THE RESOLUTION OF 1-(4-CHLOROPHENYL)-2,2,2-TRICHLOROETHANOL. SOME CHEMICAL AND INSECTICIDAL STUDIES ON THE SEPARATED ALCOHOLS.

A THESIS

BY

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HISTORICAL

General Introduction.

The compound 1,1-di(4-chlorophenyl)-2,2,2-trichloroethane (DDT I) has assumed great importance with the discovery by the Geigy Chemical Company that it is a very potent contact insecticide. Their results are summarized in a paper by Lauger, Martin and Müller (1). Patents were issued to cover this work (2). To most common insects, it is the most powerful contact insecticide known.

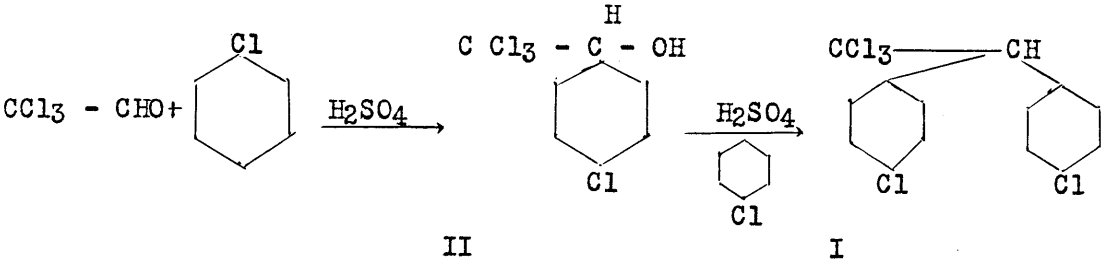
The Geigy paper is chiefly concerned with the testing of a large number of chemicals on various insects. DDT is included in a list of contact insecticides. These materials are effective only when the insect's body makes contact with the chemical. Compounds in this class bear no relation chemically to those classed as stomach poisons, which kill only on being eaten with the insect's food. Neither are they related to repellants, materials which keep flies from touching a treated surface.

The study of the chemistry of DDT is vitally important. This is because very slight changes in the molecule cause it to lose its toxicity. An approach can be made to the structural basis of insecticidal action when two closely related chemical molecules are found to have widely differing insecticidal action. This fact also indicates the contingency that it may be possible to prepare a compound even more powerfully toxic than DDT, even though its other analogues have been without insecticidal action.

Chemical studies may overcome the disadvantages of DDT as an insecticide. The compound does not kill all insect pests, but does destroy some creatures essential to plant economy, such as bees. Present day knowledge

of the specificity of DDT and other contact insecticides tends to indicate that eventually one may be able to choose from a list of chemicals, depending on the pest that is to be eliminated.

DDT is prepared by the Baeyer reaction when two moles of chlorobenzene are condensed with one of chloral in twenty moles of ninety-five percent sulfuric acid at 30°C to give a fifty percent yield of the para-para'isomer, the toxic ingredient (3).



II I

The alcohol 1-(4-chlorophenyl)-2,2,2-trichloroethanol, written as the intermediate (II) was isolated up to as much as five percent in commercial preparations (4, 5). Several analogous alcohols were prepared by Chattaway and Muir (6), by using excess chloral in the Baeyer reaction. These alcohols gave the Baeyer product by condensation with chlorobenzene in sulfuric acid. The strongest evidence for the alcohol being the intermediate was obtained by Garmaise and Eastwood (3).

The alcohol (II) occupies a key place in the chemistry of DDT. It is the source of esters and ethers, several of which have been prepared and tested on insects. It can be reacted with aryl compounds other than chlorobenzene, giving a series of unsymmetrical diaryl ethanes, unobtainable pure by the ordinary Baeyer reaction (6).

Some of the main impurities in commercial DDT were prepared and tested insecticidally. The compound 1-(2-chlorophenyl)-1-(4-chlorophenyl)-2,2,2-trichloroethane, the ortho-para isomer of DDT, the major impurity (4) was

found non-toxic on Drosophila (7). The intermediate alcohol (II) has a relative potency of one hundredth that of DDT (7). A discussion of this is given on page 5.

As the alcohol has an asymmetric carbon atom, it can exist as optical isomers. Their separation was considered for the following reasons:-

1) It was felt desirable to determine any possible differences in toxicity between the d- and l- forms of the alcohol or its derivatives.

2) The analogue 1-(4-chlorophenyl)-1-phenyl-2,2,2-trichloroethane had appreciable insecticidal activity (7). Unlike DDT, it has an unsymmetrical structure. The asymmetric carbon atom in the d- or l-alcohol may retain its configuration on being converted to the Baeyer product, which would then be optically active also. Interesting mechanistic conclusions depending on whether or not the Baeyer product was optically active could be drawn. Insecticidal tests run on such a product would also be of interest.

The Testing of Materials as Contact Insecticides.

Methods of insecticidal testing were devised at McGill (7) to test materials to see if they had a greater ultimate relative potency than DDT. This follows the approach of Läuger, Martin and Müller (1), who methodically tested very many compounds, and succeeded in determining a few toxic materials. They tried to assign toxicity to the following mechanism. The trichloromethyl group is the toxic unit, but the molecule also requires the benzene rings to confer fat solubility for entrance into the insect. Other workers tried to relate chemical structure to toxicity (8).

The McGill workers used Drosophila as the test insect, and noted interesting facts, summarized as follows:- A very slight change in chemical structure often produces a compound of profoundly different toxicity. For example, the ortho para isomer of DDT, 1-(2-chlorophenyl)-1-(4-chlorophenyl) -2,2,2-trichloroethane has no action on Drosophila (7), neither has the compound 1,1,1,2-tetrachloro-2,2-di(4-chlorophenyl) ethane. Only one of the stereoisomers of hexachlorocyclohexane (666) is toxic, the others being inactive (9).

Studies on the physiological effects of optical isomers have shown that there may or may not be considerable differences between the d- and l- forms. Where they do exhibit a specific difference, it seems probable that diastereoisomers are produced by the reaction of the optically active reagent with some optically active component of the living tissue. Such diastereoisomers have different properties and hence would be expected to have different physiological action. A likely source of optically active body com-

ponents is found in the enzymes.

The difference in physiological effect of the d- and l- forms may be due in part to the formation of different amounts of the diastereoisomers at equilibrium. This effect was observed by McKenzie (10) and reviewed by King (11). The inequality in amounts may be so great that only one can be isolated (12, 13). Or it may be that d- and l- forms react at different rates with the optically active tissue component. The inactive isomer does not react at a rate fast enough to cause accumulation of the physiologically active product.

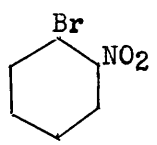
The situation has been summarized by Cushny (14) in the general statement that when differing effects of d- and l- isomers are observed, the controlling reagents are probably optically active enzymes or other asymmetric cell constituents which are able to exert a selective influence on metabolites through differential reaction, absorption or catalysis.

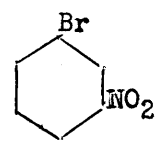
Principles Governing the Resolution of Alcohols and other Racemic Modifications into their Constituent Isomers.

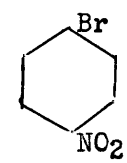
Introduction.

One of the most commonly observed phenomena in organic chemistry is that of the existence of isomers, whose empirical formula is the same, but which differ in at least one of their physical or chemical properties. The cause of this difference was realized early to be a result of the different arrangement of the atoms within the two molecules. Two types of isomerism can be distinguished. In the first, the functional groups of the two isomers are not related chemically. The second class includes all types where the relative distances of the functional groups from each other are not constant, even though their type is the same.

The first type of isomerism is exemplified by the corresponding members of certain homologous series. Ethyl alcohol - CH_3CH_2OH - and ethyl ether - CH_3OCH_3 - have the same empirical formula, but differ markedly in physical and chemical properties. The second type includes position isomers of the type $CH_3CH_2CH_2CH_2CH_3$-n-pentane and isopentane $CH_3CH_2\overset{CH_3}{\overset{|}{C}}H-CH_3$, which differ in carbon skeleton, and $CH_3\overset{Cl}{\overset{|}{C}}H-CH_3$,2-chloropropane and $CH_3CH_2CH_2Cl$,1-chloropropane, which differ in point of attachment of the functional groups to the carbon skeleton. Another example of this type is the ortho, meta, and para isomers of bromo-nitrobenzene







In these cases the functional groups have different reactivities.

A special type of the second class of isomerism is stereoisomerism.

Here the two isomers possess the same molecular formula and same functional groups, but differ in the three dimensional space arrangement of the atoms or groups within the molecule. The two commonly observed types here are optical isomerism and cis-trans isomerism.

Properties of Molecules with Asymmetric Atoms.

A pair of optical isomers has indistinguishable physical and chemical properties except for one characteristic. Each isomer rotates the plane of plane polarized light in equal and opposite directions. Examination of the nature of these pairs of compounds shows that only those structures, crystalline or molecular, which possess mirror images non-superimposible on the original are able to affect plane polarized light. The isomers have the same relation to each other as do the right and left human hands, that is, each is the mirror image of the other. Their structures are termed asymmetric, or without geometrical symmetry.

With some crystals, it is found that the crystal lattice as shown by X-rays is asymmetric, non-superimposible on its mirror image. This non-identity of structure may or may not be shown by the external crystal form. Optical activity will be observed here, the material being separable into isomers called dextro (d-) or laevo (l-) forms, which rotate plane polarized light an equal amount either to the right or the left. The phenomenon will only be observed in the crystalline state, and not when the compound is a liquid or gas or dissolved in a solvent. A compound showing this type of isomerism is quartz.

Experimentally it is found that when a molecule has an asymmetrical three dimensional molecular structure, it exists in forms capable of rotating

polarized light. These forms show this property in all their physical states, thereby showing the molecule to be the fundamental asymmetric unit. The molecule and its mirror image are called enantiomorphs and are identical in all respects except that they rotate the plane of polarized light an equal amount in opposite directions. In a very few cases the asymmetry is reflected in the crystal form. Pasteur (15) found this so for sodium ammonium tartrate.

Asymmetric molecules can be divided into two groups:- (1) Compounds in which an individual atom is asymmetric. This is readily observed when any carbon atom in the molecule has four different groups attached to its valences. (2) Molecules containing no individual asymmetric atom. Their asymmetry is due to the absence of any of the necessary elements of symmetry, which permit the mirror image of the molecule to be superimposible.

Principles Involved in Separation of Optical Isomers.

Experimentally it is always observed that when a compound of asymmetrical structure is synthesized in the laboratory, the product is quite inactive when examined in a polarimeter. This is because the two enantiomorphs have been prepared in equal amounts, and their rotations neutralize each other. There is no general method for their separation per se by the usual methods of organic chemistry, for they have no difference in physical properties, for example, solubility, or boiling or melting point. However, if the product, called a racemic modification is reacted with another optically active compound, the two products obtained are not mirror images. The spatial construction of the product of reaction of the d- isomer differs from that of the reaction of the l- isomer.

These products, called diastereoisomers differ appreciably in their physical properties such as solubility, and so can be separated by fractional crystallization from a suitable solvent.

The reaction of a racemic alcohol, dl-A, with an optically active acid, l-B, may be written

$$\text{dl-A} + 2\ \text{l-B} \longrightarrow \text{d-A.l-B} + \text{l-A.l-B}$$

The diastereoisomeric esters after separation are saponified to give the separated optically active alcohols. The method was first used by Pasteur (16) for the separation of the tartaric acids.

Points of Technique in Optical Resolutions.

Like all organic reactions, those for the resolution of optical isomers have technical difficulties which reduce the versatility of the method in question. It is felt by the author that Shriner and Adams (17) have summarized these difficulties succinctly. They wrote that "The properties of a good resolving agent are:-

1) It should be readily obtainable from easily available starting materials.

2) It should react with the racemic modification in but one way. Thus a dibasic acid, which can form both normal and acid salts, is not so useful a resolving agent as a monobasic acid.

3) It must form compounds with the racemic modification stable enough to resist dissociation or decomposition on recrystallization, yet easily split after separation, by methods not drastic enough to cause racemization.

4) Its diastereoisomeric derivative must be crystallizable and less soluble than any of its components.

5) It should have a high rotatory power in order to enable the progress

of a resolution to be followed by polarimetric methods.

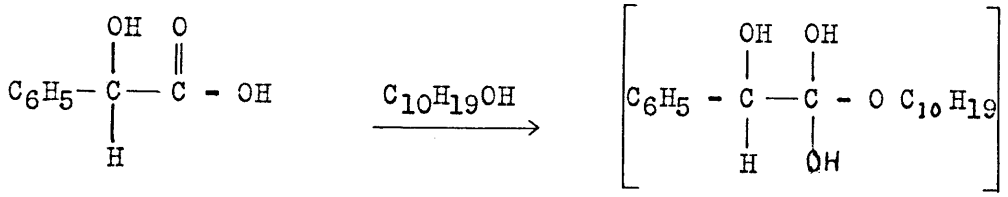
6) It should be readily recoverable for repeated use.

The above technicalities are typical of those met in organic chemical syntheses. However, there is one outstanding difficulty which occurs only in the performance of optical resolutions. One cannot predict what resolving agent will give diastereoisomers with properties which make their separation possible. The esters must be crystalline and have considerable difference in solubility in at least one solvent. Many examples of this uncertainty may be found in the literature. Linstead (18), tried five optically active bases in the resolution of a diphenic acid and six for its half methyl ester, but could not obtain crystalline salts. The acid phthalate of a glycerol mono ester gave a crystalline salt with brucine. Only a very small amount of resolution could be effected on recrystallization (19). In the purification of commercial borneol containing isoborneol, it was found that l-menthoxy acetic acid was quite unsuitable, whereas d-bornoxy acetic acid (20) gave a pure crystalline precipitate of one diastereoisomer. Oily mixtures of diastereoisomers have never been separated. They have to be crystallized first.

Chemical Pecularities of the Reaction of d- and l-Isomers with Optically Active Reagents.

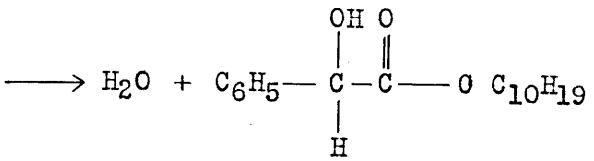
1) D- and l- isomers obviously enter into the same type of chemical reaction. However, the d- and l- forms may react at different rates with an optically active molecule. Marckwald & McKenzie (21) have shown that if dl-mandelic acid is esterified with a quantity of l-menthol insufficient to react with all the acid present, the product consists to a

large extent of l menthyl d-mandelate



dl - large amount

ll - small amount

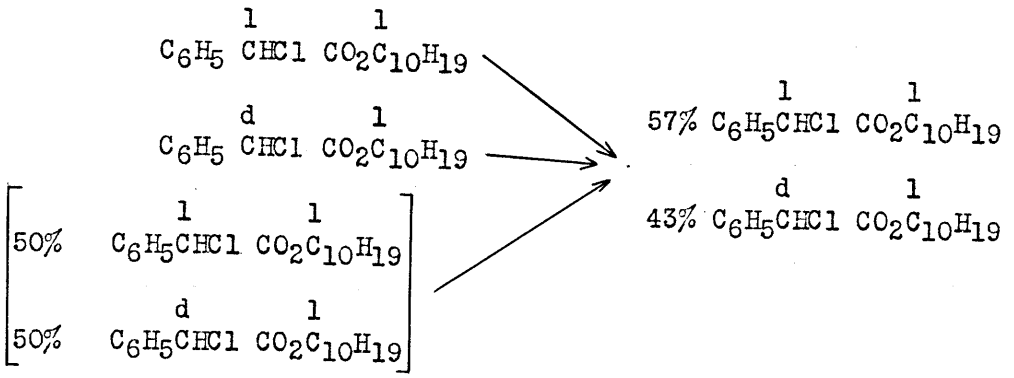


dl - large amount

ll - small amount

One reason suggested for the inequality in amounts is that esterification probably involves the formation of the intermediate addition compound shown in the brackets. The active l-menthol adds to the carbonyl group of the d- and l- mandelic acids at different rates because of the different steric influences involved. The unesterified acid contained a corresponding excess of l-mandelic acid. The hydrolysis of an equimolar mixture of the two diastereoisomers resulted in an excess of one active acid being formed.

2) The equilibrium point in the reactions of d- and l- isomers with an optically active reagent may tend to form products in one case much more than in the other. This effect was first noticed by McKenzie and Smith (10) in the preparation of l-menthyl esters of dl -α- chlorophenylacetic acid. They found that if the d-, l-, or dl- esters were treated with a trace of alkali, the isomeric esters were formed in 57 and 43% yield.

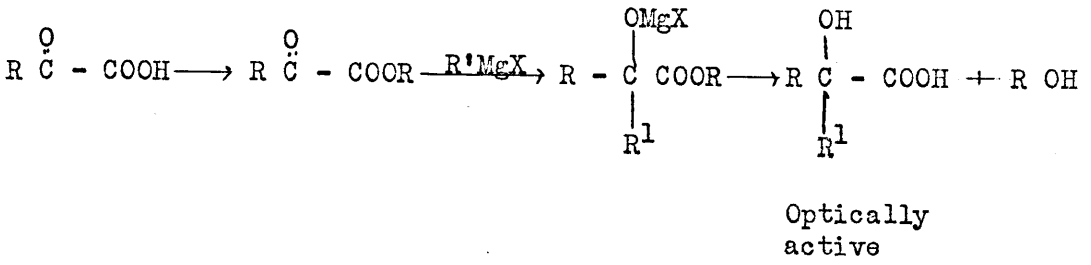


Some examples are known where the inequality may be so great that only one form can be isolated, as in the brucine salt of a certain peri-substituted naphthalene (13). The effect was summarized by King (11). Interconversion of the d- and l- forms about the asymmetric atom has taken place.

3) Differential rates of adsorption of optical isomers by optically active adsorbents have been observed. An apparatus of the type used in chromatographic work was constructed, and the column was filled with an optically active adsorbent. Henderson and Rule (22) poured a petroleum ether solution of dl-N,N^{1}-p-phenylene bis (3-imino camphor) through a column of d-lactose hydrate. After passing the solution through many times, it was found that one isomer was adsorbed by the lactose while the other remained in solution. The same method (23) was used to resolve 2,8-dimethyl-5,11 (6,12)-methanodibenzo-[b,f][1,5] diazocine (Troger's base) using the same adsorbent.

4) The final point characteristic of the reactions of d- and l- isomers does not involve the formation of diastereoisomers, or their separation. Marckwald (24) defined asymmetric syntheses as those processes which produce optically active compounds from symmetrically constituted molecules by the intermediate use of optically active reagents, but without the use of any of the methods of resolution.

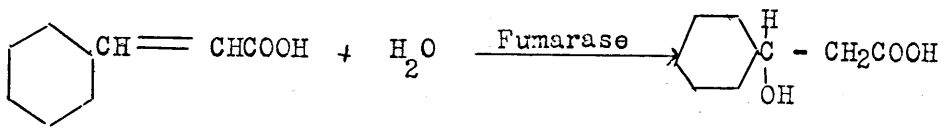
An example of this type of synthesis was found by McKenzie (25) when he treated optically active keto-esters with the Grignard reagent, and hydrolysed the product.



Optically active

Many other examples of this in many other fields of organic chemistry are known. In practically all cases, the active products obtained by asymmetric syntheses are not optically pure. The amount of one isomer usually exceeds that of the other by no more than a few percent.

Many asymmetric syntheses are brought about by enzymes. The following conversion was performed by Dakin (26).



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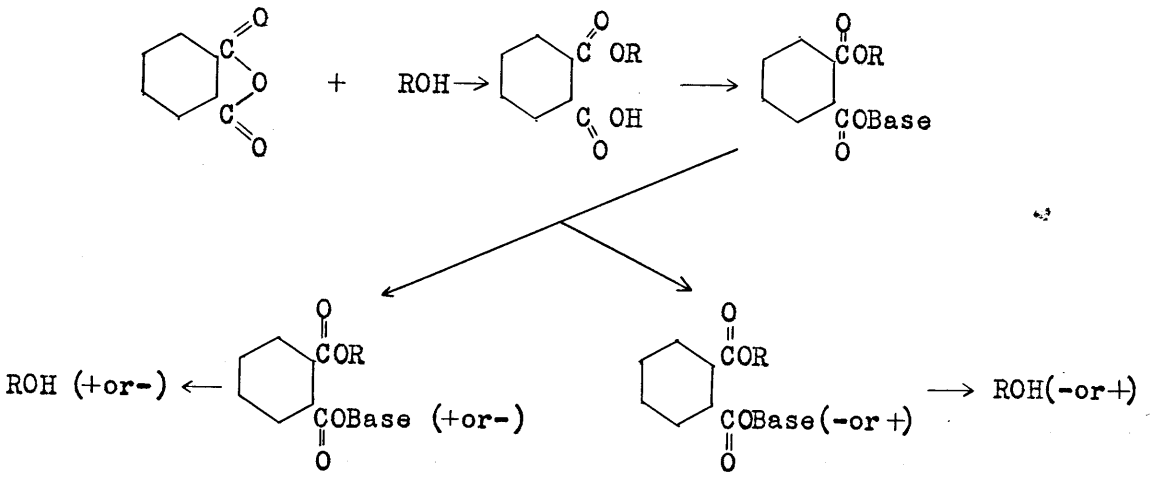
In such conversions, the product often consists mostly of one isomer and the purity is found to approach one hundred percent.

An Outline of the Methods used for Resolving Racemic Alcohols into their Pure Dextro and Laevo Forms.

(a) Hydrogen ester of the alcohol with optically active base.

Acid Phthalates or Succinates.

The great majority of simple primary and secondary alcohols form hydrogen esters of diacids with ease. Usually phthalic or succinic acids are chosen, and are heated as the anhydride with the alcohol, which is either free or dissolved in pyridine. The reaction of the acid ester with an optically active base gives a product resolvable with ease. It usually happens that only one diastereoisomer crystallizes out of the reaction solvent, in a state of considerable purity.



This is a versatile method as there are a large number of optically active bases readily available. Several dibasic acids have also been used. Treatment of the separated diastereoisomers with dilute acid gives the acid esters. These can be saponified to give the active alcohols.

The method was first introduced by Pickard and Littlebury (27) who resolved borneol by fractionation of the l- menthyl amine salts of the acid phthalate. Series of alcohols were resolved by Pickard and Kenyon (28) and by Levene and co-workers (29). The following series have been resolved by this method:-

CH_3CHOHR	C_6H_5CHOHR
C_2H_5CHOHR	$C_6H_{11}CHOHR$
$(CH_3)_2CHCHOHR$	$CH_2 = CHCHOHR$
$(CH_3)_2CHCH_2CHOHR$	$CH_2 = CHCH_2CHOHR$

where R = various normal or branched chains from methyl to pentadecyl.

