really consisting not in the migration of a chlorine atom, but in the regrouping of the cation*. (177) Meerwein and his collaborators also established that the conversion of camphene hydrochloride and other camphene hydrate esters into the corresponding isobornyl ester is a reversible process, the equilibrium strongly favoring the isobornyl ester. (178)

Meerwein and Wortmann (179) extended the ionic hypothesis to all cases of Wagner rearrangement, the function

*See Page 38

of the acid used in bringing about the change, being first to esterify the hydroxyl group, the ester then ionising to produce an ion in which the real migration occurs. The modern electronic theory admits of the possibility of an incipient ionisation, a prior dissociation into ions, as one possible manner in which an "open sextet" may be formed, but considers in addition. that any removal of a group with its complete octet of electrons from another atom, thus necessarily leaving an "open sextet" on this atom, as the cause of the occurrence of a rearrangement. Thus, the application of the ionic hypothesis by Meerwein and Wortman to the isoborneol-camphene and analogous rearrangements is not valid unless independent evidence of a tendency to ionise is forthcoming. That is to say, the ionic mechanism of rearrangements is applicable only to such cases where there is evidence of the ability to ionise of the molecules concerned.

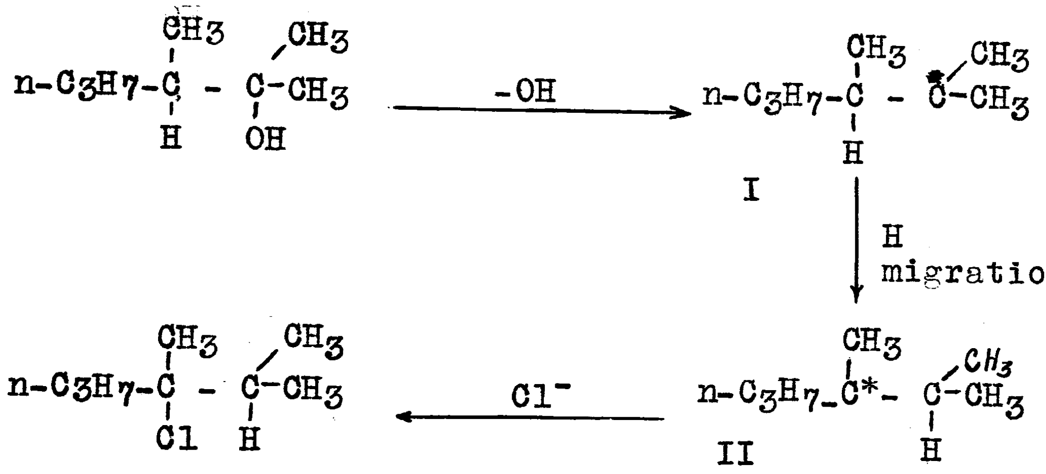
The transformations which 2,3-dimethyl hexanol-2 have just been shown to undergo during the reaction with hydrochloric acid may first be considered on the above basis:-

(1) Some evidence was cited at the beginning of this discussion* which indicated that tertiary hydroxyl groups, the most readily replaced of their type, might be directly replaced without rearrangement occurring. Some of the 2-chloro,2,3-dimethyl

* See Page 80

-hexane may be produced in this manner.

(2) The removal of the hydroxyl group from the carbinol leaves an "open sextet" on the fragment (I) which rearranges to fragment (II), which in turn forms the corresponding chloride on entry into the molecule of the chloride ion.



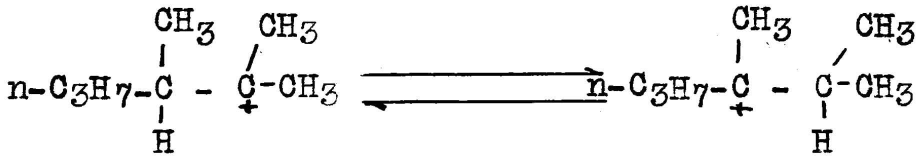
The isomeric tertiary chloride 3-chloro, 2,3-dimethyl hexane is thus formed.

(3) The characteristic property of tertiary halides however, with the exception of the special structures studied by Bartlett and coworkers* is their tendency to dissociate into ions, it being manifested by the extraordinary mobility of their halide groups. The halide group may be rapidly and quantitatively eliminated by shaking with water or alcohol even in the cold, the ease of this hydrolysis decreasing with increased molecular weight probably because of decreasing solubility (180). Hughes has shown that their hydrolysis is unimolecular, the

*See Pages 63 and 64

the measured rate being that of ionisation of the halide. That is to say, tertiary chlorides possess the special structural conditions necessary for ionisation. The 2 and 3-chloro 2,3-dimethyl hexanes then may be regarded as tending to ionise to form the cations I and II respectively.

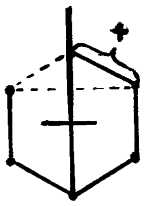
Analogously to the Meerwein postulation that camphene hydrochloride and isobornyl chloride form cations which are in equilibrium with each other, the cations I and II may be considered to form an equilibrium system.



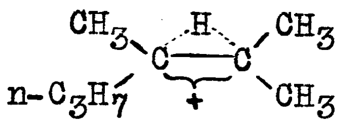
$$n\text{-}C_3H_7\text{-}\underset{H}{\overset{CH_3}{C}} - \underset{+}{\overset{CH_3}{C}}\text{-}CH_3 \rightleftharpoons n\text{-}C_3H_7\text{-}\underset{+}{\overset{CH_3}{C}} - \underset{H}{\overset{CH_3}{C}}\text{-}CH_3$$

II

A secondary rearrangement of the isomeric chlorides formed by processes (1) and (2) may thus occur. The interconversion of the free ions might be expected to be relatively rapid, since it involves only a movement of electrons, together with the attached hydrogen atom. In fact, it has been suggested that the intermediate ion in the camphene hydrochloride-isobornyl chloride conversion may be mesomeric between the two corresponding cations. (181)



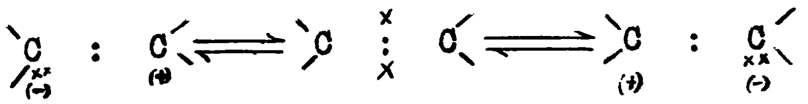
The mesomeric structure in the case of the cations I and II may be formulated (III);-



III

In the former case, the preferred structure of the mesomeric form must approach the structure of the isobornyl cation, since the equilibrium favors the formation of isobornyl chlorides. In the latter example, the formation of approximately equal amounts of the two possible chlorides and carbinols appears to indicate the symmetrical nature of the mesomeric structure.