In the resolution of alcohols by acid ester formation, all the common optically active bases, brucine, quinine, strychnine, and/or cinchonidine have been used. The 3-nitro derivative of phthalic anhydride has proved more useful than the unsubstituted material for resolving 2-methyl-butanol-1, 3-phenyl-butanol-1, and 4-phenyl-pentanol-1. The phthalates, consisting of oily masses gave only oily salts, or crystalline ones which could not be separated, or which dissociated on recrystallization, giving some free base. (30, 31). In these cases, pure diastereoisomers, easily resolvable, were obtained from the 3-nitro phthalates. Tetrachloro phthalates of simple secondary alcohols such as butanol-2, were prepared (32, 33). Their diastereoisomeric salts could not be separated, however. The hydrogen succinates of menthol (33), and various members of the series -

CH_3CHOHR (33)

$(CH_3)_2CHCHOHR$ (34)

C_2H_5CHOHR (35)

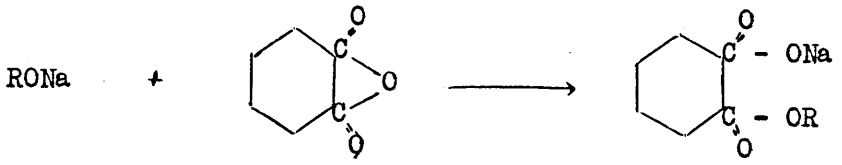
have been prepared and resolved with optically active bases. The succinates

are superior to the phthalates when more soluble or more stable salts are required, or when completing resolutions only partly effected by means of the phthalates (34, 35).

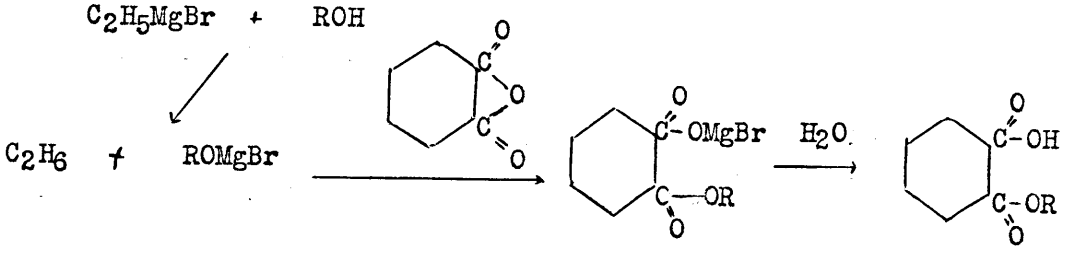
Modifications to Overcome Inapplicability of the Method.

This method of resolution cannot be used when the anhydride fails to react with, or dehydrates the alcohol. This is often the case with tertiary alcohols.

(1) One alternative method of synthesis of the phthalate was developed by Fuller and Kenyon (36). It consists in the addition of a solution of powdered potassium and the alcohol in benzene to a solution of phthalic anhydride in benzene. By this method, the hydrogen phthalates of α-terpineol, dl-α- and β- santalols, and dl- linalool (37, 38) were prepared.



(2) Acid phthalates have also been synthesized by Fessler and Shriner (39) by the reaction of their magnesium halides with phthalic anhydride. The acid phthalate of benzohydrol, prepared in about 14 percent yield by direct esterification, was synthesized in 84 percent yield by this modification -



The acid phthalates of tertiary alcohols were prepared in good yield by this method. It has not been used to synthesize phthalates as resolution intermediates.

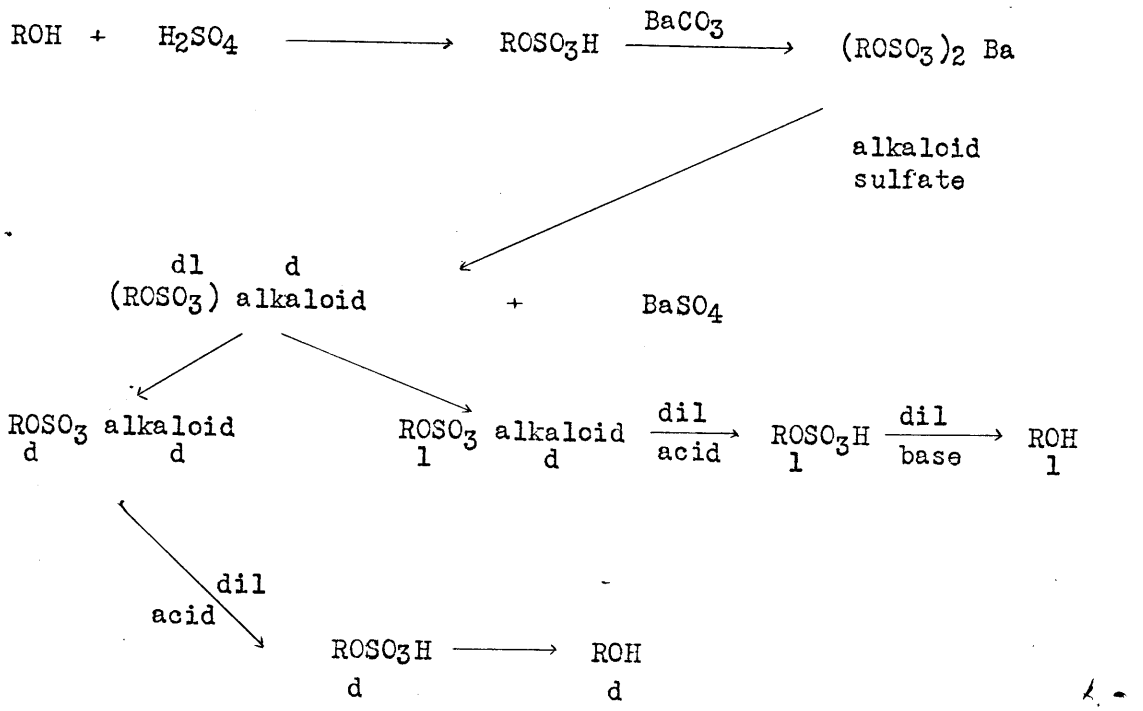
(3) The 4- toluene sulfonates of numerous alcohols have been shown to undergo an ionic reaction of the following type with salts of carboxylic acids (40).

$$ROSO_2C_7H_7 + CH_3COO^- \longrightarrow ROC(=O)CH_3 + C_7H_7OSO_2^-$$

Potassium benzoate, potassium acetate, lithium chloride and other salts will react thus. Apparently potassium acid phthalate, which theoretically should react to give the alcohol acid phthalate, had not yet been used in this reaction.

Acid Sulfates.

A few alcohols can be resolved somewhat completely by reaction of their hydrogen sulfates with optically active bases. The method is easily applied to glycols which form stable sulfates (41), as well as to cyclohexane diol (42, 43, 44). The glycol is sulfated by reaction with excess concentrated sulfuric acid at -15°C, and the product is isolated at the barium salt. This is reacted with an alkaloid sulfate. Removal of the barium sulfate by filtration leaves a solution of diastereoisomeric sulfates separable by fractional crystallization. Saponification with dilute alkali gives the active alcohol.



The sulfates of most alcohols are too unstable to work with (45). Pentyl - 1-hydrogen sulfate (46), hexyl-3-hydrogen sulfate (47) and butyl-2-hydrogen sulfate alkaloid salts were only partially or unsuccessfully fractionated (32). Racemization is very noticeable on hydrolysis of these esters (48).

No other acid esters except phthalates, 3-nitro phthalates, succinates and sulfates have been used for resolutions of alcohols.

(b) The Action of an Optically Active Acid on the Alcohol.

A study of diastereoisomeric esters was made by Frankland and Price (49,50). A crystalline product was obtained from the reaction between l-2-methyl-butanol-1 and dl-α,β -dibenzoyl propionic acid. However, the diastereoisomers could not be separated by recrystallization. The corresponding dl- alcohol l-acid was a liquid. Marckwald and McKenzie (21) (51), effected partial resolutions of dl- mandelic and related acids with l- menthol and d- borneol, and of dl- octanol with d- tartaric acid.

L- Menthyl Isocyanate.

This reagent was used by Pickard and Littlebury to form crystalline urethanes with alcohols and phenols. They easily separated the urethanes of (52) dl-1-phenyl-1-p-hydroxy phenyl ethane and (53) dl-ac-tetrahydro-2 naphthol, obtaining only one optically pure however. Hydrolysis was achieved by refluxing with dilute alcoholic potassium hydroxide. However, dl-isobornyl l-menthyl urethane cannot be separated as it forms mixed crystals inseparable by fractional crystallization. The l- menthyl urethane of 1:3 methyl cyclohexanol is a viscous oil.

D- Camphoric Acid.

It has been found that the hydrogen camphorate esters of such alcohols as 1-phenyl-propanol could not be separated by fractional crystallization (54, 55).

D- and l- Mandelic Acids.

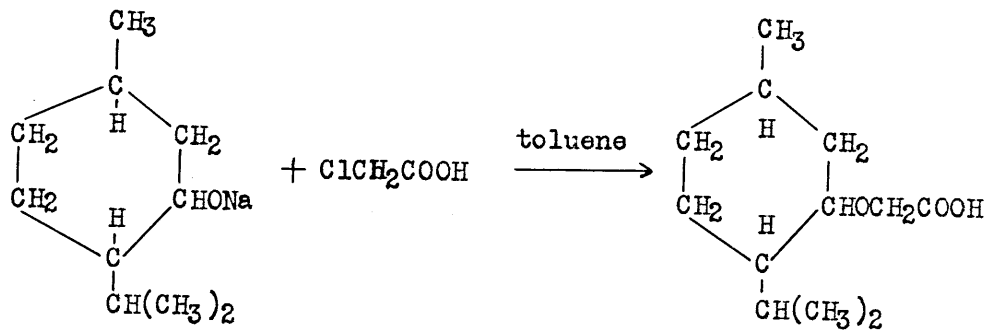
Dl- menthol has been completely resolved by the use of d- and l- mandelic acids. Hydrolysis of the mandelate menthyl esters results in the racemization of the resolving agent (56, 57).

D- and L- Camphor Sulfonyl Chloride.

The separation of d- from l- menthol has also been achieved by fractionation of the crystalline esters with d- and l- camphor sulfonyl chloride. The method was first used by Read and Grubb (58). Hydrolysis of the esters was accomplished by the steam distillation of a 50% oxalic acid solution. A low yield of isomers was obtained.

L- Menthoxy Acetyl Chloride.

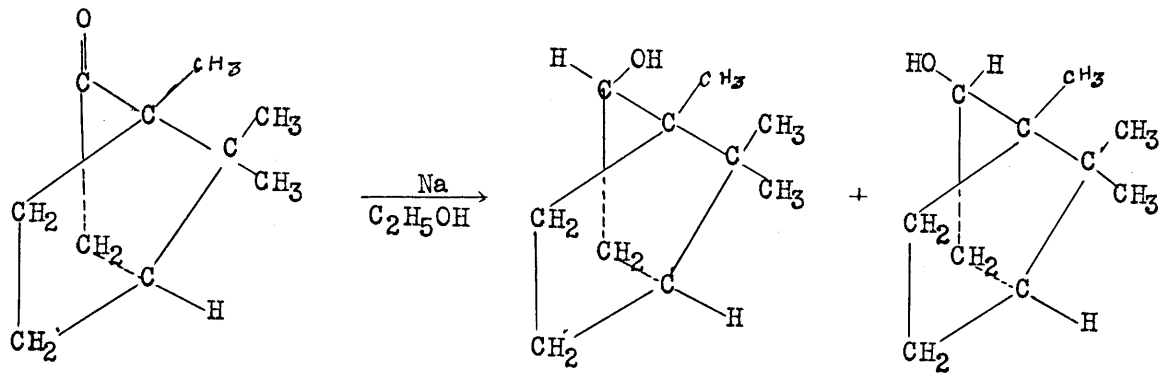
The above reagents all lack at least one property from those listed by Adams as desirable. The use of l- menthoxy acetyl chloride by Read and co-workers (59, 60, 61) surmounted many difficulties. Alkoxy acetic acids are easily prepared from chloroacetic acid and the sodium derivatives of active alcohols such as l- menthol or d- borneol.



A good yield of the crystalline diastereoisomers is obtained from dl-menthol and l- menthoxy acetyl chloride in pyridine. These are easily separated by fractional crystallization and have convenient rotations. Mild conditions are used for the hydrolysis. 1% alcoholic potassium hydroxide serves for the menthol resolution. The alcohol and resolving agent can be isolated optically pure.

In a resolution, after the less soluble diastereoisomer separates out, the mother liquor contains the other one, together with byproducts. Most resolution methods do not permit the purification of the second alcohol. Here the impure product can be saponified and reacted with d- menthoxy or d- bornoxy acetic acid, both of which are readily available. Now the other antipode separates as the least soluble diastereoisomer. For example, dl- menthol (59), dl- neomenthol (62) and dl- equilenin (63) have been completely resolved by successive application of d- and l- menthoxy acetic acids. These reagents were also used in the following experiment. D- camphor was reduced with sodium in ethanol, yielding a mixture of d- borneol with some l- isoborneol. This mixture was converted to the alkoxy acetic acid and reacted with further impure d- borneol. Fractional crystallization gave pure d- bornyl-d-bornoxy acetate, which on hydrolysis gave pure d- borneol and pure d- bornoxy acetic acid. Similarly l- camphor was converted into pure l- borneol, by way of l- bornoxy acetic acid (20). The equation is given below.

In the following scheme, "impure" d- borneol signifies a mixture of d- borneol and l- isoborneol, which is obtained by the reduction of d- camphor.



d- camphor d- borneol l- isoborneol

$C_{10}H_{17}ONa$ + Cl CH_2COOH

sodium derivative of impure d- borneol — chloroacetic acid

$NaCl + C_{10}H_{17}OCH_2COOH \xrightarrow{SOCl_2} C_{10}H_{17}OCH_2COCl$

impure d- bornoxy acetic acid — impure d- bornoxy acetyl chloride

$C_{10}H_{17}OCH_2COCl + C_{10}H_{17}OH \longrightarrow C_{10}H_{17}OCH_2COOC_{10}H_{17}$

impure d- bornoxy acetyl chloride — impure d- borneol — impure d- bornoxy acetate of d- borneol

fractionally crystallize

pure d - bornoxy acetate of d- borneol $\xrightarrow[KOH]{alc.}$ $C_{10}H_{17}OH + C_{10}H_{17}OCH_2COOH$

d-borneol — d-bornoxy acetic acid

The l- menthoxy acetates of dl-trans-cyclohexane-1,2-diol (64) and of a polynuclear phenol with restricted rotation (65) were separated by frac-

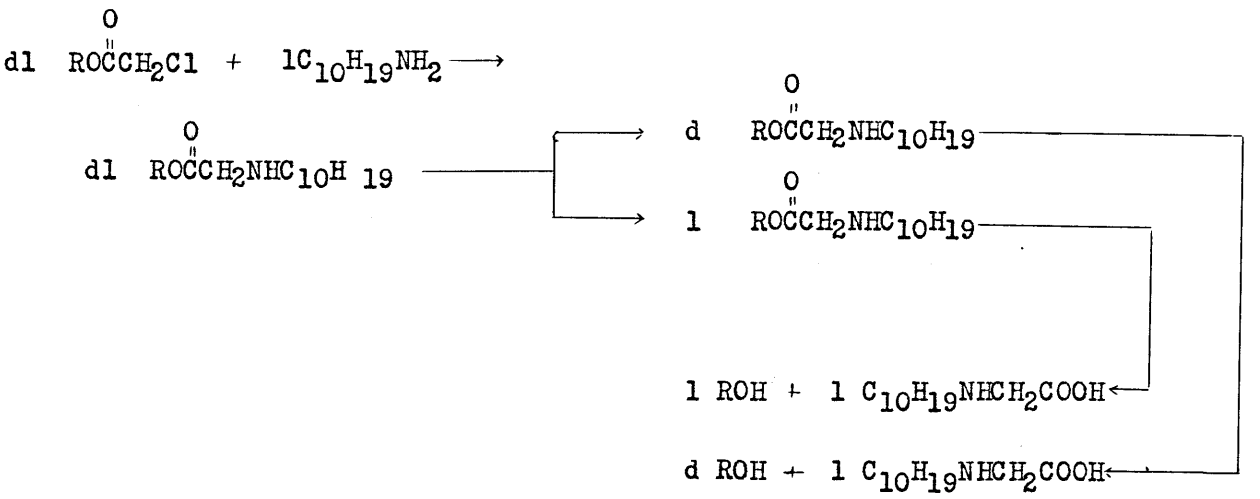
tional crystallization and each gave pure d- or l- isomers on hydrolysis.

L- menthoxy acetates of some lower alcohols are oils. Sometimes, it is found that even when crystalline, the esters cannot be separated (66).

L- Menthyl Glycine.

Although resolution is theoretically an elegant technique in organic chemistry, yet the chemist is sometimes compelled to try several resolving agents before crystalline diastereoisomers of widely differing physical properties are obtained. There is no way of foretelling the properties of the diastereoisomers, or of choosing with certainty the correct resolving agent. An extreme example of this was found by Linstead (18) when he was unsuccessful in resolving a diphenic acid or its half methyl ester, even though he used six optically active bases on each.

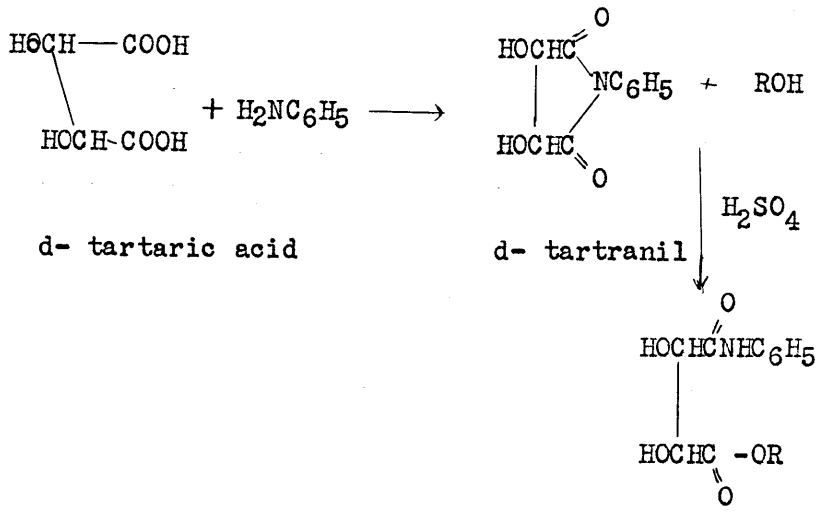
For the resolution of alcohols, the formation of l- menthyl glycine esters is a method which overcomes many of these difficulties. These are prepared by reacting the monochloroacetate of the alcohol with l- menthyl-amine. They are separated by fractional crystallization and saponified by dilute alkali to give the active alcohol and pure l- menthyl glycine which can be used again.



The advantage of this method is that if the diastereoisomeric mixture should not happen to be crystalline, salts or N- acyl derivatives can be prepared which will crystallize with the requisite difference in physical properties. Alternatively, one diastereoisomer can be purified through one salt; the mother liquor is then hydrolysed and then is converted into another salt or an N- acyl derivative which can be easily purified from another solvent. Clark and Read (67) resolved dl- menthol by this method. L- menthyl l- menthyl glycine was purified as the sulfate, and d- menthyl l- menthyl glycine as the 4-nitro benzoate. The recovered l- menthyl glycine or its N- acyl derivative was used in further resolutions, being reacted directly with the alcohol. The versatility has not yet been further extended by using other optically active amines.

D- Tartranilic Acid.

D- tartranil will react with certain alcohols forming mixtures of diastereoisomeric tartranilates. The reaction is usually acid catalysed.



The versatility can be increased by using other amines. The reagent is not recovered. The usual difficulties caused by non-reactivity of the alcohol, or failure of the diastereoisomers to separate are found with this

(c) Reaction of the Racemic Alcohol with an Optically Active Alcohol, giving an Ether.

The general reaction of an acetohalo hexose with an alcohol was used by Helferich and Hiltmann (69) for the resolution of dl-trans-cyclopentane-1,2-diol to the acetylated monoglucoside. The dl- modification was reacted with d-β-acetobromo glucose and silver carbonate. Fractional crystallization followed by deacetylation gave a product which was hydrolysed by emulsin, giving the pure dextro isomer in moderate yield.

Barry (70) has treated 1-(4-chlorophenyl)-2,2,2-trichloroethanol with d-α-acetobromo glucose, but obtained a non-crystalline product. The catalyst used was silver oxide.

(d) Miscellaneous Methods of Resolution.

There are numerous reactions attempted where but partial resolutions have been observed. Some of them are mentioned on page 12, and depend on the fact that d- and l- isomers react at different rates with another partially active reagent. The product consists of a mixture composed of a slight excess of one isomer over the other. Little time was spent on this line of research, as the separated isomers were to be tested insecticidally.

Other reactions which prepare diastereoisomers come to an equilibrium as mentioned on page 11. The equilibrium point tends to the formation of products more in the case of one diastereoisomer than for the other. Again, but not always, however, this results in but a slight excess of one enantiomorph over the other, when the product is isolated.

The following methods have given one or both of the enantiomorphs in a fairly pure condition:-

1) Sobotka and Goldberg (71) found that desoxycholic acid formed a coordination compound with many functional groups, including alcohols. They fractionally crystallized the product from dl-4-phenyl-2-butanol and desoxycholic acid and isolated one isomer optically pure by decomposition with hydrochloric acid. Partial resolutions of dl- camphor, dl- limonene, and dl- methyl ethyl acetic acid have also been obtained. Digitonin is a reagent in sterol chemistry which precipitates epimers of selective configuration. The effect was first observed by Windaus (72, 73). It was also found that digitonin precipitates the digitonide of one form of α-terpineol and ac- tetrahydroβ-naphthol, when added to a solution of the racemic form (74). There were many unsuccessful attempts made with this reagent (74, 75).

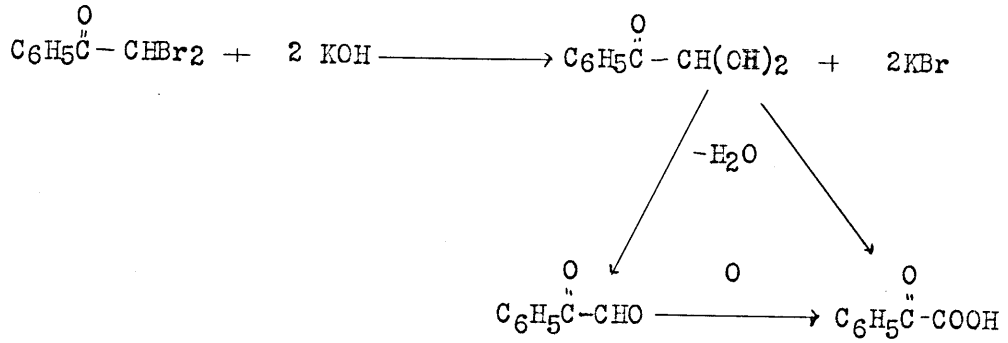
2) Mention has previously been made of two complete resolutions, using the procedure of differential adsorption on an optically active catalyst. There have been other attempts showing partial resolution using other adsorbents.

3) Asymmetric synthesis (page 12) usually gives but a slight excess of one isomer over the other, except when enzyme catalysis is used.

On the Trichloromethyl Group.

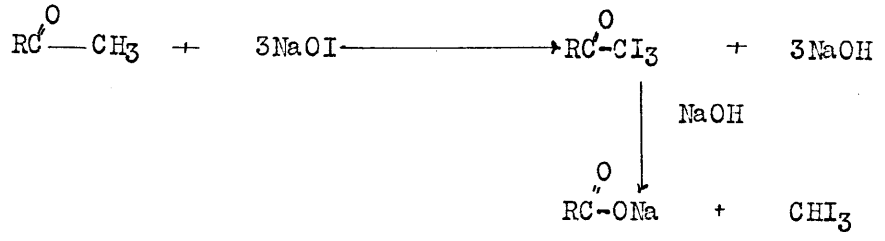
The most reactive part of the DDT molecule is the trichloromethyl group. It is decomposed in base.

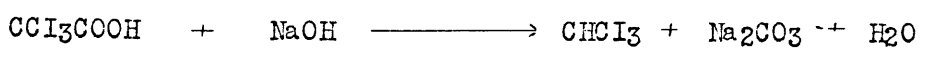
An early example of this type was the reaction of potassium hydroxide on α,α-dibromo-acetophenone. The following equation was written by Engler and Wohrle (76) -



Many thousands of replacements of one or more halogen atoms by an - OH group have been recorded. If two halogens are on the same carbon atom, the product isolated has lost the elements of water.

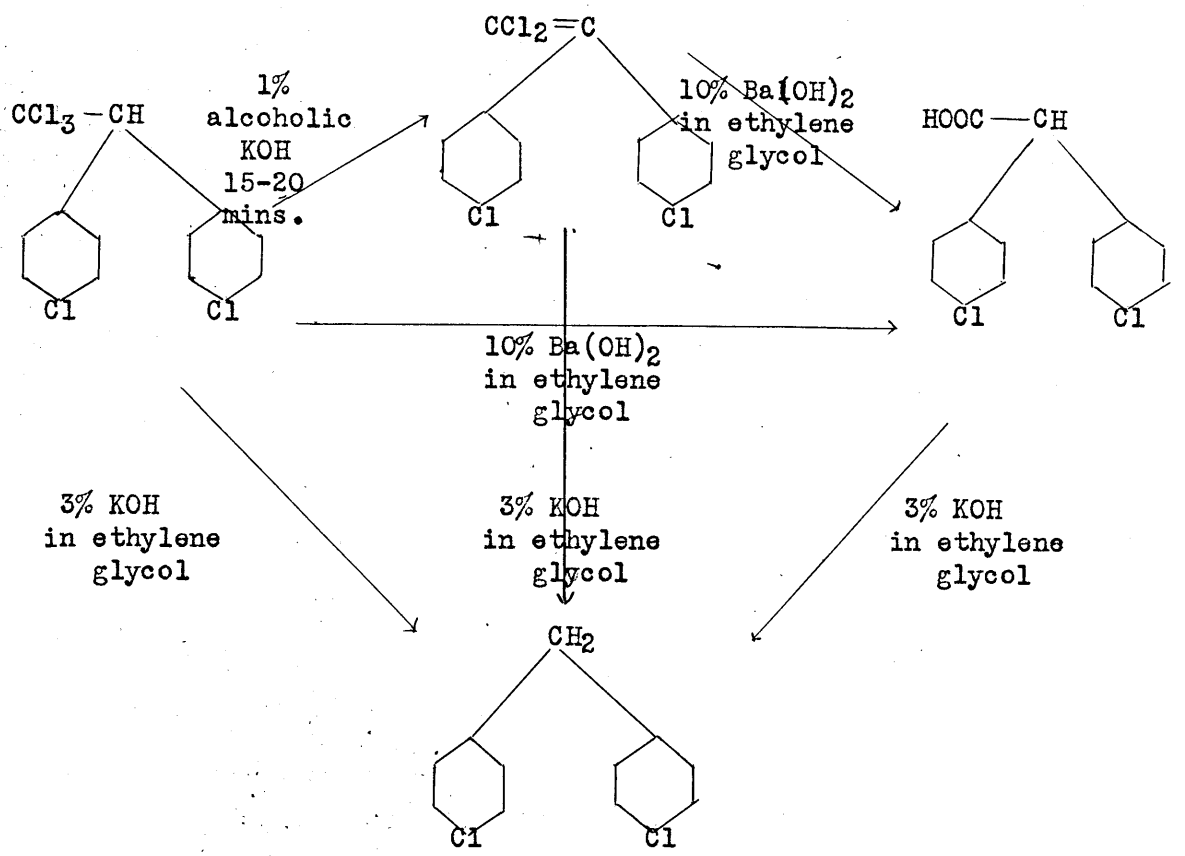
Another type of reaction is that called the haloform test. Here, all compounds which contain, or can be converted into, the acetyl group, undergo reaction with sodium hypoiodite.





This reaction has been reviewed by Fuson and Bull (77).

The DDT molecule has been found to undergo a systematic degradation in basic solution by White and Sweeney (78).



Cristol & Haller (79) have continued this work.

On the Acid Hydrolysis of Esters.

Because of the deleterious effect of aqueous basic solutions on the trichloromethyl group, a survey was made of methods for the acid hydrolysis of esters.

$$RCOOR^1 + H_2O \xrightarrow{\text{acid}} RCOOH + R^1OH$$

Many workers have come to the realization that in this reaction, the link broken is the oxygen-acyl link and not the oxygen-alkyl. Strong evidence for this was obtained by Ingold and Ingold (80). They hydrolysed the acetate of butene-2-ol-1(crotylacetate) and the acetate of 1-methyl propene-2-ol-1(α-methyl allyl acetate) and found that the corresponding alcohols were produced. The work of Burton (81) indicates that if a crotyl or an α-methyl allyl carbonium ion were formed, the same mixture of products would result from each alcohol. In other words, the oxygen-alkyl link would have been broken.

$$CH_3 - CH = CHCH_2\text{-}OCOCH_3 \longrightarrow CH_3\,CH = CHCH_2OH$$

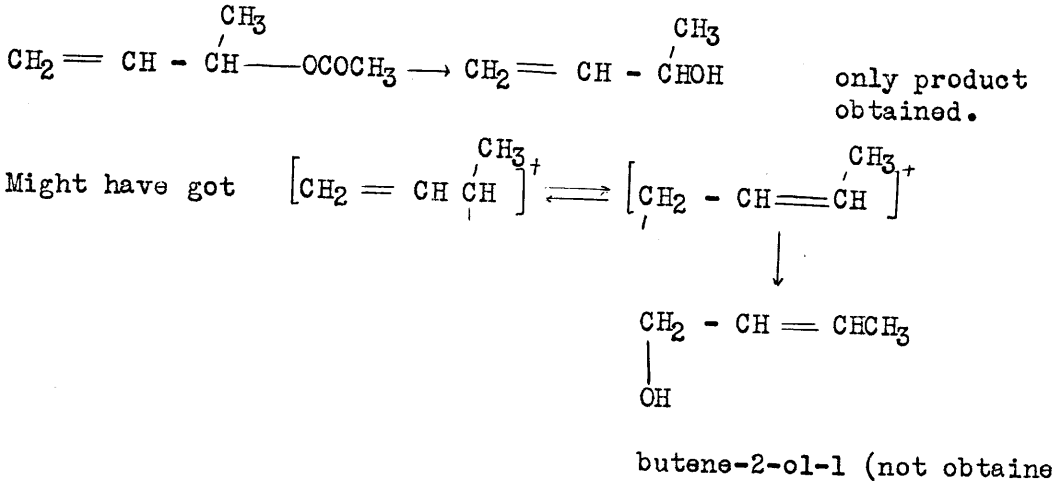
butene-2-ol-1

only product obtained.

Might have got $\left[CH_3CH = CHCH_2\right]^+ \rightleftharpoons \left[CH_3CH - CH = CH_2\right]^+$

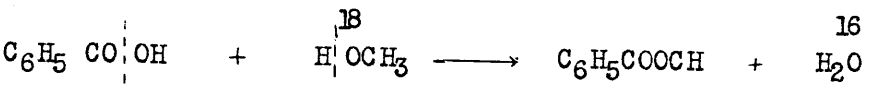
$$CH_3CH(OH) - CH = CH_2$$

1-methyl propene-2-ol-1
(not obtained)

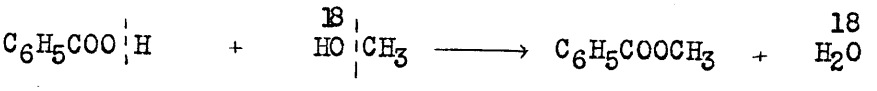


The most conclusive proof of the link severed in acid hydrolysis was furnished by Roberts and Urey (82). They performed the esterification of benzoic acid with methanol which contained oxygen 18, and found that the water eliminated had the normal oxygen composition.

The reaction must have been -

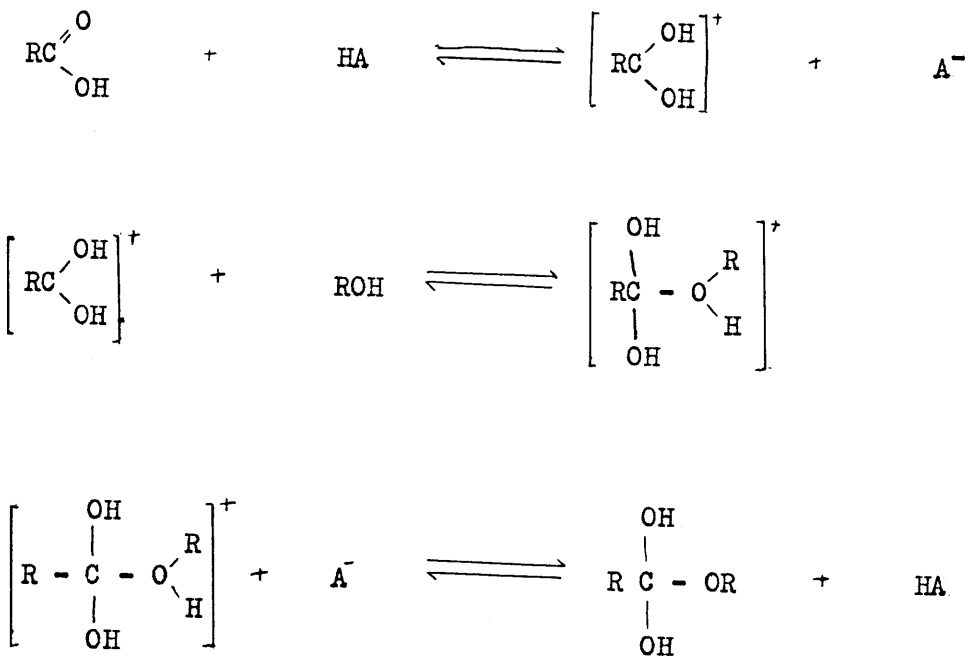


and not -



The proof for the hydrolysis reaction was furnished by Polanyi and Szabo (83). The saponification of pentyl acetate (amylacetate) in heavy water gave pentanol of normal oxygen composition.

The mechanism for the acid hydrolysis of esters was formally stated by Hammett (84) as follows -



The ester is then formed by a series of reactions analogous to the reversal of the process but with HOH instead of ROH splitting off. This equilibrium is made essentially complete in either direction by the addition of water or alcohol.

Methods Used in Acid Hydrolysis of Esters.

Houben and Weyl (85) summarize the common methods of hydrolysis by acids. Hydrochloric or sulfuric acids in dilute aqueous or alcoholic solution are often chosen as catalysts. When the hydrolysis is slow and the products are stable, these acids are used at steam bath temperatures in the concentrated aqueous form. The products can be isolated after diluting with water (86, 87). For quantitative kinetic studies, Timm and Hinshelwood (88) found benzene sulfonic acid useful. At steam bath temperatures, it usually does not esterify the alcohol product or one used as a solvent. A note by Ott (89) tells how aluminium chloride catalyses the hydrolysis of esters untouched by boiling alkali over many hours. When certain esters of tetraethyl succinic acid are fused with a little aluminium chloride, alkyl halide is immediately given off. Ethyl succinic anhydride is found as the residue.

A paper on the general catalytic of zinc salts in acid hydrolysis was published by Andreicheva (90). He states that zinc ion (Zn^{++}) always hastens hydrolysis when no other reaction interferes. Zinc nitrate shows positive catalysis, zinc sulfate negative. The catalytic effect depends very little on the concentration of zinc ion.

Very little is known of the acid hydrolysis of urethanes, esters of carbamic acid. Basic hydrolysis, although almost universally used, is not satisfactory for compounds containing a trichloromethyl group. For each example of the resolution of alcohols by this method (52, 53), hydrolysis was achieved by refluxing many hours with alcoholic solution of potassium

hydroxide. Except in these cases, urethanes have not been hydrolysed with the aim of preparing large alcohols. Usually the amine is the material sought. In an article by Jeffreys (91) is given a synthesis of pentadecyl amine. This is obtained quantitatively from the distillation of pentadecyl ethyl urethane from three or four times its weight of calcium hydroxide.

$$C_{15}H_{31}NHCOOCH_3 + Ca(OH)_2 \longrightarrow C_{15}H_{31}NH_2 + CaCO_3 + CH_3OH$$

They also say that poorer yields can be obtained by heating with concentrated hydrochloric acid in a sealed tube for five hours, at 200°C or by heating in an open container at 100°C for one hour with concentrated sulfuric acid.

On Carbonium Ion Reactions.

The existence of Carbonium Ions.

The possibility of the ionization of carbon compounds was first suspected from studies on triphenyl methyl chloride. This compound dissolves in chloroform, benzene, and ethyl acetate with the formation of colourless non-conducting solutions. However, it dissolves in sulfur dioxide giving a deep yellow colour (92). The resulting solution is an excellant electrical conductor. A solution in cresol behaves similarly. (93). Triphenyl methyl chloride is classed as a pseudo electrolyte, one which ionizes under the influence of a shared electron bond.

If to a colourless solution of the chloride in a non-ionizing solvent, is added stannic chloride or aluminium chloride, a coloured conducting solution is obtained (94, 95, 96). The most probable course of the reaction is as follows -

$$(C_6H_5)_3\ CCl + Sn\ Cl_4 \rightleftharpoons (C_6H_5)_3\ C^+ + Sn\ Cl_5^-$$

The formation of the charged stannic complex is well known in inorganic chemistry. The positively charged particle is triphenyl carbonium ion. Solvents which cause the ionization of the triphenyl methyl chloride to take place are considered to react as do the inorganic chlorides.

Triphenyl carbonium ion is also produced by the action of a very strong acid on triphenyl methanol. The resulting solution has light absorption identical with the solutions from the other sources (93). Its molecular freezing point depression is four times that of a non-electrolyte (97)(98), indicating that the following has occurred

$$(C_6H_5)_3\ COH + 2H_2SO_4 \rightleftharpoons (C_6H_5)_3\ C^+ + OH_3^+ + 2HSO_4^-$$

The situation is different when methyl and ethyl alcohols are treated with concentrated sulfuric acid. The molecular freezing point depression is only three times that for a non-electrolyte.

$$CH_3OH + 2H_2SO_4 \rightleftharpoons CH_3SO_4H + OH_3^+ + HSO_4^-$$

Triphenyl methanol ionizes in formic acid solution -

$$(C_6H_5)_3 - COH + HCOOH \rightleftharpoons (C_6H_5)_3\,C^+ + HCOO^- + H_2O$$

and in sulfur dioxide solution -

$$(C_6H_5)_3 - COH + SO_2 \rightleftharpoons (C_6H_5)_3\,C^+ + HSO_3^-$$

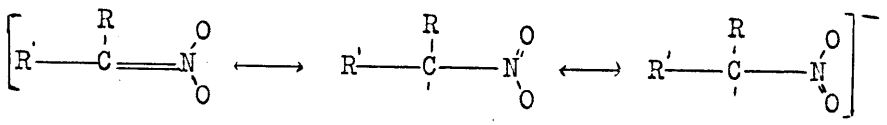
In such cases as the above, the existence of carbonium ions (and carbanions)can be directly demonstrated because they are stabilized by resonance, and their concentration becomes large. However, the work of Whitmore (99) on rearrangement mechanisms, of Gleave, Hughes and Ingold (100) on the mechanism of substitutions, and Arndt and Eistert (101) on the mechanism of the Claisen Condensation indicates that they probably appear as transient intermediates in the course of reactions that lead from non-ionic reactants to non-ionic products.

The Structure of Carbonium Ions (and Carbanions).

When an asymmetric carbon atom has one of its four attached groups removed, one of three situations may arise. (1) The remaining three groups may retain essentially their original configuration, in which case the ion or radical formed will be capable of optical activity. If this is so, the product formed from an active reactant by way of the ion or radical will be active. (2) The ion or radical may settle down in a form in which the three groups on the central carbon atom lie in one plane. Since this is a plane of symmetry, there is no possibility of activity in the product.

(3) The asymmetric form may be stable, but the energy of activation required to convert one enantiomorph into the other may be so small that the molecule oscillates between the d- and l- forms.

For carbanions, there are a few examples of retention of optical activity in the free form. The most notable example is the sodium salt of 2-nitro-butane (102), whose modern structure is the following

hybrid 

The acid function is shown by the left hand structure, and the asymmetry by the other two. Two other cases of optically active carbanions have been reported (103, 104). There is no direct evidence for the existence of optically active carbonium ions or free radicals.

The Mechanism of the Reaction between Alcohols and Benzene to give Nuclear Alkylated Aromatics, in Presence of Electrophilic Catalysts.

This discussion will be restricted to a consideration of the information obtained when optically active alcohols are used in nuclear alkylation. Prior to their use, the reactions had been studied for the condensation of benzene and propanol-2, in the presence of 70 to 80 percent sulfuric acid, by Meyer and Bernhauer (105). A similar series of reactions, catalysed by 96% sulfuric acid, were performed by Chattaway and Muir (6). They condensed substituted 1-halophenyl-2,2,2-trihaloethanols with substituted benzenes to get unsymmetrical diaryl ethanes. The same type of condensation may be brought about by boron trifluoride (106, 107), or by aluminum chloride (108), or by hydrogen fluoride (109).

McKenna and Sowa (110) felt that the products of alkylation of benzene with alcohols all indicated that an unsaturated compound was first formed. This was followed by condensations into the aromatic nucleus -

$$CH_3\,CH_2\,CH_2\,CH_2\,OH \longrightarrow CH_3\,CH_2\,CH{=\!=\!=}CH_2 + H_2O$$

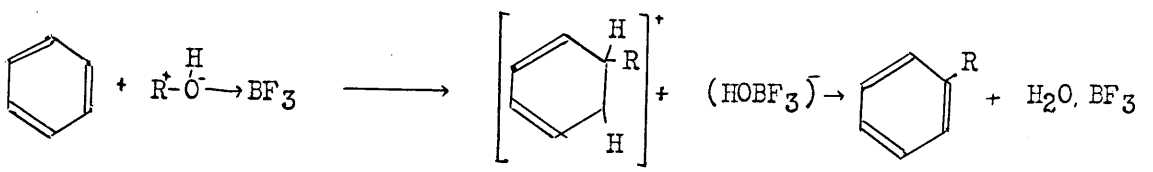
$$CH_3\,CH_2\,CH{=\!=}CH_2 + C_6H_6 \longrightarrow CH_3\,CH_2\,CH(CH_3)\!-\!\!-\!\!-C_6H_5$$

There are three pieces of evidence against this mechanism. The first, reported by Price and Ciskowski (111), is obtained from the very easy condensation of cyclohexanol and naphthalene, catalysed by boron trifluoride. They found that cyclohexanol is recovered quantitatively after treatment with boron trifluoride under conditions considerably more drastic than those required for alkylation.

Price and Ciskowski also mention another result controverting the existence of an unsaturated intermediate. They found that nuclear alkylation of aromatics by benzyl alcohol took place very easily. Benzyl-alcohol cannot form an olefin however. They put forward a mechanism, and modified it in a later paper (112), to read -

$$ROH + BF_3 \rightleftharpoons \overset{H}{\underset{|}{RO}} \rightarrow BF_3 \rightleftharpoons (ROBF_3)^- + H^+$$

$$\rightleftharpoons \overset{H}{\underset{|}{R^+\!-\!O^-}} \longrightarrow BF_3$$



The alcohol-boron trifluoride addition complex is a strong acid, and, therefore, has a weak OH bond. We may presume that it has a weak OR bond, and that there will be a tendency for the carbonium ion R^+ to exist.

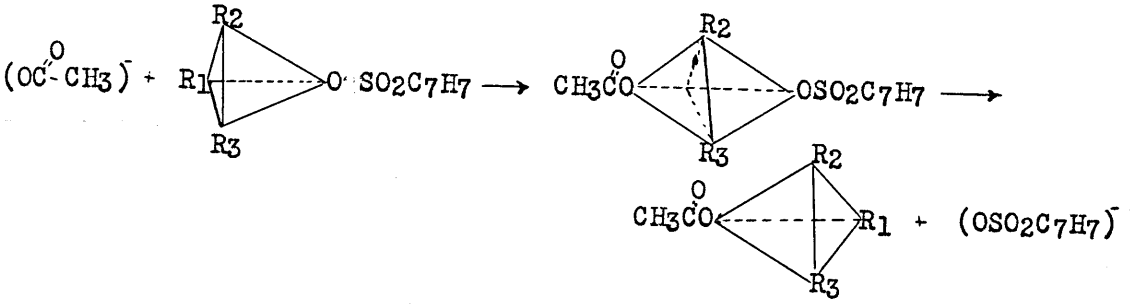
This mechanism was developed to explain an experiment which definitely disproves the presence of an unsaturated intermediate. An optically active 2-phenyl butane ($[\alpha]_D$: 0.15° and 0.16°) was prepared from d-butanol-2 ($[\alpha]_D$: 11.05° and 11.36°). Burwell (113) used other catalysts and found an aromatic product of very small, but appreciable rotation. He calculated the fractional maintenance of configuration from the rotation of pure 2-phenyl butane ($[\alpha]_D$: 23° . .) (114) (115).