The intramolecular tautomeric system as formulated for the cations I and II, in which the two cations differ only in the position of an electron pair with its accompanying hydrogen atom, recalls the controversy originated by Kharasch and Darkis (182) concerning the possibility of the existence of electromeric forms of ethylene compounds, the limits of the unsymmetrical displacement of the pair of electrons in this case being the two ionized forms;-



When the radicals attached to the carbon atoms of the double bond are about the same in electronegativity, the addition of the halogen acids to yield nearly equivalent amounts of the two possible addition products (183) indicates that the tendency for the formation of the two ionized forms is nearly equal. The relative electro-negativities (184) of the n-propyl and the methyl groups on the two carbon atoms of structure III involved in the mesomeric formulation differ but slightly, so that theoretically the tendency toward the formation of the cations I and II and thus their derivatives also is approximately equal, in agreement with our results.

The ionic mechanism as applied to the Wagner-Meerwein rearrangement of camphene hydrochloride into isobornyl chloride has been modified in recent years. Nevell, de Salas, and Wilson (185) deduced that this rearrangement proceeds in two steps from a study of exchange experiments with radioactive chlorine, the first step involving the rapid establishment of an ionic equilibrium by the separation of chlorine, and the second a relatively slow bimolecular reaction between the organic cation so produced and a molecule of hydrogen chloride. The exchange experiments with radioactive chlorine showed that at 20° even under conditions during which no appreciable rearrangement occurred, halogen exchange was rapid and complete, indicating that ionisation cannot be the rate determining step in the rearrangement. Interconversion of free ions might be expected to be relatively rapid, since it involves only a movement of electrons, together with perhaps a slight readjustment of molecular strain. That the rearrangement might proceed by elimination of hydrogen chloride and re-addition rather than by ionisation is not supported by the formation of camphene hydrate and not camphene from camphene hydrochloride.(186) The rearrangement proceeded at about one-fifteenth of the speed of chlorine exchange and thus of ionisation, at 0° in chloroform solution, and was found dependent upon the presence of hydrogen chloride. The way in which this dependence was accounted for was to assume that the slow stage of the rearrangement is a bimolecular reaction between the organic cation and a molecule of hydrogen chloride to give isobornyl chloride. On this basis the mechanism of this transformation involves a reaction of the organic ion with hydrogen chloride.

Bartlett and Pockel (145) had drawn this conclusion earlier from stereochemical considerations, for they pointed out that the process could not involve the cation of isobornyl chloride since this ion is of a type believed to be configurationally unstable (187) and would thus be expected to yield a mixture of bornyl and isobornyl chlorides. The product is however almost pure isobornyl chloride. Furthermore, of the two stereoisomeric chlorides, isobornyl chloride is the thermodynamically unstable form, being slowly converted to bornyl chloride under the same conditions as those causing rearrangement. This fact too might be thought to disprove the intervention of the isobornyl ion. That is to say, whilst the cation from camphene hydrochloride might be a real intermediate, the isobornyl cation seems never to attain kinetic freedom during the rearrangement. In this manner the maintainence of the stereochemical identity of the isobornyl structure in this transformation is explained.

In the light of these recent studies on the mechanism of the camphene hydrochloride-isobornyl chloride conversion, the simple formulation just given on the basis, of the electronic theory as stated by Whitmore and of the ionic hypothesis as proposed by Meerwein, for the transformations of 2,3 dimethyl hexanol-2 established in this investigation must accordingly be somewhat extended. Stereochemical considerations must also be applied. The phase of the study of Intramolecular Rearrangements which considers these processes on the basis of the present knowledge of substitution Process and Walden Inversion, has been somewhat neglected.

The reactions of optically active 2,3 dimethyl hexanol-2 and its derivatives may now be pictured as follows, (Scheme 3-p. 107)

(1) The first step in the reaction of this carbinol with hydrochloric acid involves the formation of an oxonium salt, IV, (cf. pp. 40,59,65) which will be ionised in the aqueous medium used in these experiments.

(2) This intermediate oxonium salt tends to lose water to form the fragment, V, thus leaving carbon atom #2 with only six electrons. As this dissociation proceeds, the face centered bond must necessarily be progressively increased in strength. That is to say, the carbon atom #2 becomes increasingly more reactive so that the fragment becomes more and more unstable and must undergo a change which will eliminate the "open sextet" being thus formed. The fragment V may be formulated as a cation.

(3) The elimination of the 'open sextet may be effected by a union with a chlorine ion to form 2-chloro, 2,3-dimethyl hexene VII. This normal substitution product will be formed by a bimolecular mechanism, the entering chloride ion being attracted by the face-centered bond to the side of the carbon atom opposite to the hydroxyl group just eliminated. This chloride must be obtained optically active since the optically active carbon #3 is not involved in this normal substitution.

(4) The 2-chloro, 2,3-dimethyl hexane, a tertiary halide, being capable of at least a minimal ionisation, will no doubt rapidly establish an ionic equilibrium, by the separation of the chlorine, with the cation V, similar to the equilibrium shown by Nevell, de Salas and Wilson, (see p. 101) in the case of camphene hydrochloride, another tertiary chloride.