Catalyst	Observed rotn. of 2-phenyl butane	Fractional Maintenance of Configuration
hydroflouric acid	0.17°	0.0072
sulfuric acid	0.08	0.0034
phosphoric acid	0.15	0.0064
boron trifluoride	0.17	0.0072

The product has suffered a great deal of racemization, and, therefore, the alcohol has existed as a carbonium ion for an appreciable time. Burwell points out that the life of the intermediate (R^+) should not be many times the period of one molecular vibration. A small proportion of the ions would then react so soon after formation as to give a final product with a slight excess of one configuration.

This mechanism is very different from that now given for Walden Inversion. A clear cut example of this is the conversion of the 4-toluene sulfonate of 1-methyl-2-phenylethanol ($[\alpha]_D$: 31.11°) to the acetate

($[\alpha]_D$ = 7.06°) by reaction with potassium acetate (40). This has been proved an inversion with no racemization by observing the optical rotation of the reactant and product alcohols. The mechanism given for it and all other complete Walden Inversions is as follows -



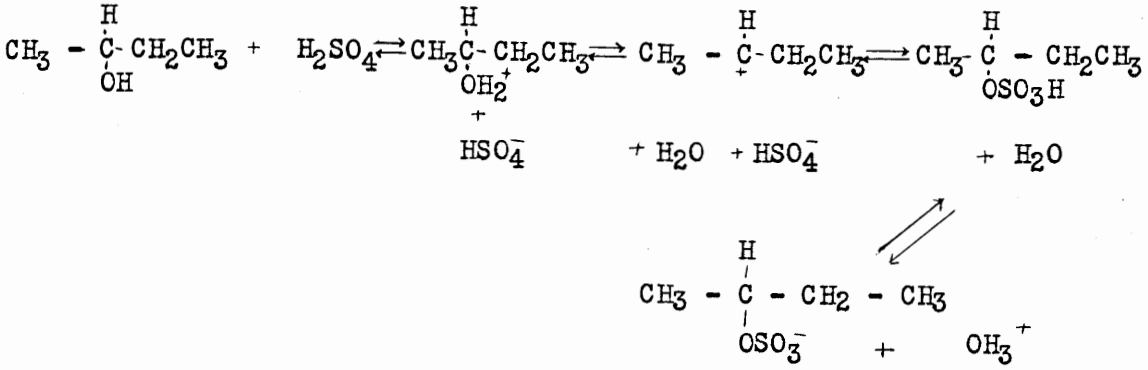
There is no formation of carbonium ion. The acetate approaches as the tosyl ion recedes.

Some information on the maintenance of configuration of d-butanol-2 in sulfuric acid was obtained by Burwell (48). He prepared barium d-butyl sulfate with three different catalysts

Rotation of alcohol	Catalyst	Rotation of Ba.Salt.
$[\alpha]_D$ +5.29°	dioxane sulfotrioxide	$[\alpha]_D$ +4.34
+5.29	chlorosulfonic acid	+0.50
-2.09	sulfuric acid	-0.38

There is no proof of the absolute configuration of the product, either here or in the case of nuclear alkylation. Even though the configuration of the alcohol had been apparently maintained, there was considerable racemization in the highly acid media. Dioxane sulfotrioxide, a medium of low acidity, greatly reduced racemization. This configurational instability in acid medium was shown by an attempted hydrolysis. In neutral solution, the salt was stable, and was recovered unchanged. The reaction went easily in acid, giving an alcohol with but 30 percent of its original rotation.

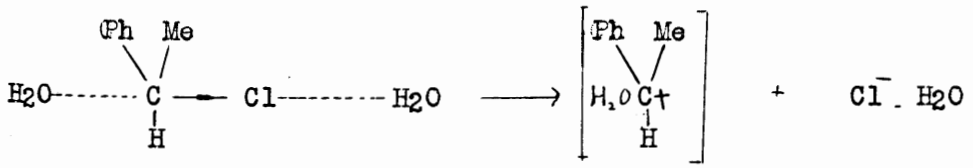
The following mechanism was proposed by Burwell (48) -

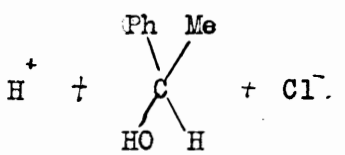


Acid conditions appear to favour the formation of the carbonium ion , which is followed by the usual racemization.

A Short Consideration of the Mechanism of the Hydrolysis of Alkyl Halides.

The observation was made on phenyl methyl chloromethane that it was hydrolysed to the alcohol with considerable, but not complete, racemization (123). A carbonium ion was indicated as the intermediate. Ogg and Polanyi (125) point out that the transition to the ionic state can only take place if both ions are formed as hydrates, or otherwise the activation heat would be inaccessibly high. This had previously been pointed out by Olsen and Voge (126) and Hughes and Ingold (124). At the moment of its formation, the carbonium ion can add a water molecule only on its side opposite the halogen link. Therefore, it is to this side that the hydroxyl group formed on decomposition of the carbonium hydrate, will become linked.





When the ionization to a carbonium ion occurs, it is the rate determining step. When this happens complete racemization should occur. Hammett (127) says that the inversion can be accounted for by supposing that the reaction of the carbonium ion and solvent molecule occurs after ionization has taken place, but while the two ions are still so close together that the halide ion shields the carbonium ion against attack from the side from which the halide has separated. The racemized product is then attributed to the cases in which reaction occurs after a separation of the ions. Hammett emphasizes the difference between the solvation of the halide ion, with the accompanying electronic redistribution and probable shift in the relative positions of the nuclei, which converts the homopolar alkyl halide to an ion pair, and the subsequent separation of the ion pair.

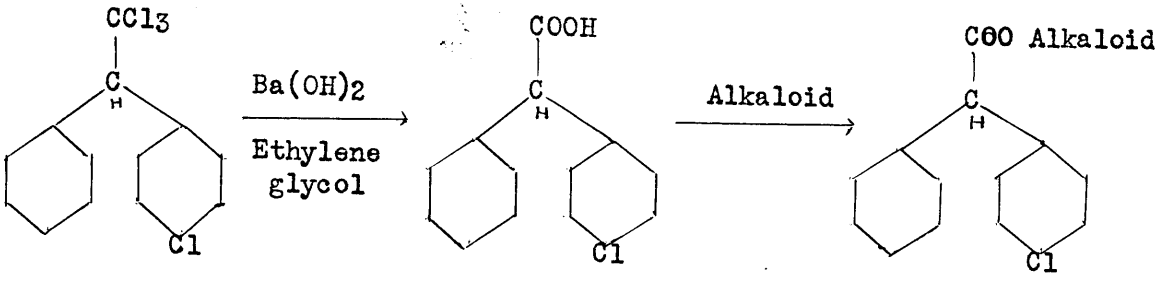
DISCUSSION

The Conversion of Optically Active 1-(4-chlorophenyl)-2,2,2-trichloroethanol to 1-(4-chlorophenyl)-1-phenyl-2,2,2-trichloroethane.

The condensation of the dl- alcohol with benzene by means of 96 percent sulfuric acid was carried out. The product melted at 76.5 - 77°C, two degrees higher than reported by Chattaway and Muir (6). The yield of crude product was almost quantitative. The dl- alcohol acetate underwent conversion to the same product in about 80 percent yield.

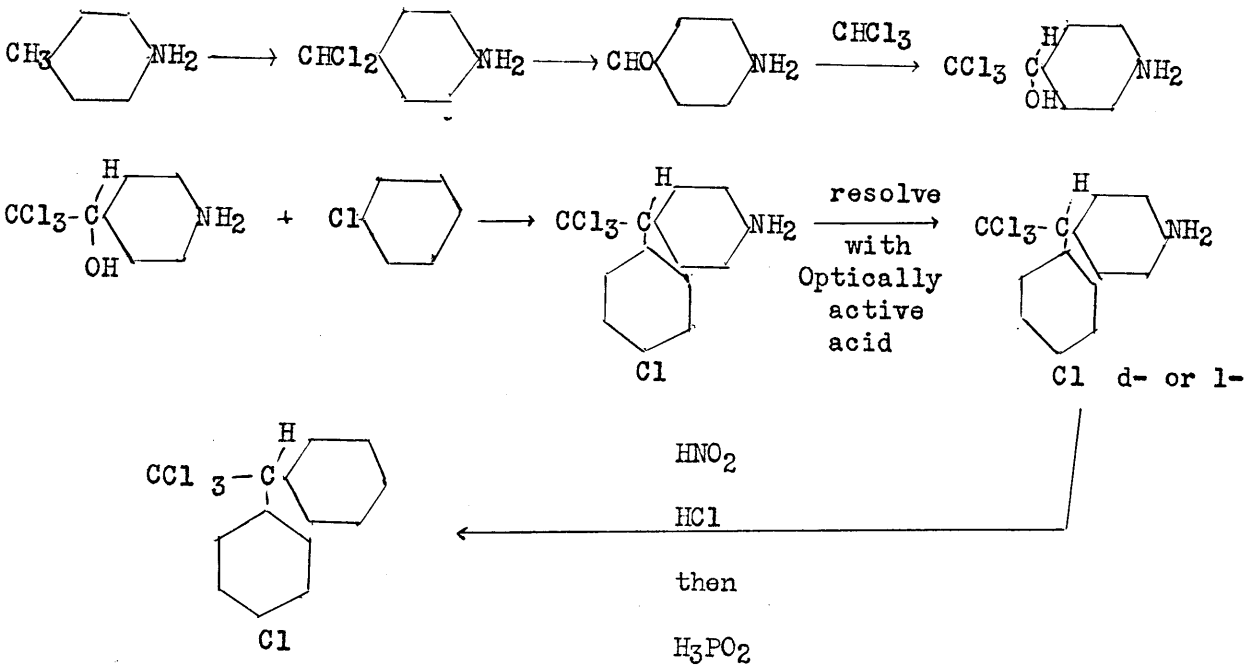
The product contained an asymmetric carbon atom and, therefore, was theoretically resolvable into optical isomers. The condensation was performed with l- alcohol ($[\alpha]_D = -33.8°$). The product had a slight optical rotation $[\alpha]_D = +2.2°$. The product from the conversion of the l- acetate ($[\alpha]_D = -61.5°$) had no detectable rotation.

In the case of butanol-2, discussed above (113), the alkyl benzene had a small rotation, but this could be shown to be a product of 99% racemization, for the d-2-phenyl butane had been completely resolved by other methods (114, 115). In the present case such a separate resolution must await the preparation of optically pure Baeyer product. An indication of the extent of racemization, if any, could be obtained by treating the acid obtained by hydrolysis of the trichloro-methyl group with an optically active base. The separation and determination of the amounts of the diastereoisomers will give an indication of the amount of racemization that has taken place. An optically pure Baeyer product will, of course, give but one diastereoisomer.

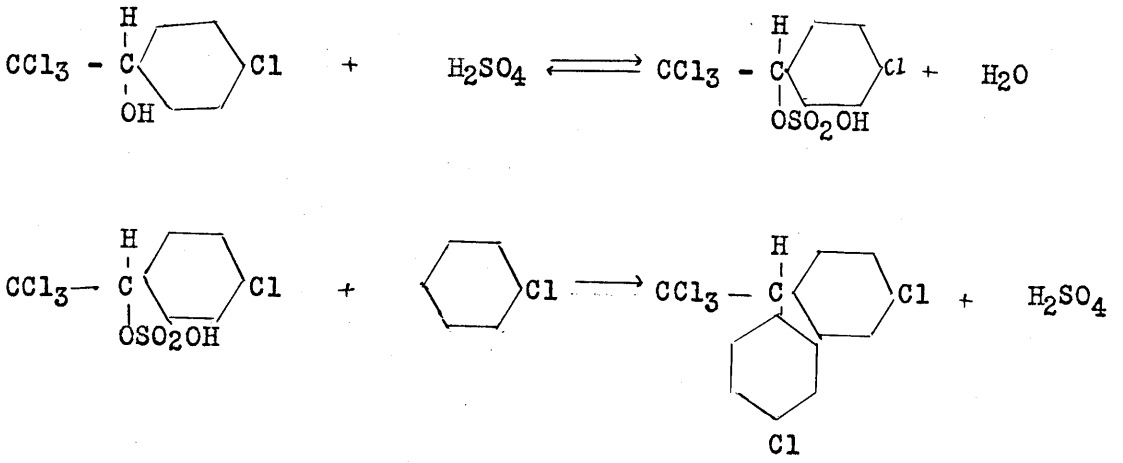


dextro dextro d alkaloid d Baeyer. (+ d alkaloid l Baeyer, if product is a racemic modification.)

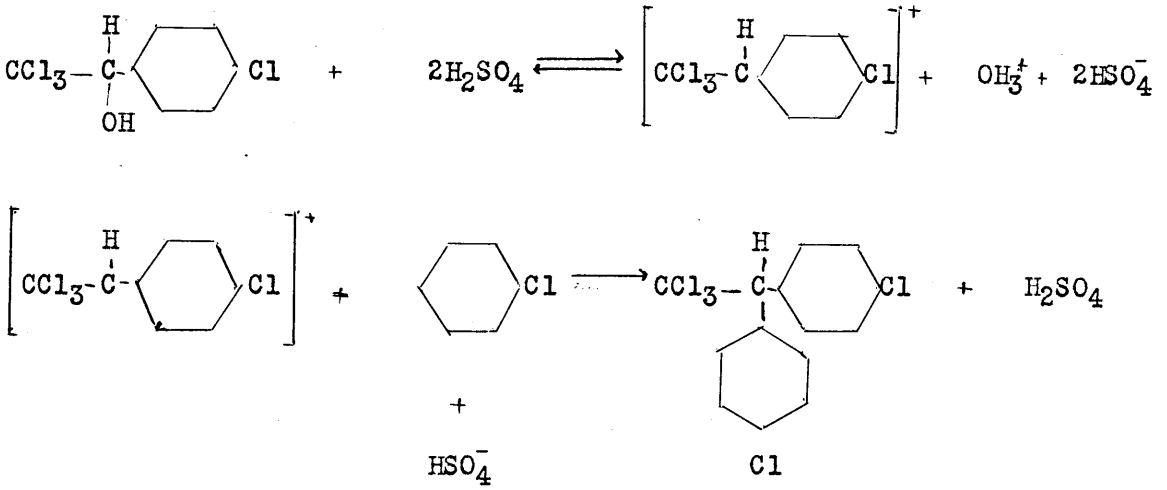
A better method of determining the extent of racemization would be, of course, to resolve the Baeyer product, and determine its rotation. Such a step might be performed as follows:-



For the conversion of the alcohol to DDT, the following mechanism has been advanced (116, 117)



A slightly modified version was presented by Garmaise (3) -



This mechanism emphasizes the importance of the carbonium ion as an intermediate structure. Information about its existence free in the reaction mixture can be obtained from two sources:-

(1) Examination of the optical purity of the product obtained from the d- and l- alcohols.

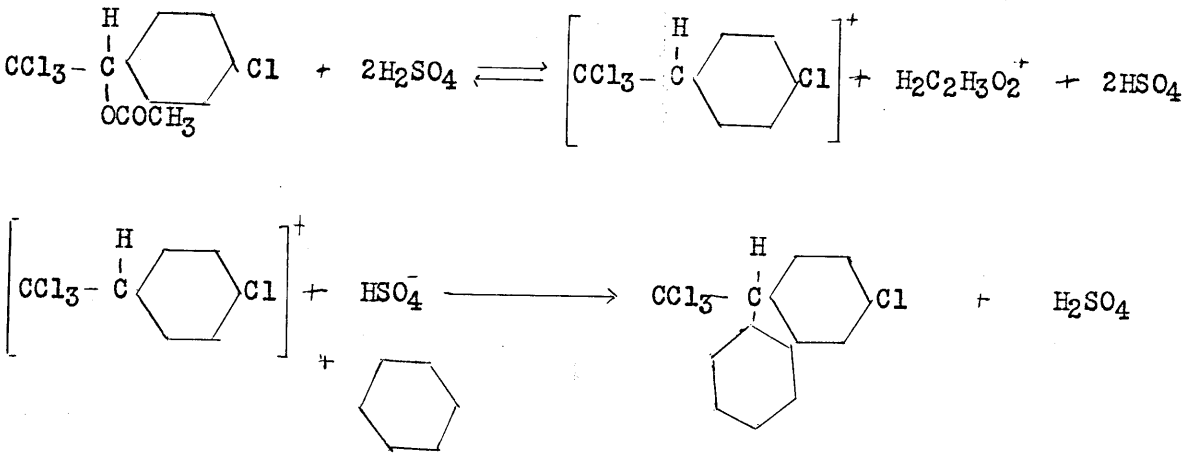
(2) Determination of the molecular freezing point lowering of a solution of the alcohol in sulfuric acid. As shown on page 35, the existence of a carbonium ion can be demonstrated for a triphenyl methanol solution in

sulfuric acid by its having a value four times that of a non-electrolyte. No carbonium ion exists in a methanol solution, for its molecular freezing point lowering is but three times that of a non-electrolyte.

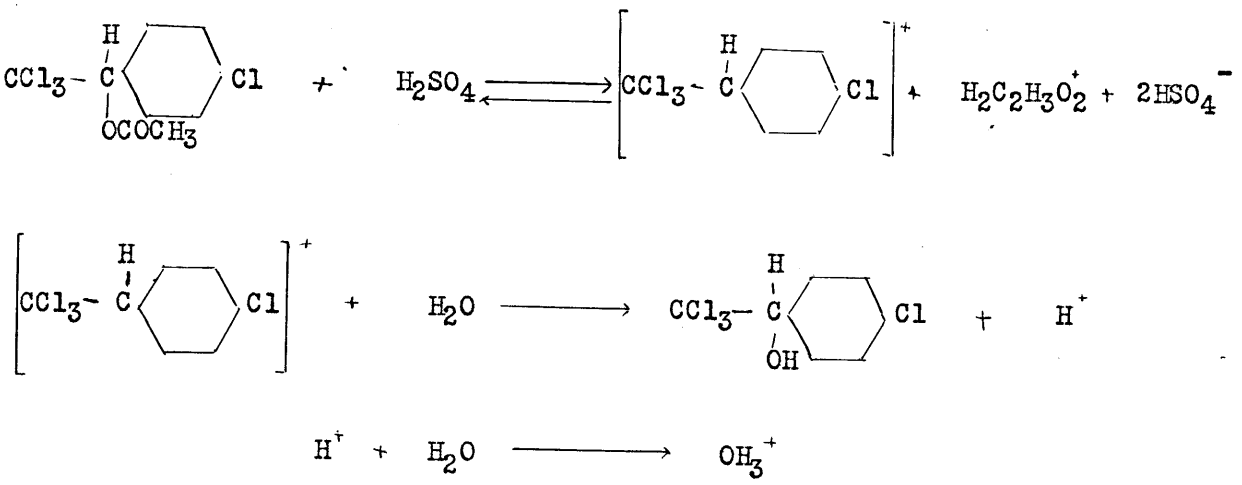
$$(C_6H_5)_3\,COH + 2H_2SO_4 \rightleftharpoons (C_6H_5)_3\,C^+ + OH_3^+ + 2HSO_4^-$$

$$CH_3OH + 2H_2SO_4 \rightleftharpoons CH_3HSO_4 + OH_3^+ + HSO_4^-$$

The conversion of the acetate to DDT and analogues can probably be shown as follows -



The above intermediate is the same as that given for the alcohol. It is felt that some evidence for this is obtained from the hydrolysis of the acetate, which was accomplished with concentrated sulfuric acid. This can be postulated as follows:-

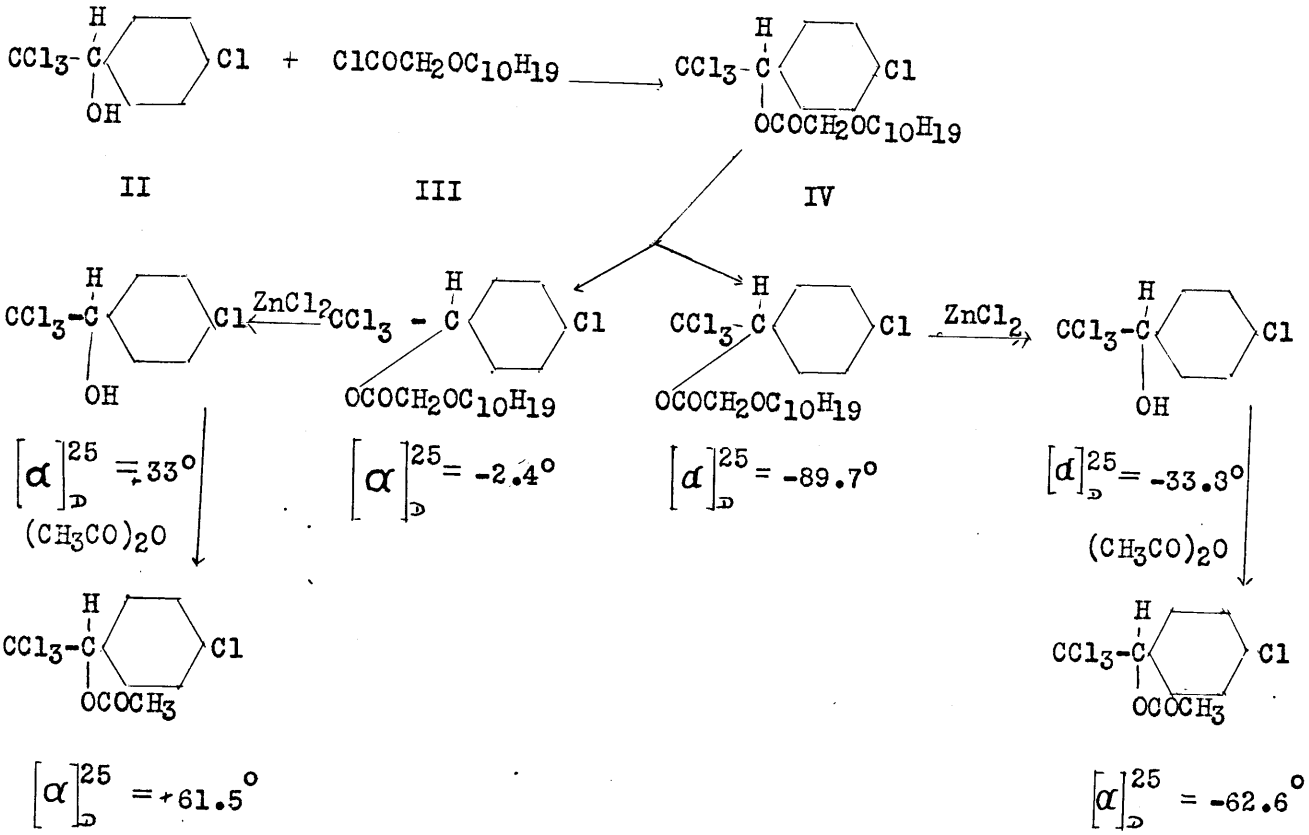


Eastwood (118) has prepared the barium hydrogen sulfate of the alcohol by its reaction with dioxane sulfotrioxide and converted it to DDT with no added catalyst. Information similar to that obtained by Burwell for d-butanol-2, could be obtained for the optical stability of this alcohol in sulfuric acid solution, by performing this reaction on the optically active alcohol, and converting the product to DDT. This product, in contrast to that from the sulfuric acid condensation, might have considerable rotation.

An Account of the Difficulties Encountered in the Resolution of 1-(4-chlorophenyl)-2,2,2-trichloroethanol into its Optical Isomers.

The successful resolution using l- menthoxy acetyl chloride.

The resolution of 1-(4-chlorophenyl)-2,2,2-trichloroethanol (II) was accomplished by fractional crystallization of its l- menthoxy acetate (IV). The yields of active alcohols were very low, for both the fractionation and subsequent hydrolysis was accomplished in poor yield.



The preparation of the menthoxy acetates was performed by dissolving l- menthoxy acetyl chloride and the alcohol in equivalent amounts in benzene. Excess pyridine was added, and a quantitative yield of pyridine hydrochloride was removed by filtration. Crystals of the l- menthoxy acetates of the

dl- alcohol were then isolated. When the reaction was performed in pyridine solution, only a non-crystalline oil could be isolated, even though the solution of the product in ether was washed thoroughly with dilute aqueous acid and base.

Although a quantitative yield of crude dl-1-(4-chlorophenyl)-2,2,2-trichloroethyl-1-menthoxy acetate was obtained, the loss on fractional crystallization, especially on the first crystallization, was heavy. This had also been found in the resolution of dl- menthol (59). The least soluble diastereoisomer, the l- menthoxy acetate of the l- alcohol, was isolated in 28% yield and had a specific rotation $[\alpha]_D^{25} = -89.7^\circ$ in chloroform.

As the other diastereoisomer was contaminated with a strongly laevorotatory material, prolonged fractional crystallization was necessary for its isolation. Eventually it was obtained in 8.1% yield, and had a specific rotation of $[\alpha]_D = -2.4^\circ$.

The hydrolysis of the diastereoisomers was performed in methanol solution using zinc chloride catalysis. The method was adapted from an article describing the general effect of zinc salts in acid catalysis (90). It was first used on the unsubstituted acetate of the alcohol, and a nearly quantitative yield of crude crystalline alcohol was obtained. When the method was applied to the hydrolysis of the l- menthoxy acetates, the yield was around 25%. The yield was determined by conversion of the oily alcohol, which contained l- menthoxy acetic acid, to the acetate, weighed after several recrystallizations.

The constants of the acetates were -

$[\alpha]_D^{25}$ = 61.5° and -62.6° in chloroform

M.P. = 91 - 92.5° 91 - 93°

These were converted to the free alcohols by hydrolysis with zinc chloride, and the crystalline optically active alcohols were obtained in about 80% yield.

The constants of the alcohols were -

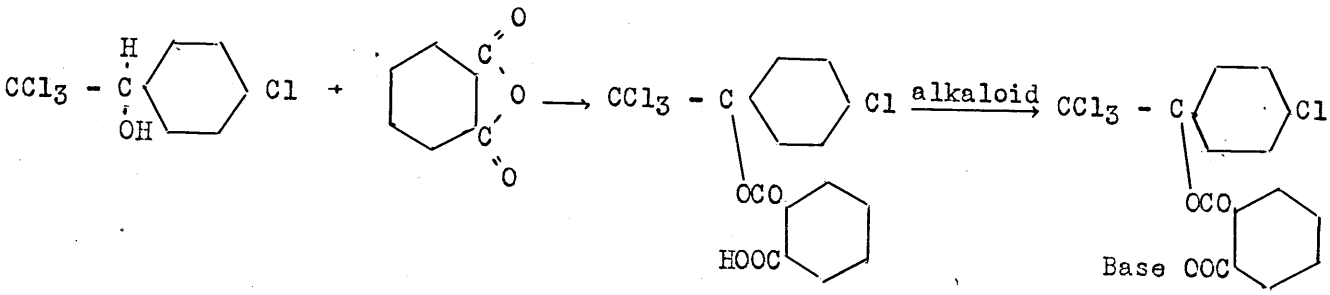
$[\alpha]_D^{25}$ = 33.0° and -33.8° in chloroform

M.P. = 50 - 52°C and 51.5 - 53°C

It was considered that the use of a dextro resolving agent would facilitate the production of the d- alcohol in better yield. So d-bornoxy acetyl chloride was substituted for the l- menthoxy in the above reaction. The compound dl-1-(4-chlorophenyl)-2,2,2-trichloroethyl-d-bornoxy acetate was obtained in crystalline form, and crystallized to constant melting point and rotation. Hydrolysis and conversion to the acetate with acetic anhydride was then performed. Only the inactive product, identical with the original alcohol acetate, was obtained. The diastereoisomers had not been separated on recrystallization.

Unsuccessful Attempts at Resolution.

Acid Ester of Alcohol with an Alkaloid.



Many unsuccessful attempts were made to prepared the acid ester of the alcohol. Equimolar quantities of the alcohol and the anhydride of phthalic or succinic acid were heated together with or without pyridine. Then water was added to precipitate the organic material as an oil, which was thoroughly extracted with chloroform. The chloroform solution was thoroughly extracted with 10% aqueous sodium carbonate. Acidification of this solution yielded only phthalic acid, which presumably was dissolved in the chloroform as the anhydride. The chloroform solution was dried and the solvent removed by distillation. An acetone solution of the residual oil was titrated with 0.1 N sodium hydroxide, but only a small fraction of the organic oil was titratable. The base absorbed was probably due to the presence of phthalic anhydride.

In a paper by Fessler and Shriner (39) are listed some acid tetrachlorophthalates that are insoluble in 5% sodium hydroxide. All the phthalates used by Pickard and Kenyon (28) or Levene and co-workers (29) were soluble in aqueous sodium carbonate. Stress was laid on the solubility, for it enabled the acid ester to be purified by extraction of the other organic material from the aqueous alkaline solution with ether. However, on the

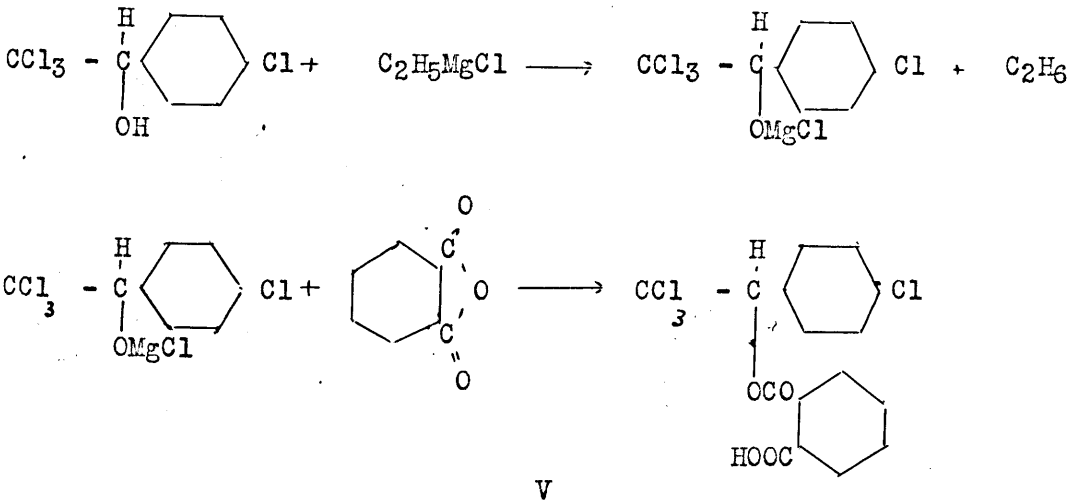
chance that the product from the experiment was the acid phthalate, in spite of its base insolubility, it was dissolved in boiling acetone with an equivalent of brucine. No crystalline salt could be precipitated, however.

The phthalic anhydride was still present in a large amount when the reaction was preformed in a sealed tube at 100°C for 16 hours. A similar treatment at 200°C caused decomposition of the alcohol with loss of hydrogen chloride gas. Use of catalysts other than pyridine did not bring about the condensation.

It was attempted to prepare the sodium derivative of the alcohol for condensation with phthalic anhydride, but only sodium chloride was obtained.

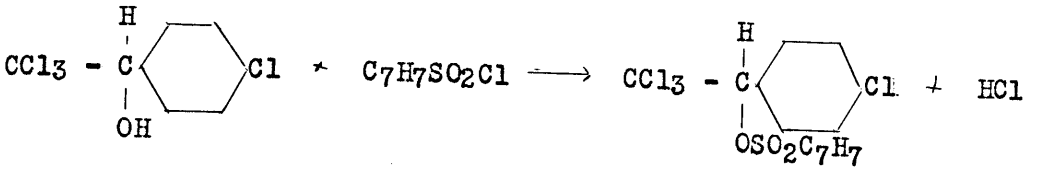
Miscellaneous Indirect Attempted Esterifications.

Fessler's and Shriner's procedure (39) was attempted in the preparation of the acid phthalate (V). The alcohol was converted to the alkoxy magnesium halide, which was then stirred with phthalic anhydride. A mixture of products, none of which was acidic, was obtained. The reaction attempted was -

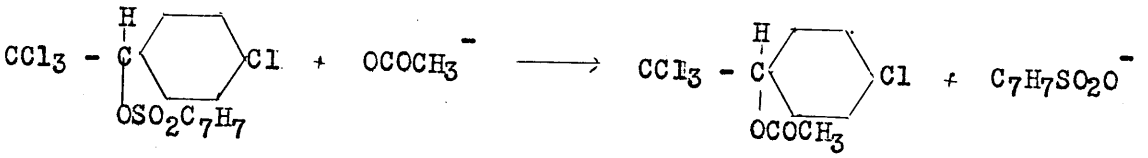


V

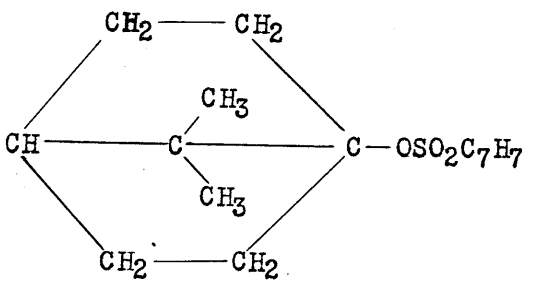
The alcohol was converted to its 4- toluene sulfonate ester (VI), and a few unsuccesful attempts were made to replace the tosyl radical by the anion of a carboxylic acid.



VI

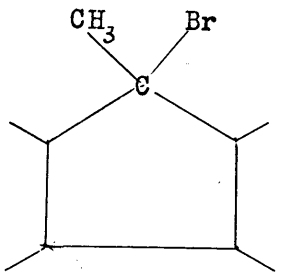


This reaction had been reported for 1-methyl-2-phenyl ethanol (40) and other secondary alcohols. However, the reaction is easily hindered by steric effects. Lithium chloride and potassium acetate were tried. Potassium acid phthalate was also used, although it had not been reported previously. The tosyl ester was recovered, however. Bartlett (119) says that the failure of the ester(VII)to undergo conversion to an acetate is due to the cage of carbon radicles which prevent the apprcach of the displacing ion.

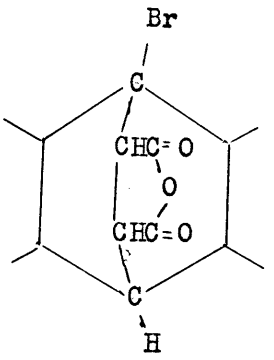


VII

It is possible that the space-filling trichloromethyl group might do the same. Bartlett says that the compound is reactive when it undergoes reactions that do not depend on displacement mechanisms. The point is clearly illustrated also by the reactivity of the bromine in VIII and its unreactivity in IX (120).



VIII



IX

A few attempts were made to prepare acid sulfates of the alcohol with sulfuric acid. The method was not pursued extensively, for all reports (32, 48) said that the hydrolysis of such structures was followed by much racemization. Eastwood (118) prepared the sulfate with dioxanesulfotrioxide, and converted it to DDT with chlorobenzene.

Maleic anhydride was recovered as the acid after it was heated with the alcohol for several hours. This is not surprising, as the same effects hindering the reaction of phthalic and succinic anhydrides would surely apply here.

Oxalyl chloride can be used to prepare diesters if the reaction is run at 0°C in pyridine. Adams and Gilman (121) prepared diphenyl oxalate by this method. A reaction was attempted between one mole of the alcohol

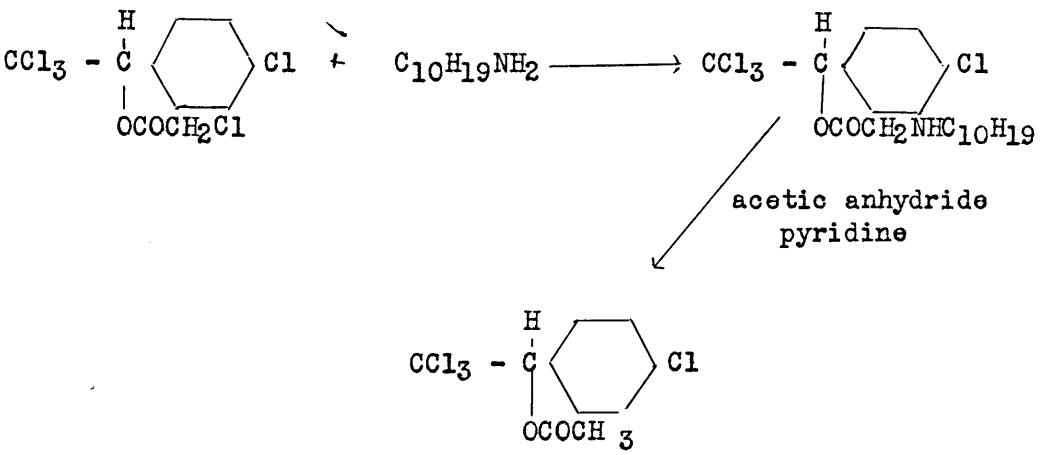
and one of the chloride. The only acid material recovered was oxalic acid, however.

Phthalyl chloride reacted vigorously with the alcohol in pyridine solution. An oil, insoluble in sodium carbonate, was obtained which could not be crystallized.

Alcohol with Optically Active Acid Derivative.

L- Menthyl Glycine with Alcohol.

The preparation of 1-(4-chlorophenyl)-2,2,2-trichloroethyl chloroacetate and l- menthyl amine are described in the experimental. The reaction procedure is also described there, and follows that of Clark and Read (20). This procedure failed to give the crystalline 1-(4-chlorophenyl)-2,2,2-trichloroethyl ester of l- menthyl glycine (X). So the oil was esterified with acetic anhydride in pyridine. This apparently caused hydrolysis of the glycine ester, for the alcohol acetate was the only material isolated. The yield was 68.4%.

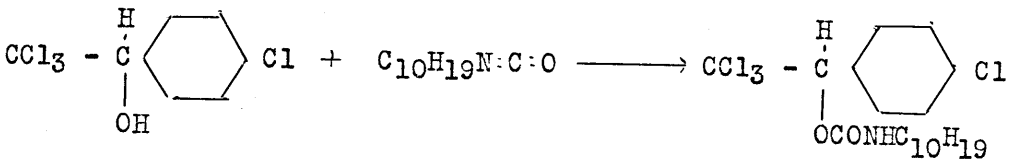


X

A hydrolysis of the acetyl-oxygen linkage had apparently occurred at some stage. The most probable stage is at the addition of pyridine. Glycine esters are not difficulty hydrolysed, the reaction requiring only dilute base.

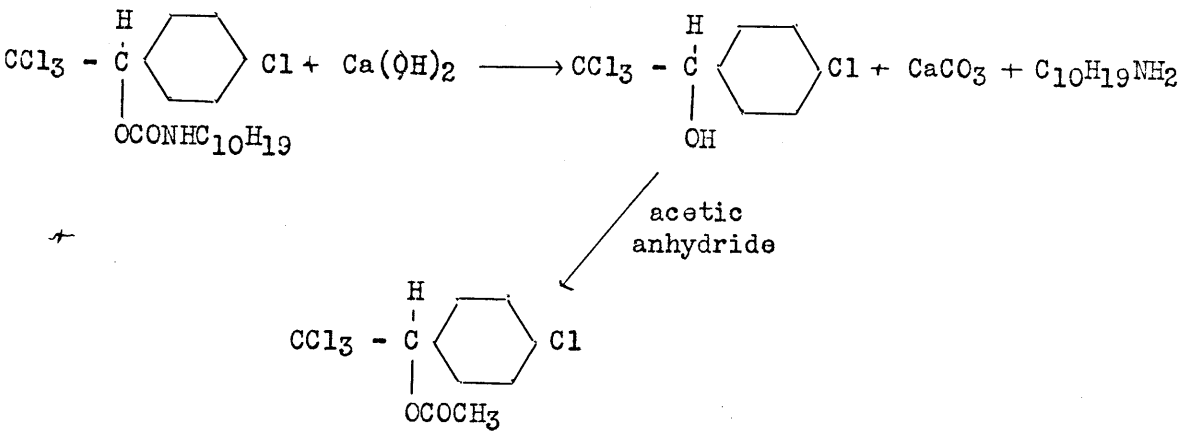
L- Menthyl Isocyanate with Alcohol.

This procedure resulted in the isolation of the l- alcohol in very poor yield. L- menthyl isocyanate was reacted with the alcohol and the resulting dl-1-(4-chlorophenyl)-2,2,2-trichloroethyl-N-l-menthyl urethane (XI) was fractionally crystallized from petroleum ether.



XI

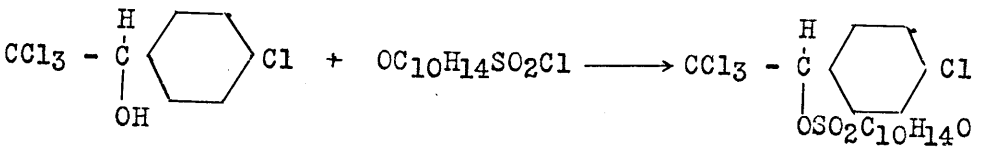
The purified product, the ester of the l- alcohol, was dry distilled from calcium hydroxide in a high vacuum and some oil was obtained which was converted to the acetate. The product was crystallized and shown to be the l- acetate by mixed melting point. The menthyl ester of the d- alcohol was not obtained crystalline.



On none of the previous resolutions by this method (52, 53) was a good yield obtained, or more than one isomer obtained pure. The above procedure lacks a good recrystallizing medium and method of hydrolysis.

D- Camphor Sulfonyl Chloride with Alcohol.

This reaction was performed in dry pyridine solution and in dry benzene solution. However, the d- camphor sulfonate (XII) could not be crystallized in spite of the most vigorous attempts to do so. It is felt that if the reaction had been done in dry benzene and the pyridine hydrochloride removed by filtration before adding water, as in the case of the preparation of the l- menthoxy acetate, a crystalline product would have been obtained. The very easy hydrolysis of the l- menthoxy acetate, the monochloroacetate, and the acetate of the alcohol by zinc chloride would make it appear that the esters are decomposed by the addition of water which permits the formation of chloride ion from the pyridine salt. In the successful preparation of the l- menthoxy acetate, the chloride was all removed by filtration of a dry benzene solution, before the addition of water took place.



XII

An indication of the source of impurity present in this reaction was given by Hess and Stenzel (122) who found the following side reaction in the tosylation of glucosides -

ROTs + Pyrid. HCl ⟶ RCl + Pyrid. TsOH

The Tests on the D- and L- Alcohols as Insecticides.

Tested on Drosophila Melanogaster, the separated alcohols showed appreciable difference in ultimate toxicity. The tests were designed to compare them with DDT acting in its most effective way, which is a contact insecticide over a long period. The laevo had a relative potency of twice that of the dextro, which was slightly less active than the racemic modification.

Three directions are indicated for future research on this subject. (1). Tests could be performed on the separated acetates of the optically active alcohols, and on any other derivatives that were toxic in the racemic form. (2) Insects other than Drosophila should be used. Specificity of physiological action is often shown on relatively few species. (3) The tests should be performed over a wide range of times of exposure of the flies to the treated surface. When d- and l- forms show specificity of physiological action, it is usually shown as a time effect, one isomer acting more quickly than the other.

EXPERIMENTAL

The Preparation of Pure Alcohol 1-(4-chlorophenyl)-2,2,2-trichloroethanol, and of its esters. Hydrolysis studies on the esters.

I Alcohol Preparation by Condensation of Chloral and Chlorobenzene with Aluminium Chloride.

This procedure is that of Dinesmann (128), modified somewhat. A solution of 73.7 gm. of chloral (48.8 cc., 0.5 mole) in 112.5 gm. chlorobenzene (102 cc., 1.0 mole) was prepared in a three-necked flask, fitted with a mercury-sealed stirrer. The other two necks were corked, except during the addition of 13.3 gm. aluminium trichloride (0.1 mole). This was added over 4 hours, during which the reaction was stirred vigorously at room temperature. Stirring was continued for two days. The deep red reaction mixture was shaken with 2 volumes of water, and acidified with a few cc. of concentrated hydrochloric acid. A yellow oil separated from the water, which was distilled at 4 mm. pressure. A pale yellow product of boiling point 138 - 9°C was obtained. It weighed 55.5 gm., a yield of alcohol of 29.6%. The residue from the distillation was dissolved in boiling ethanol. On cooling, 5.2 gm. of DDT, M.P. 107.5 - 108°C, was obtained.

The alcohol could not be crystallized by the usual techniques such as cooling in dry ice, either free or in solvents, or washing with non-solvents. It was put in the refrigerator for 2 weeks, but did not crystallize.

The acetate was prepared following the procedure of Howard (129). 5.5 gm. of the oil (0.02 mole) were heated with 4.4 gm. (0.04 mole) of acetic anhydride at 120 - 130°C for 3 hours. On pouring into water, a

gummy material precipitated, which crystallized on being allowed to stand overnight. It was crystallized from 70% acetic acid, weighed 1.3 gm., a yield of 20%, and melted at 121- 122°C.

Another run was made when the alcohol (26.0 gm., 0.1 mole) was heated for 8 hours at 120 - 140°C with 20.4 gm., acetic anhydride (0.2 mole). When the mixture was treated as in the previous run, only 14.2 gm., of crystalline acetate, a yield of 47%, could be obtained. From the mother liquor of this acetylation was isolated 18.2 gm., of an oil which failed to give acetate on further treatment with acetic anhydride. So the alcohol, prepared by aluminium chloride catalysis, was discarded.

II Preparation of Alcohol by Condensation of 4-chlorobenzaldehyde and Chloroform by Potassium Hydroxide.