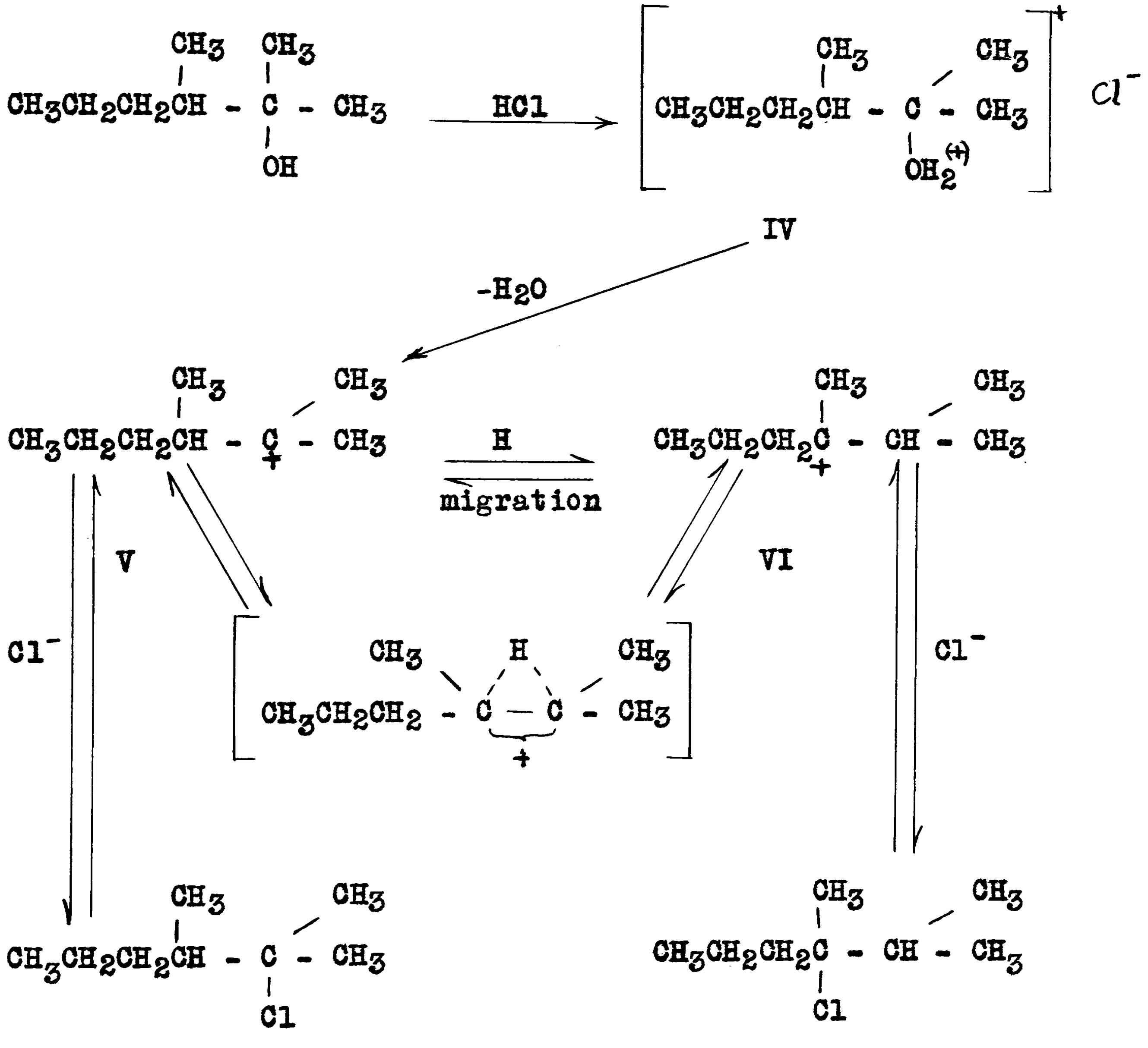
Processes 1,2,3,4, do not involve the optically active centre, carbon atom #3, so that the optical activity will not be effected.

(5) The steadily increasing strength of the face-centered bond in process (2), may attract an electron pair from the next carbon, carbon atom #3, the hydrogen atom held by the shifting electron pair migrating with it to form the fragment, (II), in which this other tertiary carbon atom has the "open sextet", the migrating hydrogen atom in this case also being attracted by the face-centered bond to the side of the carbon atom opposite to that of the removed hydroxyl group. Similarly fragment VI, may be formulated as a cation. The optically active carbon, #3, is thus deprived momentarily of an electron pair.

(6) The new fragment VI, can then combine with a chloride ion to form the 3-chloro,2,3 dimethyl hexane VIII. This rearranged chloride thus formed might be expected to be optically active but considerably racemised by analogy with the formation of the somewhat racemised dextro tertiary chloride, 2-chloro-1-phenyl-2-methyl butane from levo 2-methyl-2-phenylbutanol-1 as shown by Wallis and Bowman using thionyl chloride (188). The removal of the hydrogen atom by migration and the entry of the chloride ion would be expected to take place on opposite sides of the carbon atom. The transformation may thus have taken place by a Walden Inversion mechanism.

(7) The above tertiary chloride, isomeric with 2-chloro 2,3-dimethyl hexane, possesses the same fundamental tertiary structure, so that the two chlorides may be considered to behave almost identically, showing the same tendency to ionisation, to the same extent and in the same manner. Thus an ionic equilibrium between this chloride, 3 chloro-2,3-dimethyl hexane and the fragment VI will also no doubt be rapidly established. In any case, this optically active tertiary chloride would be readily racemised, the racemizing effect of halogen ions on optically active compounds, of the same halogen being well known, especially in compounds wherein the halogen undergoes ready replacement.(190)

(8) Finally the two cationic fragments V & VI may also be considered in ionic equilibrium as previously formulated, both carbon atoms #2 & #3, attracting the electron pair and its attacked hydrogen atom equally since the groups attached to these carbon atoms are practically equal in electronegativity. Should these two carbon atoms share the electron pair and the accompanying hydrogen atom (by a hydrogen bond), the resulting structure would be the mesomeric structure (III), which has been considered previously.



VII Scheme 3 VIII

A similar scheme may be formulated for the isomeric tertiary carbinol, 2,3-dimethyl hexanol-3.