4- toluidine was converted to 4- chlorotoluene in 68.5% yield, following a procedure outlined in Organic Syntheses (130). The yield is there reported as 70 - 79%. This was converted to 4- chlorobenzaldehyde by the procedure outlined in Organic Syntheses (131). The alcohol was prepared following a procedure outlined by Howard (129), as follows:-

A solution of 115 gm. 4- chlorobenzaldehyde (0.82 mole) in 150 gm. chloroform (1.26 mole) was prepared. Powdered potassium hydroxide (10.0 gm., 0.18 mole) was added over an hour. The mixture was stirred for 2 hours. The mixture was cooled in ice water during the addition, and then looked cloudy and slightly yellow. The mixture was diluted with an equal volume of ether, and an inorganic precipitate was filtered off. The ether was removed by evaporation, and the mixture steam distilled till no more crystalline precipitate came over. This took about a half to

three quarters of an hour. 38.3 gm. of 4- chlorobenzaldehyde were recovered here. The residue was extracted with chloroform, the extract dried over sodium sulfate, and the solvent removed by evaporation. The alcohol was distilled at 103°C at 0.5 mm. pressure. The yield was 58.1 gm. (27.3%). Based on the 4- chlorobenzaldehyde not recovered, it was 41.2%. A thin film of the white distillate crystallized on standing several weeks. This was added to the main distillate, and the whole solidified. Three recrystallizations from petroleum of boiling point 100 - 102°C gave a product of melting point 46.5 - 47.5°C in poor yield.

The acetate of the crystalline alcohol was prepared according to Howard's procedure given above (129). An 88.5% yield of crystalline product was obtained.

Attempted Hydrolyses of Esters of the Crystalline Alcohol.

1) The acetate of the alcohol was studied first. 1.0 gm. was boiled with 20 cc. of 10% aqueous sodium hydroxide, and with 20 cc. 10% sodium carbonate. In both cases a clear aqueous solution was obtained, showing that the alcohol had decomposed. With sodium bicarbonate, the acetate was recovered unchanged after many days boiling.

2) 10 gm. of acetate were stirred for 11 hours with 25 cc. of 96% sulfuric acid at room temperature. The mixture now contained a gelatinous precipitate and was diluted with ice water. The mixture was extracted with ether, the extract was dried over sodium sulfate, and the solvent was removed by evaporation. The residual oil was distilled in vacuo. B.P. 132°C at 2 mm. pressure. The oil weighed 7.2 gm., a yield of 84%. This procedure did not work for the monochloroacetate. When

the temperature was raised to 95°C, the product obtained was insoluble in petroleum ether, and did not crystallize on seeding with alcohol.

3) The monochloroacetate was stable to boiling concentrated hydrochloric acid over several hours. It was also recovered from an alcoholic solution of hydrogen chloride, after a half hour of reflux. Equal weights of concentrated hydrochloric acid and aluminium chloride were mixed and a little monochloroacetate was added. After several minutes at steam bath temperatures, the reaction mixture was diluted with water. The monochloroacetate was recovered from an ether extract.

4) A successful hydrolysis of the chloroacetate and of the acetate was accomplished as follows. A solution of 1.3 gm., of the ester and 1.3 gm., anhydrous zinc chloride in 100 cc. absolute methanol was refluxed a half hour on the steam bath. It was then diluted to 300 cc. with water. This caused the formation of a flocculent precipitate. 2 cc. of hydrochloric acid were added, causing the precipitate to become an oil. The mixture was thoroughly extracted with several portions of ether, until the aqueous layer was clear and colourless. The extract was dried over sodium sulfate, and the solvent removed by evaporation. The residual white oil was seeded with alcohol, and crystallized completely. The yield in this case was nearly quantitative. M.P. 43 - 5°C. The melting point of a mixture of this compound with authentic alcohol was 42 - 6°C.

The method worked only with acetate and substituted acetates. The following esters were recovered unchanged by this treatment:- 4-chlorobenzoate, 4- toluene sulfonate, N-phenyl urethane.

The Resolution of 1-(4-chlorophenyl)-2,2,2-trichloroethanol.

Methods of Resolution Attempted.

I Hydrogen Esters of Alcohol and Alkaloid.

Attempts to Prepare a Hydrogen Ester of the Alcohol.

(a) Acid Phthalate or Succinate by Direct Esterification.

1) A mixture of 1.3 gm. of alcohol (0.005 mole) and 0.8 gm. phthalic anhydride (0.005 mole) was heated in a test tube for 11 hours at 115 - 120°C. During this time the tube was stoppered with a calcium chloride tube. During the period of heating, a few crystals of phthalic anhydride had sublimed out of the mixture, which was then a clear liquid. This was poured into 10 cc. of 10% sodium carbonate (0.01 mole). The resulting mixture was allowed to stand 3 days at room temperature. A considerable portion of the material remained undissolved. Then the organic material was extracted with ethyl ether. The solvent was evaporated, and left a clear oil which could not be crystallized by cooling or scratching or washing with solvents. The aqueous residue was acidified with hydrochloric acid. The white crystalline precipitate was collected on a filter. It was phthalic acid, recovered in 33% yield. M.P. about 200°C with decomposition.

2) 1.3 gm. alcohol (0.005 mole) and 0.8 gm. phthalic anhydride (0.005 mole) were dissolved in 20 cc. dry pyridine (distilled from barium oxide). The white clear solution was allowed to stand at room temperature for 11 hours, and then was heated on the steam bath for an hour. The white liquid was poured into 100 cc. of water and 20 cc. of concentrated hydrochloric acid.

The organic material was removed by extraction with chloroform. The extract was dried over calcium sulfate, and the solvent was removed by evaporation. The residual clear white oil could not be caused to crystallize by cooling or scratching or washing in solvents. It was insoluble in sodium carbonate, and weighed 1.8 gm. It was dissolved in 10 cc. reagent acetone and 2.0 gm. brucine was added. No crystalline material could be obtained on evaporation or cooling.

The white oil was prepared again. It was dissolved in acetone and titrated with 0.1 N aqueous sodium hydroxide, using phenolphthalein as indicator. Only 12.3% of the volume of alkali required for the titration of the acid ester of the alcohol was taken up by the solution.

3) A solution of 2.6 gm. alcohol (0.01 mole) in 60 cc. of chloroform was treated with 1.5 gm. (0.01 mole) phthalic anhydride. The chloroform was distilled from the reaction mixture over 5 hours. Cold 10% sodium carbonate solution was added, and the mixture was stirred till no more organic material appeared to dissolve. The aqueous extract was acidified with 20% hydrochloric acid. The precipitate was collected on a filter. It weighed 1.0 gm. and was found to be phthalic acid, melting indefinitely at 210 - 215°C. When the amount dissolved in the water was accounted for, the phthalic acid was recovered in 95% yield.

4) In a sealed tube at 100°C was placed 1.3 gm. of alcohol (0.005 mole) and 1.0 gm. phthalic anhydride (0.0068 mole). The temperature was maintained for 16 hours and then the tube was cooled. Phthalic anhydride was recovered almost quantitatively by extracting with chloroform and collecting the anhydride on a filter.

5) In a sealed tube at 200°C was placed 1.3 gm. of alcohol (0.005 mole) and 1.0 gm. phthalic anhydride (0.0068 mole). The temperature was maintained for 16 hours and then the tube was cooled. The mixture was now a black tar. Considerable pressure had developed in the tube due to the formation of hydrogen chloride. The mixture was dissolved in 50 cc. chloroform, and a few crystals of phthalic acid were removed by filtration. After boiling with charcoal for 10 minutes, the solution was pale brown. The chloroform was distilled off, leaving 1.3 gm. brown crystals of M.P. 120 - 128°C. They were washed with petroleum ether, and recrystallized from a 1:1 mixture of ethyl ether and chloroform. The product weighed 0.5 gm. and melted at 130 - 134°C. It was not characterized as it was insoluble in 10% sodium carbonate solution, and produced in such low yield; also the evolution of hydrogen chloride indicated a breakdown of the trichloromethyl group.

6) Phthalic anhydride was converted to the 3-nitro derivative. Yield of recrystallized product 20.4%. (132)

A solution of 1.0 gm. of the anhydride (0.005 mole) and 1.3 gm. of the alcohol (0.005 mole) was mixed with 10 cc. pyridine in a flask. The temperature of the reaction mixture rose a few degrees. The mixture was allowed to stand overnight, and then poured into 100 cc. water with 10 c.c. concentrated hydrochloric acid. The organic material was extracted with ether, and the solvent was removed by evaporation. As the product was not acidic, it was discarded.

7) 25 cc. of dry xylene were used to dissolve 1.3 gm. of alcohol (0.005 mole) and 1.0 gm. of 3-nitro phthalic anhydride (0.005 mole). The solution was refluxed for 3 hours. A small insoluble residue was collected on a filter, and the xylene removed by distillation. The residue was dissolved in 75 cc. of boiling benzene, the solution filtered hot, and allowed to stand overnight in the refrigerator. A precipitate of light yellow needles was collected on a filter. It weighed 1.0 gm., and was identified as 3-nitro phthalic acid. M.P. 219 - 228°C. Yield 91%. Concentration of the benzene solution gave a small amount of alkali soluble material, recovered in poor yield on acidification.

8) 1.5 gm. of phthalic anhydride (0.01 mole) was heated with 2.6 gm. of alcohol (0.01 mole) in a flask on the steam cone. On addition of 2 cc. of 40% hydrobromic acid (0.01 mole approx.) the reaction mixture solidified. 50 cc. of 10% sodium carbonate solution was added, and the mixture was stirred till no more organic material appeared to dissolve. The mixture was then extracted with ether to remove unchanged alcohol. The aqueous layer was acidified with 20% hydrochloric acid and the crystalline product collected on a Buchner funnel. The melting point of the product, identified as phthalic acid, was 201°C.

9) A solution of 3.2 gm. of alcohol (0.012 mole) and 0.8 gm. phthalic anhydride (0.012 mole) in 25 cc. chloroform was refluxed with 20 drops of concentrated sulfuric acid for 16 hours. The cooled reaction mixture was extracted with dilute sodium carbonate. The extract was acidified with dilute hydrochloric acid. The white crystalline precipitate was collected

on a Buchner funnel, and was identified as phthalic acid of melting point 210 - 213°C.

10) Two condensations were attemped with succinic anhydride, with no catalyst present. In one, equimolar portions of the reactants were maintained in an oil bath at 140 - 150°C for seven hours. In the other case, reactants were maintained at what was apparently the boiling point. No alkali soluble product could be isolated.

Miscellaneous Preparations of the Phthalate.

1) An attempt was made to prepare the sodium derivative of the alcohol, for reaction with phthalic anhydride. To 50 cc. dry toluene was added 1.15 gm. clean sodium (0.05 mole). The toluene was warmed till the sodium melted, then cooled while the mixture was stirred. The sodium was now in the form of fine powder. Now a solution of 13.0 gm. (0.05 mole) of alcohol in 10 cc. toluene was added. A gas was slowly given off. The reaction was maintained at 50°C for an hour, and then was diluted with dry ether. A dark brown precipitate was formed immediately. It was collected on a filter and found to weigh 4.7 gm. It did not burn in a Bunsen flame and was presumed to be inorganic. The yield, on the basis of the product's being sodium chloride, was 80%.

2) An attempt was made to synthesize the alcohol acid phthalate by combination of the carbinyl magnesium halide with phthalic anhydride. For the preparation of ethyl magnesium chloride, 0.4 gm. of magnesium (0.015 mole) was placed in a 125 cc. Grignard raaction flask. This was equipped with a

mercury-sealed propellor stirrer, and a reflux condanser, having a calcium chloride tube in the open end. Through the third neck, a glass tube was led into 10 cc. of ethyl ether, which covered the magnesium. This glass tube was connected to an ampoule of ethyl chloride, cooled in dry ice. The reaction commenced after three quarters of an hour of stirring, and the addition of a crystal of iodine. Within half an hour the magnesium had all dissolved, forming a black solution. 50 cc. of dry ether were added to the flask. A solution of 3.9 gm. alcohol (0.015 mole) in 10 cc. dry ether was added to the flask from a separatory funnel, which replaced the ethyl chloride tube. The solution was added dropwise. With each drop, a vigorous evolution of gas, probably ethane, occurred. After this, the mixture had a white cloudy appearance. 2.2 gm. phthalic anhydride (0.015 mole) were added altogether in a finely ground form. The mixture was refluxed with vigorous stirring for three hours. During this time a white precipitate was continuously present. It was then poured over 50 gm. of ice and 20 cc. 2N hydrochloric acid. This mixture was allowed to s tand overnight. The reaction mixture had dissolved in either the ether or the water. This indicated that the phthalic anhydride had reacted. The ether layer was separated, dried over sodium sulfate, and evaporated. Oily crystals weighing 4.2 gm. were isolated. Cold chloroform was added, and a white crystalline material was collected on a filter. It weighed 1.2 gm. and melted at 173 - 175°C. The mother liquor was decolourized to a pale brown with charcoal, and the solvent removed by evaporation. The yellow crystalline product melted at 123 - 125°C. This material was dissolved in ether and evaporated on a watch glass. Four distinct crystal types could easily be discerned. This explained why successive runs gave high melting

material of melting point 170 - 185°C, and low melting material from 120 - 160°C. These products sometimes raised and sometimes lowered their melting points on recrystallization.

3) An attempt was made to synthesize the acid phthalate of the alcohol through a transesterification reaction of potassium acid phthalate with the 4- toluene sulfonate of the alcohol. To prepare the tosyl derivative, 1.3 gm. alcohol (0.005 mole) and 1.0 gm. of 4- toluene sulfonyl chloride (0.005 mole) were dissolved in 10 cc. dry pyridine. The flask was allowed to stand at room temperature for 12 hours, and the reaction mixture was diluted with 100 cc. of water. The organic material was extracted with ether, the extract dried over sodium sulfate, and the solvent removed by evaporation. The residue was crystalline, melting at 118 - 122°C, and weighing 1.0 gm. (Yield 47%) On recrystallization from diethyl ether, large white rhomboids were obtained, melting at 123 - 4°C.

Equimolar quantities of this ester and potassium acetate, lithium chloride and potassium acid phthalate were refluxed in 10 cc. of anhydrous ethanol, for 25 hours. In each case dilution with water gave the unreacted tosyl ester with nearly quantitative recovery.

Acid Sulfates.

An equivalent of 96% sulfuric acid (1.5 cc., 0.013 mole) was added to 3.3 gm. of alcohol (0.013 mole). The mixture was stirred at room temperature for three hours, and then contained a large lump of red solid. 100 gm. ice water was added. This precipitated a white powder which was collected on a filter and weighed 2.5 gm. Its melting point was 43 - 45°C.

The melting point of the mixture of this material with the alcohol was 43 - 46°C. The filtrate was then neutralized with barium carbonate, and barium sulfate was removed by filtration. Nothing could be precipitated from solution by the addition of acetone, dioxane, or ethanol. The barium salt of butyl hydrogen sulfate was precipitated by solvents at this stage.

A slight excess of 96% sulfuric acid (9 cc., 0.15 mole) was heated with 3 gm. alcohol (0.012 mole) on the steam bath a half hour. The mixture then consisted of a dark red oily bottom layer and a white top layer of roughly equal volume. The reaction mixture was diluted with water, and a large amount of water insoluble brown oil was precipitated. This was partly soluble in petroleum ether. This solvent was removed and the residue was found to be insoluble in barium carbonate. On cooling the oil a week in dry ice methanol, a few white crystals were obtained, melting at 123 - 6°C . These gave a negative test for $-SO_2OH$. (133). (Benzene sulfonic acid was used as a known sample.)

This compound was not analysed but was thought to be the ether formed by the condensation of two alcohol units.

Miscellaneous Attempts at Esterification.

Maleic anhydride, oxalyl chloride and phthalyl chloride were condensed with equivalent amounts of alcohol, using the techniques outlined above. No acidic materials were obtained. Maleic anhydride was recovered unreacted, oxalic acid was recovered, and a non-crystalline oil was the product from the reaction with phthalyl chloride.

II Alcohol with Optically Active Acid Derivative.

(a) L- Menthyl Glycine with Alcohol.

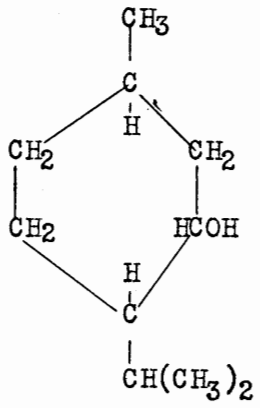
Preparation of the Reagents.

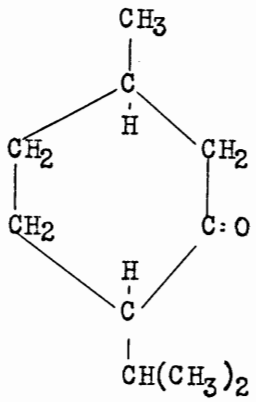
1) Alcohol chloroacetate --- Monochloroacetyl chloride was prepared in 75% crude yield by the action of phosphorus trichloride on monochloroacetic acid. The crude product was fractionated from dimethyl aniline. A mixture of 8.6 gm. of alcohol (0.03 mole) and 11 cc. of monochloroacetyl chloride (16.5 gm. 0.15 mole) was refluxed together for 25 hours. The product was poured into 100 cc. of water. The brown oil crystallized on standing a few hours. The product weighed 5.5 gm., a yield of 55%. It was decolourized by boiling a petroleum ether solution with charcoal, and recrystallized twice from petroleum ether. The product was then obtained as cream coloured needles of melting point 90 - 1°C.

2) L- menthyl amine --- L- menthol was converted to l- menthone by the method of Beckmann (134). The optical rotation in ethanol solution of the menthol usedwas -

$$[\alpha]_D^{25} = \frac{-2.57 \times 100}{1 \times 5.15} = -49.9^\circ$$

The Merck Index (135) reports the rotation as $[\alpha]_D^{25} = -50^\circ$ for a 20% ethanol solution.





A solution of 120 gm. (0.41 moles) of potassium dichromate and 100 gm. of 96% sulfuric acid (54.5 cc., 0.98 mole) was prepared. Finely ground l- menthol (90 gm., 0.58 mole) was added all at once. After a moment's stirring, the solid turned black. Gentle agitation was continued for a half hour, during which there was a slow rise in temperature. At 53°C the black addition compound decomposed, and a brown layer formed on top of the aqueous solution. The mixture was allowed to s tand for an hour, and was then extracted twice with 100 cc. and once with 50 cc. of ethyl ether. The extract was washed with 100 cc. portions of water, 5% sodium hydroxide, and then water. The extract was now colourless. The ether was removed by evaporation, and the menthone steam distilled. It collected in the receiver as a transparent white liquid on top of the water. The product was separated and found to weigh 77.5 gm., a yield of 87.2%.

The optical rotation of the product in ethanol solution was -

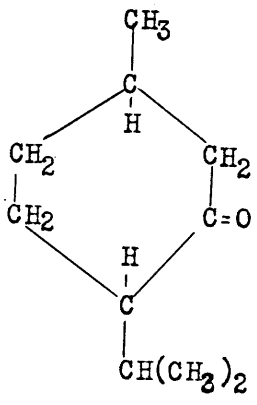
$$[\alpha]_D^{25} = \frac{-4.73 \times 100}{2 \times 9.908} = -23.8^\circ$$

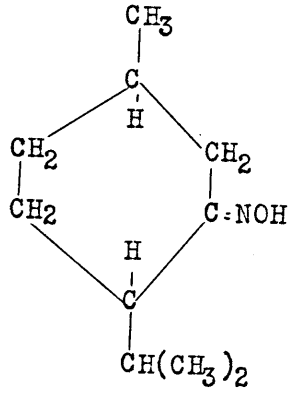
The optical rotation of the pure menthone was -

$$[\alpha]_D^{25} = \frac{-25.83}{1 \times 0.895} = -28.5^\circ$$

Merck's Index reports the rotation as $[\alpha]_D^{20}$: -24.8° for a 20% alcohol solution.

L- menthone oxime was prepared according to the method of Beckmann (134) -





A solution of 75 gm. of l- menthone (0.49 moles) in 225 cc. of 90% ethanol was mixed with 45.0 gm. of hydroxylamine hydrochloride (0.65 mole). Upon the addition of 59 gm. of sodium bicarbonate (0.70 mole) there was a rapid evolution of carbon dioxide. The mixture was allowed to stand 10 hours, and then refluxed a half Hour. The white solid was then collected on a filter, and found to contain no more carbonate. The solvent was removed from the filtrate by evaporation. It was then diluted with water. An oil was thrown down which would not crystallize.. The oxime was extracted with petroleum ether, the extract dried over sodium sulfate, and the solvent removed by evaporation. The oxime was distilled in vacuo. B.P. 85 - 90°C at 1.5 mm. pressure. The product was a clear white oil which rapidly crystallized as needles, melting at 51.5 - 54°C. The product weighed 43.5 gm., a yield of 52.9%.

The optical rotation of the product in ethanol was -

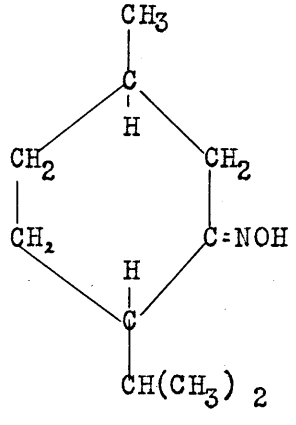
$$[\alpha]_D^{25} = \frac{-9.31 \times 100}{2 \times 9.984} = -46.5^{\circ}$$

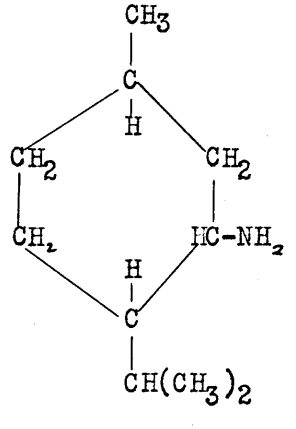
Beckmann reported the rotation $[\alpha]_D^{20} = -42.5^\circ$ in 10% ethanol.

Further distillation did not change the specific rotation or the melting point. Crystallization from dilute alcohol was performed with great difficulty, for the product showed a great tendency to come down as an oil. When this was accomplished, the melting point was raised to 56.5 - 57°C. The reported value (Beckmann) was 58°C.

The oxime of l- menthone was also prepared with hydroxylamine acetate (136). Their product was reported with a rotation of $[\alpha]_D^{15} = -39.7^\circ C$ in ethanol. The yield of crude oxime was only 30%. The yield of crude l- menthone oxime based on l- menthol was 38.6%.

L- menthyl amine was prepared according to the procedure of Wallach(137)-





A solution was prepared of 43.3 gm. of l- menthone oxime (0.256 mole) in 350 cc. absolute ethanol, 65 gm. of clean sodium (2.8 moles) was added to the boiling solution in small pieces over an hour. Toward the end of this period, two 100 cc. portions of alcohol were added, as the reaction mixture tended to solidify. The mixture was steam distilled in an apparatus protected from carbon dioxide. First clear ethanol came over. As soon as the distillate appeared cloudy, the receivers were changed, and distillation was continued until no more cloudy liquid came over. The amine formed a

transparent pale yellow layer on top of the water. This layer was separated and found to weigh 33.2 gm., a yield of 83.7%. The liquid amine was converted to the hydrochloride by the addition of 20% hydrochloric acid. Evaporation of the water left 36.1 gm. of grey crystals, a yield of 88.4%.

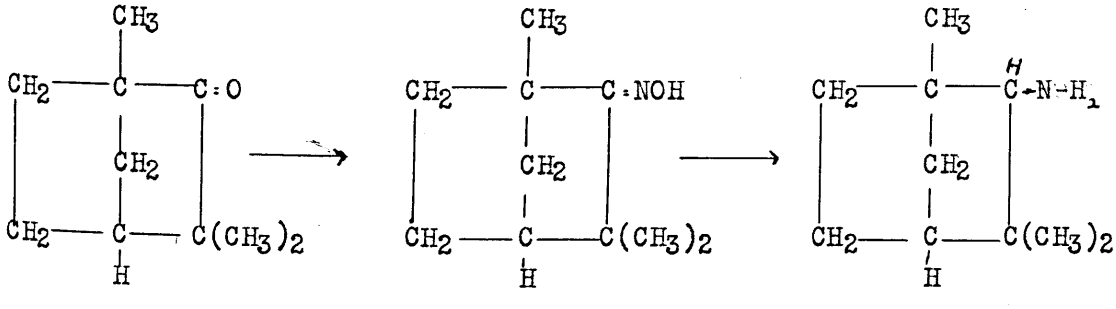
The optical rotation of a solution in water was -

$$[\alpha]_D = \frac{-3.15 \times 100}{2 \times 5.682} = -27.7^\circ$$

Tutin and Kipping (138) report that the optical rotation of the crude l- menthyl amine $[\alpha]_D = -28.0^\circ$. One isomer can be separated by systematic fractional crystallization from water to give a product of $[\alpha]_D = -36.6^\circ$

3) D- fenchylamine --- L- fenchone was converted to the oxime by the method of Wallach (142). The crude product was easily crystallized and was formed in 96% yield. One recrystallization from ether gave a pure product of melting point 161 - 162.5°C. The yield here was only 33.8%.

Wallach reports also the reduction of the oxime to the amine with sodium in ethanol. The yield was 41% of clear liquid. The procedure follows closely that for the preparation of l- menthyl amine, except that the d- amine is produced.



The Resolution Reaction.

An intimate mixture of 9.2 gm. of d- fenchylamine (0.06 mole) and 10.6 gm. of alcohol chloroacetate (0.03 mole) was heated in a flask immersed in an oil bath at 100 - 120°C. The flask had been swept out with nitrogen, and was protected from the atmosphere by soda lime tubes. The heating was continued for 11.5 hours. A hard resinous material was formed on cooling. This product was dissolved in chloroform and the solution was washed several times with 2 N hydrochloric acid, followed by several washes with water. The solution was then dried over sodium sulfate and the solvent removed by evaporation. A brown oil remained which could not be crystallized by any mixture of common solvents, or by thorough cooling in dry ice methanol.

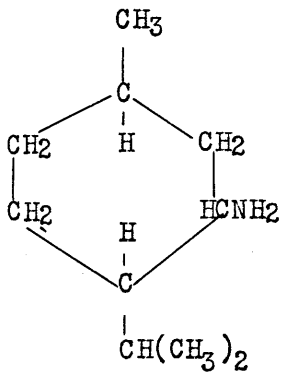
To make an acetyl derivative, the oil was dissolved in 6 cc. of dry pyridine, and 6 cc. of acetic anhydride were added. This mixture was allowed to stand for 3 hours, and then poured into 100 cc. of water containing 5 cc. of concentrated hydrochloric acid. A crystalline product was formed immediately. It weighed 11.6 gm. and melted at 95 - 120°C. The product was recrystallized from methanol. 6.5 gm. of product were obtained. The melting point of these long needles was 123.5 - 125°C. The same melting point was observed with a mixture of this product with alcohol acetate. The yield of recrystallized alcohol acetate was 68.4%. The material was quite inactive in the polarimeter.

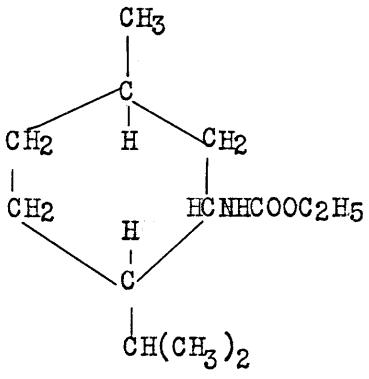
An attempt was made to condense l- menthyl amine with the alcohol chloroacetate. The reaction conditions were exactly similar to those outlined above. Crystals of pure alcohol acetate, in good yield were the only product isolated, however. Crude l- menthyl amine of $[\alpha]_D = -28°$ was used.

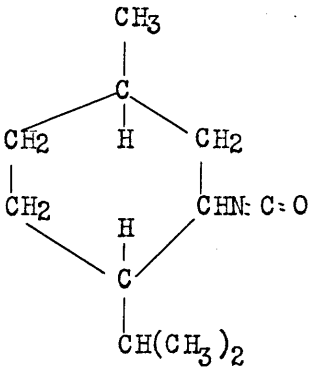
(b) L- Menthyl Isocyanate with Alcohol.

Preparation of the Reagents.

The conversion of l- menthyl amine to the isocyanate was performed according to the method of Neville and Pickard (140).







Crude l- menthyl amine hydrochloride was prepared as outlined on pages 72 - 75 . The reduction product was purified by systematic fractional crystallization from water. 18.5 gm. of the pure hydrochloride was obtained from 36.1 gm. of the crude, a yield of 51%.

18.5 gm. of the purified hydrochloride was mixed with 25 cc. of 20% sodium hydroxide, and the mixture was steam distilled. The yield of water-white l- menthyl amine was 14.6 gm. (97%). The yield of pure amine from the reduction of the oxime is 36.8%. The yield of pure amine from l- menthol is 17.0%.

A solution of 14.6 gm. l- menthyl amine in 100 cc. petroleum ether (B.P. 30 - 60°C) was prepared in a 300 cc. three neck flask. This was fitted with a mercury-sealed stirrer, a reflux condenser and a dropping funnel. Solid sodium bicarbonate (8.4 gm., 0.1 mole) was suspended in the petroleum ether, and then refluxing and stirring was commenced. Pure

ethyl chlorocarbonate (10.2 gm., 0.094 mole) was added through the dropping funnel during twenty minutes. A heavy precipitate formed immediately, and was present during the succeeding two hour period of stirring and refluxing. The cooled reaction mixture was diluted with 200 cc. of water, and the whole was poured into a separatory funnel. Two clear layers formed. The petroleum ether layer was dried over sodium sulfate and the solvent distilled until crystallization commenced. The flask was then cooled, and the product collected on a filter. It weighed 12.4 gm., a yield of 58.8%, M.P. 59.5 - 60.5°C.

The optical rotation of a chloroform solution was -

$$[\alpha]_D^{25} = \frac{-6.04 \times 100}{2 \times 4.324} = -69.8^\circ$$

Neville and Pickard (140) report the following constants -

M.P. 54 - 59 C $\qquad [\alpha]_D$ = -64 to 68.9°

They reported a quantitative yield, however.

A 50 cc. Claisen flask was fitted with a distilling flask directly attached to it as a receiver, but did not have a bubbling tube. Vacuum was obtained by water pump giving 10 mm. pressure. The N-l-menthyl ethyl urethane was divided into 3 gm. portions. For a distillation, a portion was mixed with 4.5 gm. solid phosphorus pentoxide and then the mixture was transferred to the distillation assembly. A clear white oil distilled at 115 - 120°C at 13 mm. pressure. Most of this came over at 118°C. The product weighed 2.1 gm., a yield of 87.8%.

The optical rotation of the product in benzene solution was -

$$\left[\alpha\right]_D^{30} = \frac{-2.55 \times 100}{2 \times 2.250} = -56.6^{\circ}$$

Neville and Pickard reported the boiling point of the crude product to be 90 - 160°C. Their product, after being fractionated three times, had an optical rotation of $\left[\alpha\right]_D$ = -54.97 - 54.79° in benzene. They do not mention their yield. It apparently is necessary to purify the l-menthyl ethyl urethane before conversion to the isocyanate.

The isocyanate was prepared from the l- menthol in 8.8% yield, and from the pure l- menthyl amine in 51.7% yield.

The Preparation and Hydrolysis of the N- Phenyl Urethane of the Alcohol.

Preparation of the Urethane.

A mixture of 2.6 gm. of alcohol (0.01 mole) and 2.3 gm. of phenyl isocyanate was prepared in a test tube bearing a calcium chloride tube. The tube was immersed in an oil bath at 160°C for a half hour. The mixture was then cooled, but could not be crystallized by scratching or washing in solvents. It was allowed to stand several days in the refrigerator. The mass solidified rapidly when a seed appeared. 3.9 gm. of oily crystals, a yield of 80%, were obtained. After four hours recrystallization from a 1:1 mixture of ethyl ether and petroleum ether, a very small yield of white needles was obtained. M.P. 137 - 9°C.

Attempted Hydrolysis of the Urethane.

1) A solution of 0.2 gm. of the urethane in 20 cc. of 50% acetic acid was refluxed for an hour. On cooling the hot clear solution, the urethane was recovered almost quantitatively. The melting point of the mixture of this material with the reactant was not depressed.

2) A solution of 0.4 gm. of urethane and 0.4 gm. anhydrous zinc chloride in 10 cc. absolute methanol was refluxed for a half hour on the steam bath. 50 cc. of water containing 1 cc. of concentrated hydrochloric acid was added. The aqueous mixture was thoroughly extracted with ethyl ether. Removal of the solvent from the dried extract left a solid of melting point 128 - 133°C. The melting point of a mixture of this material with the urethane was 130 - 135°C.

3) 0.3 gm. of urethane was refluxed for seven hours with 20 cc. of 25% hydrochloric acid. Then the product consisted of water soluble material with a little undissolved oil. The mixture was extracted with ether, and the oil obtained from the dried extract was treated with acetic anhydride. The product obtained from this reaction could not be crystallized on seeding with alcohol acetate, however.

4) An intimate mixture of 20 gm. freshly prepared dry calcium hydroxide and 5 gm. N- phenyl ethyl urethane was distilled at atmospheric pressure. A white clear liquid of boiling point 78°C was obtained.

A mixture of 1.4 gm. of the N- phenyl urethane of the alcohol and 4.5 gm. calcium hydroxide was heated in an oil bath to 120°C. Then a vacuum was applied, and a liquid distilled over at 120°C at 1 mm. pressure. This was a brown oil, which crystallized on adding a seed of alcohol. The product weighed 0.7 gm., a yield of 85%. Its melting point, and the melting point of a mixture of this product with alcohol was 43.5 - 48°C.

The Resolution Reaction.

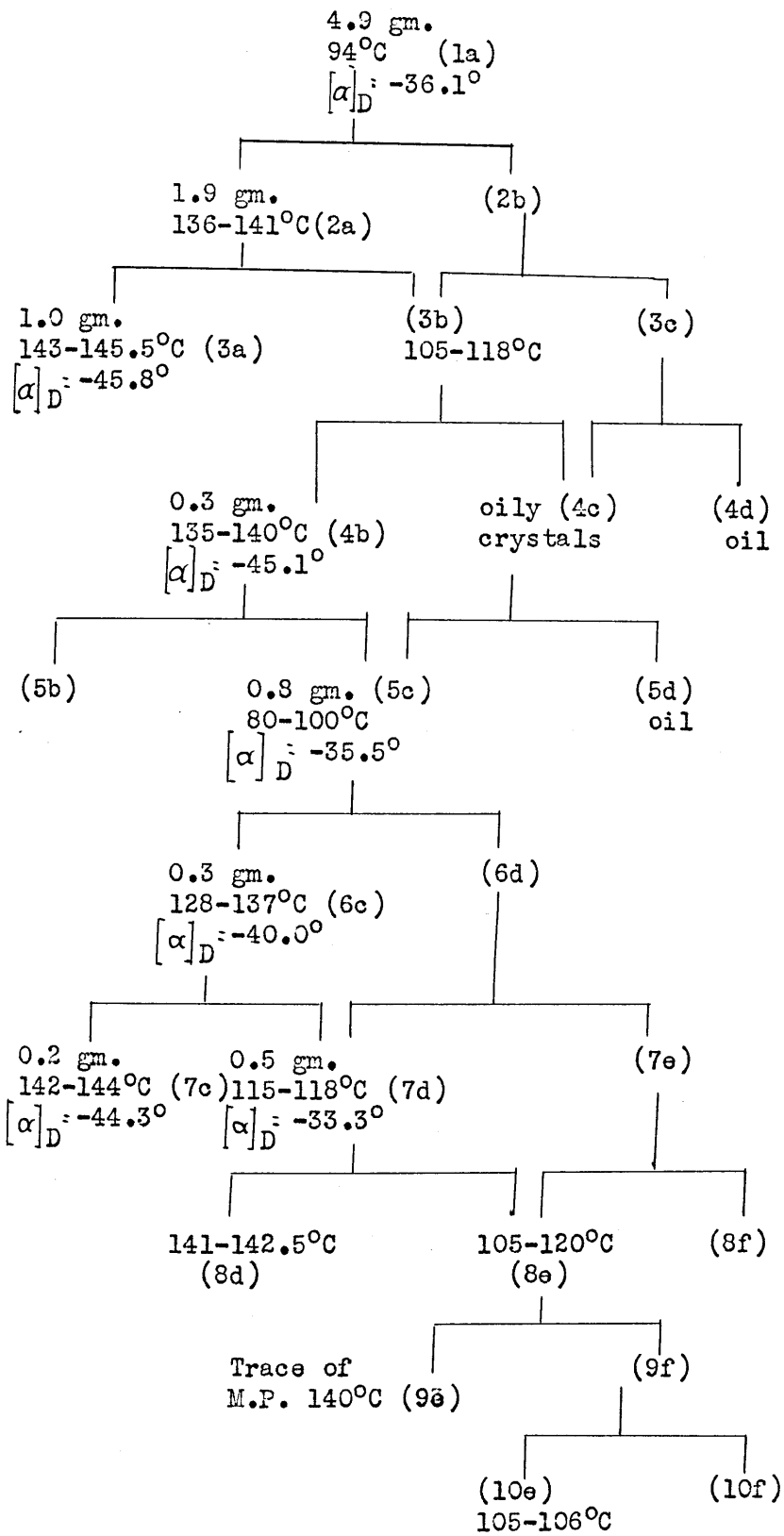
A mixture of 3.1 gm. of l- menthyl isocyanate (0.017 mole) and 4.5 gm. of alcohol (0.017 mole) was heated for three hours at an oil bath temperature of 140°C. The cooled reaction mixture then consisted of a brown tacky solid. The product was difficult to crystallize. It was allowed to stand three days in the refrigerator with a few drops of petroleum ether, and was then observed to have crystallized. The product was recrystallized from petroleum ether (B.P. 60 - 80°C). The filtrate was allowed to stand in the refrigerator overnight, with a little petroleum ether, and an additional crop of oil crystals were obtained.

The residual oil was dissolved in ethyl ether, and the solution was washed with 10% hydrochloric acid. The solvent was evaporated from the dried extract, but the residue did not crystallize.

To remove unreacted alcohol, the oil was placed in a vacuum distillation apparatus. The oil bath was heated to 210°C, and one drop of material was distilled. It had a boiling point of 140°C at 1 mm. pressure.

The oil was dissolved in 100 cc. petroleum ether, and the solution was poured through a column of "super-filtrol" clay, 20 cm. long by 3 cm. diameter. Then 100 cc. more petroleum ether was poured through as eluate. The combined filtrates were evaporated and the oil crystallized overnight. The column was pushed out of the tube, and divided in thirds. These were extracted with ethyl ether, and the solvent removed from each fraction by evaporation. The oil from the bottom third crystallized overnight.

The combined amounts of crystals obtained from the above experiment weighed 4.9 gm., a yield of 64.5%. They were systematically fractionally crystallized from petroleum ether, as follows:-


4.9 gm.
94°C (1a)
[α]D: -36.1°
1.9 gm.
136-141°C(2a)
(2b)
1.0 gm.
143-145.5°C (3a)
[α]D: -45.8°
(3b)
105-118°C
(3c)
0.3 gm.
135-140°C (4b)
[α]D: -45.1°
oily (4c)
crystals
(4d)
oil
(5b)
0.8 gm. (5c)
80-100°C
[α]D: -35.5°
(5d)
oil
0.3 gm.
128-137°C (6c)
[α]D: -40.0°
(6d)
0.2 gm.
142-144°C (7c)
[α]D: -44.3°
0.5 gm.
115-118°C (7d)
[α]D: -33.3°
(7e)
141-142.5°C
(8d)
105-120°C
(8e)
(8f)
Trace of
M.P. 140°C (9e)
(9f)
(10e)
105-106°C
(10f)

Fraction (3a) was presumed to be the N- l- menthyl urethane of the l- alcohol. Yield based on total crystals obtained 20.2%.

Anal. calcd. for $C_{19}H_{24}O_2N\,Cl_4$

	C, 51.83;	H, 5.49;	Cl, 32.20
Found	C, 51.88	H, 5.58	Cl, 31.88
	51.95	5.69	31.98
	51.92	5.64	31.93

Fraction (3a), weighing 1.0 gm. was mixed with 4.0 gm. of calcium hydroxide in a vacuum distillation apparatus. The hydrolysis was performed as described for the N- phenyl urethane of the alcohol. A white oil was obtainod, weighing 0.2 gm., a yield of 33.8%.

The optical rotation in chloroform solution was -

$$\left[\alpha\right]_D = \frac{-1.29 \times 100}{2 \times 1.985} = -32.5^\circ$$

A portion was converted to the acetate using the procedure given on page 61. The product melted at 67 - 82°C. The optical rotation was $\left[\alpha\right]_D = -50^\circ$. After recrystallization from methanol, the product melted at 84 - 88°C. A melting point of the mixture of this product with that from the l- menthoxy acetyl chloride run was 84 - 7°C.

Fractions (5b), (7c) and (8d) were combined and found to weigh 0.3 gm. This material was distilled from calcium hydroxide in the manner outlined above. The distillate was still laevorotatory.

The other diastereoisomer was not obtained in a crystalline form.

(c) D- Camphor Sulfonyl Chloride with Alcohol.

Preparation of the Reagents.

D- Camphor was obtained from stores, and had a rotation in ethanol solution of -

$$[\alpha]_D^{25} = \frac{3.42 \times 100}{1 \times 8.35} = 41^\circ$$

The rotation was reported by Merck's Index (141) was $[\alpha]_D = 41\text{-}42^\circ$.

D- camphor sulfonic acid --- The procedure followed was that of Reychler (142), as modified by Armstrong and Lowry (143, 144).

Concentrated sulfuric acid (10.2 gm., 0.1 mole) was mixed with 20.4 gm. of acetic anhydride (0.2 mole) while the flask was cooled in ice water. Then 15.2 gm. d- camphor (0.1 mole) was added in pulverized form. After a few hours at room temperature, a clear heavy yellow liquid had formed in the flask. Within a day, precipitation of the sulfonic acid had commenced. After 5 days, the precipitate was collected on a filter. It was washed with ethyl ether, and recrystallized from ethyl acetate, and found to weigh 5.3 gm., a yield of 22.6%. The yield is reported as quantitative by Reychler, after he allowed the reaction to stand for two weeks. The product was found to melt at 193 - 194°C, as reported.

For conversion to the acid chloride, the product (5.3 gm., 0.0023 mole) was treated with 10 cc. thionyl chloride (16.4 gm., 0.14 mole) and refluxed two hours. The excess thionyl chloride was distilled off, and the product was recrystallized twice from dry benzene. 1.7 gm. of white needles (29.4%) yield were obtained, of melting point 67 - 68.5°C, the reported value.

The optical rotation of a solution in chloroform was -

$$\left[\alpha\right]_D^{25} = \frac{1.51 \times 100}{2 \times 2.286} = 33.0^\circ$$

The value reported by Armstrong and Lowry (144) was $\left[\alpha\right]_D^{18} = 31.1^\circ$

Attempts at Resolution with the Acid Chloride.

1) A solution in 10 cc. dry pyridine was made of 1.0 gm. of the acid chloride (.004 mole) and 1.0 gm. of alcohol (0.004 mole). The solution was prepared while the flask was submerged in ice water. The flask was allowed to stand overnight, then the contents were poured into 100 cc. of water with 10 cc. of concentrated hydrochloric acid. The oily precipitate was extracted with ethyl ether. The solvent was removed from the dried extract by evaporation. An oil was obtained which could not be crystallized by cooling in dry ice, or precipitating from mixtures of the common solvents. It was allowed to stand in the refrigerator many weeks, but only a few crystals of the alcohol crystallized.

2) A solution of 0.26 gm. alcohol (0.001 mole) in 5 cc. anhydrous pyridine was prepared and 0.24 gm. d- camphor sulfonyl chloride (0.001 mole) was added. The solution was refluxed 5 hours. Then water was added. The mixture was extracted with ether, and the extract was washed with dilute hydrochloric acid. However, removal of the solvent from the dried extract left only an oil which could not be crystallized by the usual techniques.

3) A solution of 1.8 gm. d- camphor sulfonyl chloride (0.0072 mole) and 0.4 gm. alcohol (0.0015 mole) in 10 cc. dry benzene was prepared, and 1 c.c. pyridine (0.013 mole) was added. This mixture was allowed to stand for 5½ days, then poured into 100 cc. of water and 2 cc. of concentrated sulfuric acid. The organic material was treated as in the experiments above, but only a non-crystalline oil could be obtained after prolonged attempts at crystallization.

(d) D- Camphoric Anhydride with Alcohol.

The reagent was prepared by the oxidation of d- camphor with nitric acid. The anhydride crystallized out of a mixture of acetic anhydride and acetyl chloride with a melting point of 223 - 224°C. The value given in Merck's Index (145) is 216 - 217°C. The procedure followed was that of Noyes (146). Their period of heating was shortened from 65 hours to 48 hours. This decreased the yield from 62% to 54%. The anhydride was obtained in 70% yield (reported 68%).