The resultant of the ionic equilibrium in processes 4,7 and 8, is the formation, theoretically as well as experimentally equal amounts of the two tertiary chlorides, this mixture being optically inactive when optically active 2,3-

dimethyl hexanol-2 is used in the experiments. If these ionic equilibria were not effective, the mixture of the chlorides obtained by the combined processes 3,5,6, that is the normal substitution and the substitution through rearrangement only, would be expected to be optically active due to the optical activity of the normal substitution product. It has been found that the product obtained is optically inactive. This definitely indicates that the chlorides first formed must be undergoing a secondary rearrangement. Furthermore, the loss of the optical activity shows that this secondary rearrangement has likely occurred in a reversible system, to such an extent and ease, that all optical activity was lost. Such a reversible system is that represented by the ionic equilibria in processes 4,7 and 8.

Whether the tramsformation of one chloride to the other involves a bimolecular mechanism similar to that established for the camphene hydrochloride-isobornyl chloride transformation or proceeds through an ionic mechanism analogous to that proposed by Meerwein or through the mesomeric structure III cannot be definitely stated from the evidence available. From the point of view that the mesomeric structure represents a resonating system, the products derived therefrom would be considerably if not totally racemized (cf.p.66A.) On the other hand, this mesomeric intermediate ion resembles closely the intermediate postulated by Winstein and Lucas (p. 61) to explain the retention of configuration in the conversion by hydrogen bromide of dl-threo-3-bromo-butanol to dl-2,3-dibromobutane. If the "face shielding effect" operates here the transformation might be proceeding at least in part by a mechanism wherein the hydrogen atom, attracted to the back of the carbon atom, which holds the hydroxyl or chlorine, shields this carbon atom from a Walden Inversion mechanism. This process would facilitate direct substitution on carbon #2 and also rearrangement through a Walden Inversion mechanism, the chloride ion approaching the side of carbon #3 opposite to that holding the hydrogen atom. However, it is not possible at present to say by which of the intimate mechanisms these transformations proceed.

The reversible rearrangement of a chloro 2,3 dimethyl hexane to 3 chloro, 2,3 dimethyl hexane differs from the camphene-hydrochloride-isobornyl chloride conversion in that the stereochemical identity of the compounds here was not maintained. This racemization may have occurred by either of two likely paths;

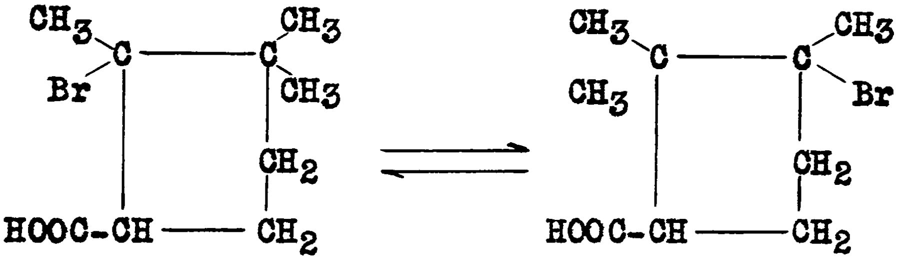
(1) By the racemization of the optically active 3 chloro-2,3-dimethyl hexane, or

(2) by racemization through the reversible ionic equilibria as formulated.

The evidence at hand does not allow of a more definite statement of mechanism, but quite definitely indicates that an "ionic mechanism" is applicable to this rearrangement (both chlorides possessing an equal tendency to ionise). That is to say, whereas a true ionic mechanism might not be applicable to the camphene hydrochloride-isobornyl chloride transformations, it would seem that such a mechanism is actually in effect in this case.

The original formulation of the transformation observed by Stevens of dextro n-propyl tert butyl carbinol to levo 2 chloro, 2,3-dimethyl hexane must now be reconsidered. It is now apparent that the observed optical activity cannot be attributed to the tertiary chloride as this undergoes further rearrangement with loss of optical activity under the experimental conditions employed. The observed optical activity must therefore be attributed to the formation of the corresponding secondary chloride by a Walden Inversion. The change of sign and also the low value of the optical rotation observed ($\alpha_D = -0.72$) are thus explained, the secondary chloride having been shown present only to the extent of 5%.

The present investigation has established then the occurrence of a molecular rearrangement in substances of the simple aliphatic type structure, $R_2CH-C(X)R_2$, the tertiary hydrogen atom migrating in reactions involving the removal or the replacement of the tertiary group, X. Substances of the analogous type, $R_3C-C(X)R_2$, wherein no tertiary hydrogen atom is present, but a hydrocarbon radical being in its place, have not as yet been reported as undergoing rearrangement. In fact, Bartlett (132) has assumed the production of the corresponding chloride of diethyl tertiary butyl carbinol. The interconversions of the hydrobromides of the campholytic acids reported by Noyes (189) exemplify the latter system in the cyclic series, the transformation occurring in the presence of hydrobromic acid.



A methyl group has migrated in this case, under similar conditions to the migration of the hydrogen atom in the system $R_2CH-C(X)R_2$ just studied. That is to say, rearrangements may still occur in the general systems $R_2CH-C(OH)$ and $R_3C-C(OH)$ during the course of a substitution reaction, even when the ease of normal substitution is great.

This work has also shown that the method as outlined in this thesis for discovering the relationship of substitution processes and molecular rearrangements is invalid under the conditions used in these experiments; not only for the reason, as mentioned previously, that one of the necessary steps for the establishment of the configurational relationship of the original compound and the rearrangement product involves in itself a molecular rearrangement, but also for the reason, that the product resulting from the alteration of the carbon skeleton under stereochemical study, itself undergoes a further rearrangement. Thus any future application of this method must first determine the conditions necessary for the non-occurrence of this type of rearrangement. This thesis however has been concerned chiefly with the occurrence of rearrangements and the mechanisms by which these transformations take place. Although there are many cases where molecular rearrangements have proven useful there are also many cases in synthetic organic chemistry, where the necessary intermediates prove impossible to prepare due to these rearrangement processes. Having first found the mechanisms by which intramolecular rearrangements occur, the next important phase of their study is that which considers the retardation of these undesirable reactions.

EXPERIMENTAL PART

I The Preparation of α-Methyl Valeric Acid.

The preparation of α-methyl valeric acid (n-propyl methyl acetic acid) was carried out through the malonic ester synthesis, the method employed by Levene and Bass.(190). All the materials used in this synthesis were fractionally distilled and were dried very carefully.

(a) Preparation of n-propyl malonic ester.

The procedure used for the preparation of n-propyl malonic ester was an adaption of the method described by Adams and Kamm for the preparation of n-butyl malonic ester. (191) The diethyl malonate used was obtained by fractional distillation of the commercial diethyl malonate through total condensation variable take-off column, the packed section being 6½ ins. long, 1/2 in. in diameter, the packing consisting of single turned glass helices (3/16 in outside diameter) packed singly; B. P. 92° @ 17 mm. similarly, the n-propyl bromide used boiled at 71-2° C @ 764.2 mm. The anhydrous ethyl alcohol was prepared using magnesium ethylate rather than use sodium, as recommended by Adams and Kamm. The resulting n-propyl malonic ester was fractionated through the above column, B. P. 110-1° C @ 17 mm.

(b) Preparation of methyl n-propyl malonic ester. The preparation of methyl n-propyl malonic ester from the purified product obtained in the preceding step was carried out by an analogous procedure using 25% excess dimethyl sulphate as the alkylating agent. Methyl ethyl ether was observed to be a by-product of this reaction. The methyl n-propyl malonic ester was not isolated since the purification of the esters by fractional distillation was reported by Levene and Bass to present some difficulties due to the proximity of the boiling-points of the alkyl malonic esters and their respective methyl derivatives.

(c) Preparation of methyl n-propyl malonic acid. At the completion of the malonic ester synthesis in the preceding step, as much of the alcohol as possible is distilled off using a slight vacuum. The residue was then treated with a 2% solution of 3 moles potassium hydroxide per mole of methyl n-propyl malonic ester in 80% alcohol and refluxed for 12 hrs. The reaction mixture was then evaporated nearly to dryness and was then taken up in water. After acidification with 25% sulphuric acid, the free acid was extracted with ether, the ether extract washed with water and the ether subsequently evaporated off to yield the crude acid. The crude acid thus obtained was not purified but was used in the crude-form in the next step.

(d) Preparation of α-Methyl Valeric Acid.

Decarboxylation of the crude methyl n-propyl malonic acid was effected by heating the acid to 170-190°. Upon cessation of evolution of carbon dioxide, the resulting crude α-methyl valeric acid was fractionally distilled through the 6½ in. total condensation variable take-off column to yield a pure α-methyl valeric acid B. P. 99-100° @ 18-19 mm. An anilide of this acid was prepared in the usual manner, M. P. 95°, this derivative having been previously reported as M.P. 95.2°. (192)

II The Resolution of α-Methyl Valeric Acid.

The resolution of α-methyl valeric acid also referred to as methyl n-propyl acetic acid and 2-n-propyl propionic acid was attempted with three different alkaloids, quinine, brucine and cinchonidene. Levene and Mikeska resolved this acid by repeated recrystallisations of the quinine salt from 50% acetone the more insoluble salt being that of the levo acid. With the materials and facilities at hand the resolution by quinine was found unsatisfactory. There was a strong tendency for this salt to separate out even with constant stirring in a soap-like form regardless of variations in temperature as a result of which the filtrations were difficult, necessitating that it be done in the cold (outdoors), the yields per recrystallisation very low, and the extent of resolution per recrystallisation also very low. The melting point of the quinine used was 169-70° C in a sealed tube.

Bergmann carried out a partial resolution of the racemic acid by means of the brucine salt. Recrystallisation of the brucine salt prepared from the racemic acid and Eastman Brucine alkaloid (M. P. 176-178°) from 35% acetone (193), the filtration necessarily being done at 0° due to the solubility of the salt at room temperature, was little better than quinine.

Satisfactory resolution was finally accomplished using cinchonidine, the cinchonidine salt crystallising from 66% acetone at room temperatures.

(a) Procedure for Cinchonidine Resolution.

To 215 gms. α-methyl valeric acid dissolved in 66% acetone (using 2 cc. 66% acetone per gm. of cinchonidine) was added after warming the acid solution 543 gms cinchonidine (the equivalent quantity), and 66% acetone added until, on cooling the solution to room temperature on a reciprocating shaker, the cinchonidine salt crystallised out to a slushy consistency. The salt was immediately filtered, sucked dry, and recrystallised using the same procedure.

After many recrystallisations, the salt (206 gms.) was decomposed with a 10% excess over the equivalent amount of 10% hydrochloric acid, the free α-methyl valeric acid extracted with ether, the ether extract washed twice with 10%

hydrochloric acid and finally washed with 10% sodium sulphate solution the sodium sulphate facilitated separation of the ether-solution from the water used for washing until no test for chloride ion was obtained with aqueous silver nitrate solution. The ether solution was dried using anhydrous sodium shlphate overnight, and the ether removed by distillation through the fractionating column.

The resulting acid was then fractionated through this column at 9 mm. The fractions boiling at 84.5° possessed a constant refractive index, $n_D^{25} = 1.4121$, a density - $d_4^{25} = 0.920$, and a molecular rotation - $[M]_D^{25} = +8.27$ (homogeneous) the rotation being observed $\alpha_D^{25} = +13.11$ in a jacketed 2 dm. polariscope tube at 25° C. In this manner 50 gms. of α-methyl valeric acid were prepared

M. R.$_{n^2}$:- Found:- 31.38; Calculated:- 31.25

III The Preparation of the Methyl Ester of α-Methyl Valeric Acid.

α-Methyl valeric acid was converted to the methyl ester employing diazomethane. An ethereal solution of diazomethane was prepared according to the directions given by F. Ardnt Organic Syntheses (194). 47 gms. of α-methyl valeric acid dissolved in 100 c.c. ether were treated with the diazomethane ethereal solution by slow addition of the reagent till the yellow colour persisted, the solution then being allowed to stand 1 day at 0° C. 30 gms. anhydrous sodium sulphate were then added to the ethereal solution and the solution allowed to stand overnight. The solution was filtered to remove the sodium sulphate and the excess diazomethane removed through the partial removal of ether in vacuo. The remainder of the ether was distilled from the ester and the ester then fractionated through the small column. The ester distilled at 98.5 mm at 77° C, the two fractions taken possessing the same refractive index $n_D^{25} = 1.4004$. The density and molecular rotation were respectively $d_4^{25} = 0.8750$ and $[M]_D^{25} = +11.85$, the rotation ($\alpha = +15.95$ being observed in a 2 decimeter jacketed polariscope tube and maintained at 25° C

M. R.$_{n}^{\lambda}$:- Found: 36.03 Calculated 36.19.

IV Preparation of Levo-2,3-Dimethyl Hexanol-2.

The preparation of the tertiary alcohol, levo-2,3 dimethyl hexanol-2, was accomplished by the application of the **Grignard** Reaction, tertiary alcohols being usually synthesised by allowing a suitable Grignard reagent to react with either an ester or a ketone. Levo-2,3 dimethyl hexanol-2 can thus be conveniently prepared from the methyl ester of α-methyl valeric acid and methyl magnesium iodide.

In a 1-ℓ three necked, round bottom flask fitted with a mechanical stirer through a mercury seal, a separatory funnel and an efficient reflux condenser to which a sodium hydroxide (pellets) drying tower is attached, were placed 24 gms. of magnesium turnings and 200 cc. of dry ether.

A small portion (5-10 cc of the methyl iodide, 137 gms. to be used to prepare the methyl magnesium iodide, was added through the separatory funnel. After the reaction had started, 200 cc more of dry ether were added, and the remainder of the methyl iodide was added dropwise with cooling. At the end of the addition, the contents were allowed to warm up with continuous stirring and then refluxed for an additional thirty minutes. The Grignard reagent, methyl magnesium iodide was thus prepared.

The flask was then cooled in an ice-bath, and a solution of 42 gms. of dextro methyl α methyl valeric acid in 100 cc of dry ether was added dropwise to the Grignard reagent solution with constant stirring. After the solution was added, the whole was allowed to warm up slowly with stirring over night. (Final temperature of contents = 24.5°). The contents of the flask were then poured into 200 cc of a saturated ammonium chloride solution containing ice, the mixture being well stirred to ensure complete hydrolysis of the Grignard addition compound. The final temperature at the end of the decomposition was -1°C.

The ether layer was separated, the aqueous layer extracted five times with 100 cc portions of ether. The combined ether extracts were washed twice with 100 cc of water and twice with 100 cc portions of 10% potassium carbonate solution and then dried over anhydrous potassium carbonate for one day. The ether was removed by distillation through a Widmer Column with a 6½ inch spiral section. The alcohol was then fractionated through the 6½ inch column previously described.

The fractions B. P. 75° @ 29 mm $n_D^{25} = 1.4288$ and $d_4^{25} = 0.831$ were employed in further work. The rotation was determined in a 2 dm. tube jacketed at 25° C, $\alpha_D^{25} = -29.46°$. From this the molecular rotation was calculated:-

$$\left[M\right]_D^{25} = \frac{130 \times -29.46}{100 \times 2 \times 0.8314} = -15.35$$

V Preparation of dl-2,3 dimethyl hexanol-2 was prepared for comparative purposes and for the preparation of the phenyl urethanes, according to the scheme as outlined on p. 87.

(a) Preparation of Pentanol-2.

The methyl magnesium iodide was prepared according to the procedure as previously outlined from 76 gms. of magnesium turnings, 440 gms. of methyl iodide and 700 cc. dry ether in a 2 litre three inch round bottom flask fitted with a mechanical stirrer through a mercury seal, a separatory funnel, and an efficient reflux condenser to which a sodium hydroxide drying tower was attached. 216 gms. of n-butyraldehyde was added dissolved in 250 cc dry ether, dropwise with constant stirring and with cooling. The reaction mixture was stirred overnight, and decomposed the

the next day by pouring into a saturated solution of ammonium chloride and ice. The ether layer was separated from the aqueous layer and the aqueous layer extracted with ether. The combined ether extracts were washed with water and with 10% potassium carbonate solution, and finally dried over anhydrous potassium carbonate. The ether was removed by distillation, and the residue distilled through a Claisen distilling flask at atmospheric pressure. 178 gms of pentanol-2 were obtained, distilling at 118-119.5° C, $n_D^{20} = 1.4067$, $n_D^{25} = 1.4048$.

(b) The Preparation of 2-Bromo Pentane.

The preparation of the secondary bromides of n-pentane from the corresponding carbinols has received much attention in the past, a mixture of the 2 and 3-bromo compounds being obtained under all ordinary conditions. Sherrill and co-workers have shown, however, that the use of phosphorus tribromide at low temperature produces little or no rearrangement.(195)Isobutyl bromide containing but 0.6% of its tertiary isomer was obtained by Whitmore and Lux (196) from the action of phosphorus tribromide at low temperatures (-1°) on isobutyl alcohol. An adaptation of the procedure established by these latter workers was employed in this work for the preparation of 2-bromo pentane.

In a 500 cc. flask provided with an efficient stirrer, a thermometer and a dropping funnel, was placed 130 gms. of the pentanol-2. After cooling to -5°C,145 gms.

phosphorus tribromide was added slowly during 8 hours with vigorous stirring, maintaining the contents of the flask below - 1° C at all times. The whole was allowed to warm up slowly to room temperature stirring constantly and then allowed to stand for 15 hrs. The mixture separated into two layers on standing. The lower layer was separated. The upper layer was then distilled through a Claisen distilling flask, B. P. 52° @ 80 mm. The distilate was washed with 10% potassium carbonate and then dried over anhydrous potassium carbonate for 1 day. The filtered bromide was then distilled through a Claisen distilling flask. The 2-bromo pentane distilled at 50.5-51° C @ 77 mm. 171.5 gms. a yield of 77% was thus obtained. The refractive index of the product:- $n_D^{20} = 1.4414$ - the previously assigned refractive index being $n_D^{20} = 1.44125$.(197)

The procedure of Whitmore and Lux (198) was also carried out, the two layers not being separated. The refractive index of the product obtained, $n_D^{20} = 1.4418$, indicated considerable rearrangement.

(c) The preparation of 2,3 dimethyl hexanol-2.

In a 2-ℓ three-necked flask, fitted with a mechanical stirrer (mercury-sealed), condenser, to which is attached a sodium hydroxide drying tower and a separatory funnel is placed 30 gms. of magnesium turnings.

The flask was then heated gently but thoroughly with a luminous flame and allowed to cool to room temperature. The turnings were then covered with 100 cc. of anhydrous ether. 5-10 cc. of a solution of 2-bromo-pentane in 175 cc. anhydrous ether was added to start the reaction. 225 cc. of anhydrous ether were added and then the solution of 2-bromo pentane was added dropwise to the well-stirred reaction mixture. The whole was stirred at room temperature over night.

70 gms. of anhydrous C. P. acetone (dried over anhydrous potassium carbonate) in 100 cc. of anhydrous ether were slowly added, 1 drop every 3 seconds, with cooling of the flask. When the 2-bromo pentane solution has all been added, the reaction mixture is stirred for eight hours before decomposition by pouring into an iced saturated solution of ammonium chloride. Ether extraction followed, five 100 cc. positions of ether being used. The combined ether extracts were washed twice with 100 cc. of 10% water, twice with 100 cc. of 10% potassium carbonate solution, and finally dried over anhydrous potassium carbonate.

The ether was removed and the resulting residue distilled through a total condensation variable take-off column with an efficiency of 15 theoretical plates. The fractions distilling at 75° C @ 29 mm. $n_D^{25} = 1.4290$ were used in subsequent work.

VI. Preparation of 2,3 Dimethyl hexanol-3.

This tertiary carbinol was prepared using the reagents used by Whitmore and Evers,(198) methyl isopropyl ketone and the Grignard reagent of n-propyl bromide. The procedure used was similar to that used above in the preparation of the isomeric 2,3 dimethyl hexanol-2. 15 gms. of magnesium turnings 68 gms. n-propyl bromide, and 43 gms. of methyl isopropyl ketone were employed. In this case, the ether extracts were washed with 5% sodium hydroxide solution and then with water.

The resulting crude carbinol was first distilled in a Claisen flask, and then fractionally distilled through the 15-plate column. The fractions distilling at 72.5° C @ 29 mm, $n_D^{25} = 1.4301$ were used in subsequent work.

VII Preparation of Phenyl Urethanes.

1 cc. of phenyl isocyanate and 1 cc. of the tertiary carbinol, 2,3 dimethyl hexanol-2 and 2,3 dimethyl hexanol-3, were mixed at 0° C in a dry test-tube and allowed to warm up slowly and to stand at room temperature for eight days. The contents of the test-tube (sealed with collodion) were then solid. The solid contents were washed three times with cold Skelly Solve A, and then repeatedly crystallised from Skelly Solve A (filtering before crystallisation each time) until the product melted constantly. The phenyl urethane of 2,3 dimethyl hexanol-3 melted at 90.5° C and that of 2,3 dimethyl hexanol-2 at 74° C.

VIII Preparation of the Tertiary Chlorides.

(a) From levo 2,3-dimethyl hexanol-2 (199).

180 cc. of concentrated hydrochloric acid (sp.gr.1.19) were placed in a pyrex tube prepared for sealing. This was cooled and maintained at -10° in an ice-salt bath. Hydrogen chloride gas, produced from the action of concentrated sulphuric acid on concentrated hydrochloric acid in a generator as described by Fieser (200), was bubbled into the acid in the type until it was saturated. 24 cc. of levo 2,3 dimethyl hexanol-2 was pipetted on top of the acid. The tube was sealed and shaken on a reciprocating shaker for one day, being allowed to warm up to room temperature while shaking. The tube was then allowed to stand for separation, and cooled again to -10°C. After thorough cooling, the tube was opened, the chloride layer drawn off from the top of the saturated hydrochloric acid, and washed successively with five 25 cc. portions of concentrated hydrochloric acid, once with a 10 cc. portion of iced water, and finally once with an iced 3% sodium bicarbonate solution until no further carbon dioxide was evolved.

The separated chloride was dried first with anhydrous sodium sulphate and then over anhydrous potassium carbonate at 10° C. The drying agent was filtered off and the optical rotation of the chloride determined. The chloride possessed no optical activity, $n_D^{20} = 1.4352$, $n_D^{25} = 1.4330$, B. P. 43.5-44° C @ 12 mm.

Analysis (201):-

Wt. of substance.	Wt. of Ag Cl	% Chlorine
1.0131 gms.	0.9681 gms.	23.64%

Calculated for C_8H_{17} Cl (m.W. 148.6): Cl = 23.86%

(b) From the inactive tertiary octanols.-

2,3 dimethyl hexanol-2 and 2,3 dimethyl hexanol-3.

The isomeric tertiary octanols were both converted to the chlorides by shaking with a large excess of concentrated hydrochloric acid for 12 hrs. a procedure essentially similar to that recommended in Organic Syntheses (202), for the preparation of tert. butyl chloride from tert. butyl alcohol.

5 ccs. of the two carbinols, each, were shaken for 12 hrs. on a reciprocating shaker with 55 ccs. of concentrated hydrochloric acid (sp. gr. 1.19) in 125 cc. ground-glass-stoppered Erlenmeyer flasks at room temperature (28°C). The resulting chlorides were separated, shaken 5 times with 10 cc. portions of concentrated hydrochloric acid, once with iced saturated sodium sulphate solution(to reduce the solubility of the chloride in the water), once with iced 3% sodium bicarbonate solution until no carbon deoxide was evolved, once again with saturated iced sodium sulphate solution, and finally dried over anhydrous sodium sulphate. The resulting chlorides reacted very rapidly with aqueous

silver nitrate solution to produce a precipitate of silver chloride.

The refractive indices of the clear liquid chlorides were determined:-

2-chloro, 2,3-dimethyl hexane:- $n_D^{20} = 1,4351$; $n_D^{25} = 1,4330$.
3-chloro, 2,3-dimethyl hexane:- $n_d^{20} = 1,4353$; $n_D^{25} = 1.4333$.

XI Hydrolysis of Chloride.

10 gms. of the chloride obtained from levo 2,3-dimethyl hexanol-2 were placed in a five litre separatory funnel containing 3 litres of distilled water. This was shaken on a reciprocating shaker for 6 hrs. The mixture was extracted ten times with 100 cc. of purified Skelly Solve A. (by shaking with concentrated sulphuric acid, potassium permanganate solution and distilling from phosphorus pentoxide). The combined extracts were washed once with 3% sodium bicarbonate solution, twice with water and dried over anhydrous potassium carbonate. The Skelly Solve A. was removed by distillation through a Widmer column. The residue distilled at 71.5-73° C at 29 mm, $n_D^{25} = 1.4294$. The resulting carbinol was free of olefins as shown by its failure to absorb bromine in carbon tetrachloride, and also free of chlorides as shown by the negative test for chloride ion in either aqueous or alcoholic silver nitrate.

At this stage the refractometer was restandardized, using a plate whose standard value is 1.5164. The measured refractive indices were 1.5164; 1.5164, indicating the correctness of the refractive indices measured previously to this standardization.

A phenyl urethane was prepared from the above carbinol by the same procedure as used for the pure octanols. The melting point after two recrystallisations was 52-62.5°, which was not changed by a further recrystallisation.

XII. Composition of Carbinol from the Hydrolysis

(a) Refractive Index Method.

The refractive index of the carbinol from the hydrolysis was determined, $n_D^{25} = 1.4294$. Application of the Mixture Rule indicates a mixture consisting of equal amounts of the two tertiary carbinols, $n_D^{25} = 1.4294$ being the mean of $n_D^{25} = 1.4288$ and 1.4301, the refractive indices of the 2,3 dimethyl hexanol-2 and 2,3 dimethyl hexanol-3 respectively. The refractive index of a known mixture was determined; the mixture composed of 0.8257 gms. of each of the two carbinols gave $n_D^{25} = 1.4295$ which checks well with the mean as calculated. This also gives an indication of a linear relation between composition and refractive index.

(b) Thermal Analysis.

The phenyl urethane of the carbinol obtained from the hydrolysis melted at 52-62.5°. A mixture consisting of equal amounts of the two urethanes, that from the

2,3 dimethyl hexanol-2 melting at 74° and that from the 2,3 dimethyl hexanol-3 melting at 90.5° was found to melt at 56-63°. A mixed melting point of the urethane from hydrolysis and the mixture of urethanes was determined:- M. P. 53-63°, a value showing no significant difference in melting point. The melting points were determined from the temperature of the first visible signs of softening to the temperature of complete melting.

A-D-D-E-N-D-A

Analyses of Phenyl Urethanes (p. 124).

Phenyl urethane of 2,3-dimethyl hexanol-2.

Nitrogen Analysis (Dumas) ;-

Wt. Of Sample.	Vol. of Nitrogen.	% Nitrogen
3.235 mg.	0.176 cc. (corr.25 765mm.)	6.27%

Carbon-Hydrogen Analysis ;-

Wt. of Sample.	Wt. of -	%ages.
0.02456 gm.	CO_2 =0.06518 gm.	% C = 72.3%
	H_2O =0.02173 gm.	% H = 9.8%

Calculated for $C_{15}H_{23}NO$;-

N= 5.62% ; C = 72.2% ; H = 9.23%.

Phenyl Urethane of 2,3-dimethyl hexanol-3.

Nitrogen Analysis (Dumas) ;-

Wt. of Sample.	Vol. of Nitrogen.	% Nitrogen.
4.995 mg.	0.254 cc. (corr.25 765mm.)	5.86 %

Calculated for $C_{15}H_{23}NO$;- N = 5.62%.

SUMMARY

1. A survey of the present knowledge of Substitution Processes and Intramolecular Rearrangements indicated an apparently natural tendency for one group to replace another by a Walden Inversion mechanism. The present investigation was undertaken in order to establish in a general aliphatic case whether or not a Walden Inversion mechanism is the only one by which intramolecular rearrangements occur.

Accordingly one method for the elucidation of the relationships between Substitution Processes and Intramolecular Rearrangements has been described and investigated. The basis of this method is the definite correlation of the configuration of the original compound and the rearrangement product, in this case n-propyl tert. butyl carbinol and 2 chloro-2,3-dimethyl hexane.

2. Levo n-propyl tert. butyl carbinol has been configurationally related to levo 2,3 dimethyl hexanol-2, by the correlation of the configurations by direct chemical means of levo 2,3 dimethyl hexanol-2 to dextro α-methyl valeric acid.

3. An attempt to correlate the configurations of levo 2,3 dimethyl hexanol-2 to 2-chloro-2,3-dimethyl hexane by a normal substitution reaction not involving the optically active carbon atoms led to the discovery of the occurrence of an intramolecular rearrangement. The method described for the elucidation of the stereochemical mechanism of intramolecular rearrangements has thus been shown invalid under the conditions of the experiment.

4. Intramolecular rearrangements may quite readily occur even in cases where the ease of normal substitution is great.

5. The rearrangement has been formulated on the basis of the "ionic mechanism" of intramolecular rearrangement processes, an ionic equilibrium having been postulated between the cations corresponding to 2 chloro- and 3 chloro- 2,3 dimethyl hexanes.

6. The formulation of the formation of a tertiary chloride from n-propyl tert. butyl carbinol as a simple case of a retropinacolone rearrangement has been shown to be incorrect, due to the establishment of this ionic equilibrium.

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