A mixture of 2.6 gm. camphoric anhydride (0.013 mole) and 3.4 gm. alcohol (0.013 mole) with 25 cc. pyridine were refluxed together for 17 hours. The cooled mixture was poured onto ice and 30 cc. concentrated hydrochloric acid. 1.6 gm. of a white crystalline precipitate were collected on a filter, and shown to be camphoric anhydride by melting point and optical rotation. Alcohol was recovered by an extraction of the filtrate with ether.

(e) L- menthoxy acetyl chloride with alcohol.

L- menthoxy acetic acid was prepared from l- menthol and chloroacetic acid in 73% yield, and converted to the acid chloride in 91% yield. The procedures followed were those of Leffler and Calkins (147).

The optical rotation of the acid in methanol solution was -

$$[\alpha]_D^{24} \quad \frac{-5.47 \times 100}{2 \times 2.982} \quad -91.7^\circ \qquad \text{Reported} \qquad [\alpha]_D^{25} = -92.4^\circ$$

The optical rotation of the acid chloride in chloroform solution was -

$$[\alpha]_D^{25} = \frac{-4.80 \times 100}{2 \times 2.704} = -88.7^\circ \qquad \text{Reported} \qquad [\alpha]_D^{25} = -89.3^\circ$$

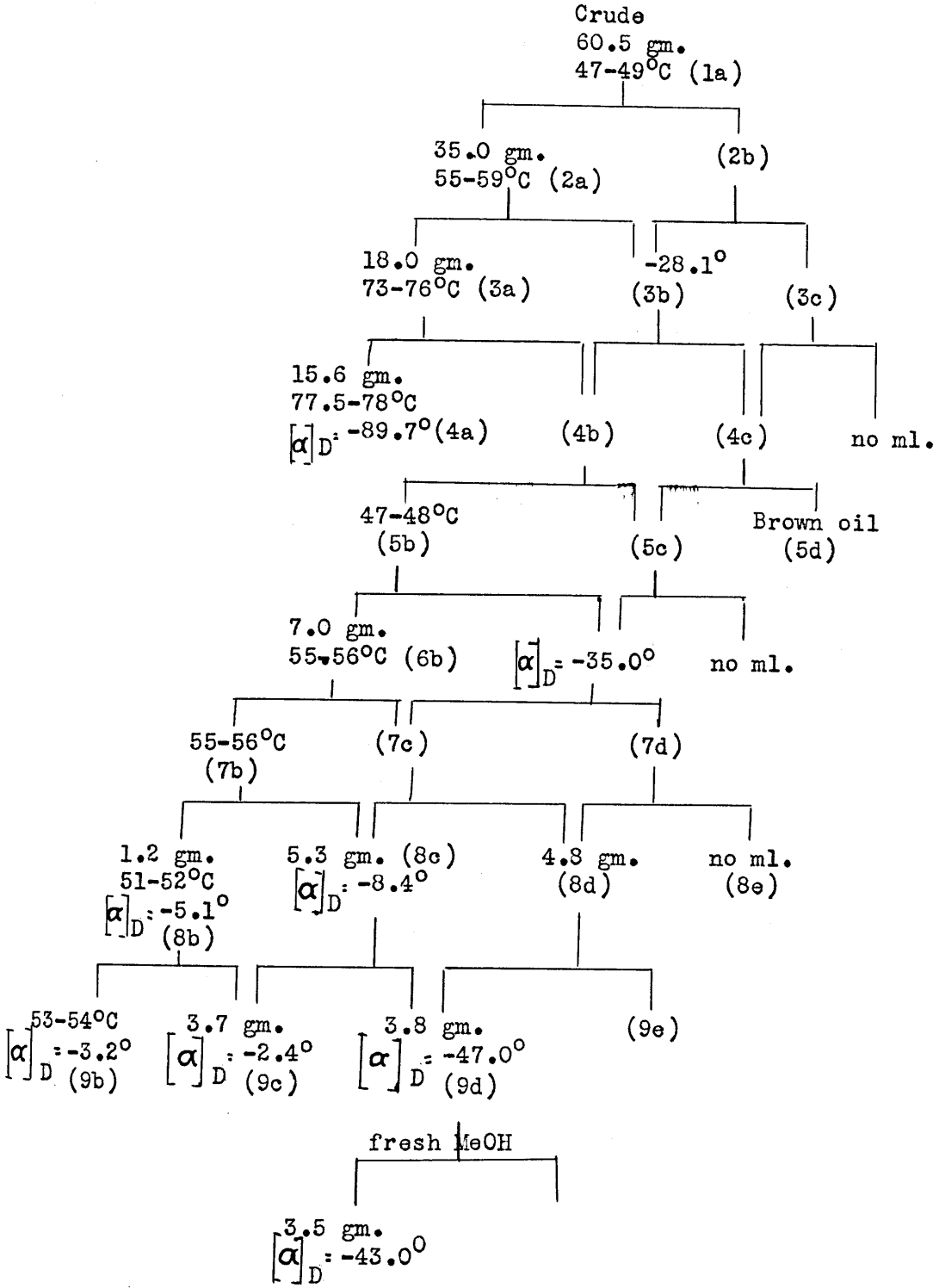
Preparation of the L- Menthoxy Acetate of the dl- Alcohol.

1) A solution of 10.4 gm. of alcohol (0.04 mole) in 40 cc. anhydrous pyridine (dried over sodium hydroxide) was prepared. 9.3 gm. of l- menthoxy acetyl chloride (0.04 mole) was slowly added, while the reaction flask was swirled in ice water. The resulting mixture was allowed to stand overnight, and then poured into 400 cc. of ice water. The organic material was extracted with ethyl ether and the extract was washed many times with 6 N hydrochloric acid, followed by thorough sodium carbonate and water washes. The solvent was removed from the extract by evaporation and the product was steam distilled to remove any unchanged alcohol. The residue was extracted with ethyl ether, and the extract dried over sodium sulfate. When the solvent was removed, a brown oil was left, which could not be made to crystallize by any of the usual techniques, such as washing with mixtures of solvents, or cooling in dry ice.

2) A solution of 32.7 gm. of l- menthoxy acetyl chloride (0.133 mole) and 34.5 gm. of alcohol (0.133 mole) in 100 cc. dry benzene (treated with sodium) was prepared. 21.4 cc. of dry pyridine (20.9 gm., 0.265 mole) were added dropwise to the benzene solution, which was kept at 5°C. (The pyridine was distilled from calcium oxide, over which it had been allowed to stand for several days.) This caused the precipitation of a white crystalline solid. After allowing the reaction mixture to stand at room temperature overnight, the solid was collected on a filter. It was very soluble in water and was presumed to be pyridine hydrochloride. The product weighed 15.3 gm., a quantitative yield of the hydrochloride.

The benzene solution was washed twice with 50 cc. portions of 5% hydrochloric acid. This was followed by a similar treatment with 5% sodium bicarbonate, and water. The benzene solution was dried over sodium sulfate, and the solvent removed by distillation. After standing one day at 0°C, complete crystallization had taken place. The crude product consisted of oily crystals, and weighed 60.5 gm., a quantitative yield.

The crude crystalline product was given a systematic fractional crystallization from water.


Crude
60.5 gm.
47-49°C (1a)
35.0 gm.
55-59°C (2a)
(2b)
18.0 gm.
73-76°C (3a)
-28.1°
(3b)
(3c)
15.6 gm.
77.5-78°C
[α]D: -89.7° (4a)
(4b)
(4c)
no ml.
47-48°C
(5b)
(5c)
Brown oil
(5d)
7.0 gm.
55-56°C (6b)
[α]D = -35.0°
no ml.
55-56°C
(7b)
(7c)
(7d)
1.2 gm.
51-52°C
[α]D: -5.1°
(8b)
5.3 gm. (8c)
[α]D: -8.4°
4.8 gm.
(8d)
no ml.
(8e)
53-54°C
[α]D = -3.2°
(9b)
3.7 gm.
[α]D = -2.4°
(9c)
3.8 gm.
[α]D = -47.0°
(9d)
(9e)
fresh MeOH
3.5 gm.
[α]D = -43.0°

Fraction (4a) was considered to be the pure l- menthoxy acetate of the l- alcohol. It was prepared in 25.8% of its expected yield.

Anal. Calcd. for $C_{20}H_{26}O_3Cl_4$	C, 52.65;	H, 5.75;	Cl, 31.18
Found	C, 52.69	H, 5.70	Cl, 31.32
	52.40	5.59	31.33
	52.55	5.65	31.33

L- Alcohol.

A solution of 15 gm. of the l- menthoxy acetate and 15 gm. anhydrous zinc chloride in 25 cc. anhydrous methanol was refluxed one hour. A mixture of 500 cc. water and 20 cc. concentrated hydrochloric acid was added. The organic material was removed by extraction with two 100 cc. portions of ethyl ether. The extract was washed with 10% sodium carbonate to remove l- menthoxy acetic acid. The solvent was removed by distillation, and the pale yellow oily residue was distilled in vacuo. The distillate had a boiling point of 95 - 115°C at 0.2 to 0.4 mm. pressure, and weighed 11.8 gm.

The optical rotation of the alcohol in chloroform solution was -

$$[\alpha]_D^{25} = \frac{2.21 \times 100}{2 \times 1.805} = -61.2^\circ$$

The acetate of this crude alcohol was prepared as follows. 8 cc. of acetic anhydride was mixed with 11.8 gm. of the distillate in a flask. This was placed in an oil bath at 160°C for 3 hours. 20 cc. of water was then added, and the mixture was allowed to s tand overnight. The organic material was removed by extraction with ethyl ether. The extract was washed with 10% sodium carbonate and dried over sodium sulfate. The solvent was removed by

evaporation. The residue consisted of a crystalline product weighing 9.0 gm., and melting at 81 - 86°C. This was recrystallized from methanol, and 3.8 gm. of heavy needles, a yield of 26.2% based on the menthoxy acetate, were precipitated. This product had a melting point of 91 - 93°C.

The optical rotation of a solution of the product in chloroform was -

$$[\alpha]_D^{25} = \frac{-2.64 \times 100}{2 \times 2.109} = -62.6^\circ$$

Hydrolysis of the acetate with zinc chloride gave pure alcohol M.P. 51.5 - 53°C; $[\alpha]_D = -33.8^\circ$.

D - Alcohol.

Fractions (8b) and (9c), 4.9 gm., were considered the pure l- menthoxy acetate of d- alcohol. This represents an 8.1% yield. The product was hydrolysed to the alcohol, following a procedure similar to that used for the l- alcohol. A yield of white oil of 4.2 gm. was isolated. The acetate was also prepared by a similar procedure. The crude acetate melted at 58 - 73°C. It was recrystallized twice from methanol and then melted at 91 - 92.5°C. The pure product weighed 0.8 gm., 24.7%, based on menthoxy acetate.

The optical rotation of the alcohol in chloroform solution was -

$$[\alpha]_D^{25} = \frac{1.25 \times 100}{2 \times 1.066} = 61.5^\circ$$

Hydrolysis of the acetate with zinc chloride gave pure alcohol M.P. 50 - 52°C; $[\alpha]_D = 33.0^\circ$.

The melting point of a mixture of equal parts of the d- and l- alcohol acetates was 120.5 - 124°C.

Some of the mixture was mixed with an authentic sample of acetate. The melting point was 122 - 124°C.

(f) D- Bornoxy Acetyl Chloride with Alcohol.

Preparation of the Reagent.

D- Camphor was reduced to d- borneol, according to the procedure of Wallach (148). A solution of 100 gm. of d- camphor (0.66 mole) in 1 l. of dry ethanol was prepared. To the boiling solution was added 120 gm. sodium (5.2 mole) in small pieces. To dissolve the last pieces of sodium added, 250 cc. additional dry ethanol had to be poured in. 6 l. of water were added, and the white crystalline precipitate was filtered off. It was dissolved in petroleum ether, and the water was removed by separation, and by drying the solution over $CaSO_4$. The solvent was removed by distillation until precipitation of solid commenced. The flask was then cooled in the refrigerator, and the product collected on a filter. It weighed 74 gm., a yield of 73%.

The optical rotation of a solution in ethanol was -

$$\left[\alpha\right]_D^{25} = \frac{4.72 \times 100}{2 \times 10.56} = 22.4^\circ$$

Clark and Read (67) report $\left[\alpha\right]_D = 21.5^\circ$

D- borneol was converted into d- bornoxy acetic acid, following the procedure of Clark and Read (67), considerably modified.

A 3-neck flask was set up, equipped with an efficient mercury-sealed stirrer and a reflux condenser with a calcium chloride tube. In it was placed a solution of 34.3 gm. d- borneol (0.226 mole) in 150 cc. toluene

(distilled from sodium). 4.9 gm. sodium (0.213 mole) were added, and the solution was refluxed in an oil bath for 18 hours. Stirring was maintained so that the liquid sodium was suspended in fine particles throughout the toluene. The sodium residue was removed from the cooled solution by filtration, and found to weigh about 0.3 gm.

The apparatus was again assembled, with a dropping funnel in the third neck. To the stirred, refluxing solution was added dropwise a solution of 10 gm. chloroacetic acid (0.106 mole) in 100 cc. toluene. A precipitate formed at this stage, which remained throughout the period of refluxing and stirring of 24 hours. The mixture was then treated with 500 cc. water and 35 cc. sulfuric acid. The toluene layer was separated and the aqueous portion was extracted three times with 100 cc. portions of benzene. The toluene was combined with the extracts, and was extracted with 10% sodium carbonate solution, twice with 100 cc. portions, followed by a water wash. The alkaline extract was acidified with 20% hydrochloric acid. The bornoxy acetic acid was extracted with three 50 cc. portions of benzene. The solvent was removed from the dried extract by evaporation. The residual brown oil crystallized after standing several days in the refrigerator. It weighed 14.3 gm., a yield of 25.9%, and melted at 62 - 68°C.

The optical rotation of a solution of the acid in alcohol was -

$$[\alpha]_D^{20} = \frac{1.49 \times 100}{2 \times 2.306} = 32.3^\circ$$

A solution of 14.3 gm. d- bornoxy acetic acid in 10 cc. thionyl chloride was refluxed for 3 hours on the steam bath. The thionyl chloride

was removed by distillation and the acid chloride distilled at the water pump. B.P. 125 - 134°C at 10 mm. pressure. 11.5 gm. of the acid chloride were obtained, a yield of 74%.

The Preparation of the d- Bornoxy Acetate of the dl- Alcohol.

A solution of 5.5 gm. of alcohol (0.021 mole) and 5.2 gm. d- bornoxy acetyl chloride (0.021 mole) in 25 cc. dry benzene was prepared. 3 cc. of dry pyridine (0.0384 mole) were added to the cooled solution. A heavy precipitate was formed. The mixture was allowed to stand overnight and was then filtered. The solution was washed with 5% hydrochloric acid and 5% sodium bicarbonate. The solvent was distilled from the dried solution.

Great difficulty was experienced in obtaining crystals of the esters. They were finally obtained by slow evaporation of a solution in thoroughly dried methanol. 9.5 gm. of crude product was obtained, a yield of 99%. The melting point was 56.5 - 59°C.

The optical rotation of a solution in chloroform of the product was -

$$[\alpha]_D = \frac{0.54 \times 100}{2 \times 1.636} = 16.5^\circ$$

The product was recrystllized six times from methanol and bunches of white needles were obtained having a constant melting point of 70.5 - 71.5°C. The optical rotation had hardly been changed $[\alpha]_D = 18.9^\circ$.

Hydrolysis of this product was accomplished as for the l- menthoxy acetate on page 90. However, on conversion of the alcohol to the acetate, only the inactive product of melting point 118 - 122°C could be obtained. The melting point of a mixture of this material with authentic acetate was not depressed.

III Miscellaneous Methods of Resolution.

(a) Formation of Co-ordination Complexes.

1) Co-ordination - Complex Formation with Digitonin.

A solution of 1.0 gm. of digitonin and 0.32 gm. of the alcohol (excess) in 100 cc. of 50% ethanol was prepared. Complete solution was achieved at room temperature. The flask was allowed to stand at room temperature for 5 hours, but no crystals were deposited. It was then placed in the refrigerator for two hours, and a fine white crystalline deposit was obtained. The melting point of the precipitate was 210 - 212°C with frothing. The Merck Index reports digitonin to sinter at 225°C and melt at 235°C. The precipitate was distilled in vacuo at a pressure of 0.5 mm. An oil was obtained which did not crystallize on seeding with alcohol, nor on cooling in dry ice.

2) Co-ordination - Complex Formation with Desoxycholic Acid.

Commercial Rohm and Haas desoxycholic acid was purified according to the procedure of Sobotka and Goldberg (71). 5.0 gm. of the acid was dissolved in 25 cc. of hot ethanol. A small insoluble residue was removed by filtration. The filtrate was concentrated to 10 cc. and poured into 75 cc. cold anhydrous ethyl ether. The fine crystalline precipitate was collected on a filter and recrystallized from absolute ethanol. 1.6 gm. of material were obtained of melting point 103 - 104°C.

1.0 gm. of the pure acid and 5.2 gm. of the alcohol were dissolved in the minimum amount (10 cc.) absolute methanol. Cooling in the refrigerator for many weeks with thorough scratching caused no crystallization, however.

(b) Differential Reaction with an Optically Active Adsorbent.

The procedure followed was similar to that used by Henderson and Rule (22) and by Prelog and Wieland (23).

Lactose (Kahlbaum) was activated by digestion for 5 min. with chloroform, which was removed by placing in a vacuum dessicator for a day. The powder was put into a chromatographic adsorption tube, and made a column 20 cm. long by 3 cm. diameter.

1 gm. of alcohol was dissolved in 500 cc. petroleum ether, and poured through the column. The liquid came through at the rate of 1 drop per second. In a similar fashion 100 cc. of petroleum ether was poured through as an eluant. Adsorption had apparently taken place, as the eluant contained alcohol, which crystallized on seeding. However, neither this material, nor further residues from elution showed any activity in the polarimeter. The column was pushed onto paper and divided in thirds. These were extracted separately with ethyl ether. However, the residues from this process showed no optical rotation.

(c) Asymmetric Synthesis of Acetate.

A solution in 40 cc. carbon tetrachloride of 1.3 gm. alcohol (0.005 mole) 1.8 gm. brucine (0.0045 mole) and 1.0 cc. of acetic anhydride was prepared. The red solution was refluxed for 16 hours. A few brown crystals had separated. These were collected on a filter and found to be brucine. The filtrate was washed with 10% sodium carbonate, then with 10% hydrochloric acid. This removed the colour from the solution. The carbon tetrachloride solution was dried over sodium sulfate, and the solvent removed by eva-

poration. A crystalline product was obtained of melting point 121 - 125°C, weighing 0.74 gm., a yield of 49%. This material rotated a fraction of a degree in the dextro direction. However, an optically inactive product of melting point 123.5 - 125°C was obtained on recrystallization from acetic acid.

III Reactions of the Optically Active Alcohols.

The Preparation of 1-phenyl-1-(4-chlorophenyl)-2,2,2-trichloroethane from the Alcohol.

In a test tube were placed 1.3 gm. dl- alcohol (0.005 mole) and 5.1 gm. of 96% sulfuric acid (0.5 mole). The mixture was stirred vigorously and 0.47 gm. dry benzene (0.006 mole) was added. Stirring was continued for 16 hours at room temperature. The reaction mixture then contained a white precipitate. It was diluted with water, and the white precipitate was collected on a filter. The product weighed 1.7 gm., a quantitative yield, and melted at 64 - 74°C. After two recrystallizations from ethanol the product melted at 77 - 78°C and was not raised by further recrystallization.

In a test tube were placed 0.35 gm. of l- alcohol (0.0014 mole) $[\alpha]_D^{25} = -33.8°$ and 2.1 gm. of 96% sulfuric acid. 0.31 gm. of benzene (0.004 mole) were added to the vigorously stirred mixture. The stirring was maintained for 16 hours. Then the product was precipitated by adding water. The precipitate was collected on a filter and weighed 0.3 gm., a yield of 70%. The product melted at 73.5 - 74.5°C. It was recrystallized once from ethanol, and melted at 76.5 - 77.5°C. It gave a rotation of $[\alpha]_D = +2.2°$ in the polarimeter.

The Preparation of 1-phenyl-1-(4-chlorophenyl)-2,2,2-trichloroethanol from the Alcohol Acetate.

A mixture of 1.4 gm. of dl- alcohol acetate (0.0046 mole) and 9.2 gm. of 96% sulfuric acid (0.095 mole) was prepared in a test tube. The mixture was vigorously stirred while 0.42 gm. benzene (0.0054 mole) was added. Stirring was continued for 11 hours at room temperature. The reaction mixture then held a white precipitate. It was diluted with water, and the precipitate was collected on a filter. The product weighed 1.4 gm., a yield of 81.5%, and melted at 73.5 -75.5°C, after two recrystallizations from ethanol. The melting point of a mixture of this product and that from the alcohol was not depressed.

A mixture of 0.3 gm. l- alcohol acetate (0.001 mole) and 2.1 gm. of 96% sulfuric acid (0.02 mole) was stirred vigorously in a test tube. 0.078 gm. of benzene (0.001 mole) was added, and stirring was maintained for 18 hours. A white precipitate had formed after 1 hour. The reaction mixture was diluted with water and filtered. The crude product weighed 0.4 gm., a quantitative yield, and melted at 67 - 70°C. After recrystallization from ethanol, it showed no activity in the polarimeter.

The Testing of the D- and L- Alcohols as Contact Insecticides.

The d- and l- alcohols, separated by l- menthoxy acetyl chloride, were submitted to the Department of Genetics, at McGill University for insecticidal testing.

The tests consisted of the exposure of Drosophila to a film of DDT on glass under standard conditions for 18 hours. The amount of DDT present was sufficient to cause a mortality of 30 to 50%. The test was repeated using a series of concentrations of the compound to be tested. That concentration which gave a mortality similar to that for DDT was noted. Its reciprocal gave the relative potency of the material.

The value for the laevo alcohol was twice that for the dextro. The value for the racemic lay slightly above that for the dextro.

The mechanism of toxicity appeared different for the alcohols than for DDT. It was easy to tell when flies had been killed by DDT, for they were shrivelled. DDT poisoning takes about six hours for the effect to set in. Flies treated with the alcohol were knocked down within an hour, but did not shrivel up for several days.

CONTRIBUTIONS TO KNOWLEDGE.

1) The alcohol 1-(4-chlorophenyl)-2,2,2-trichloroethanol has been resolved into its optical isomers.

2) These isomers have been tested for ultimate toxicity as contact insecticides on Drosophila. Over a limited range, the laevo has a relative potency twice that of the dextro.

3) The condensation of one optically active alcohol with benzene in the presence of sulfuric acid yielded the corresponding diaryl ethane, retaining some optical activity.

SUMMARY

1) The alcohol 1-(4-chlorophenyl)-2,2,2-trichloroethanol was resolved into its optical isomers. The specific rotations were $[\alpha]_D^{25} = 33.0^\circ$ and -33.8°. The specific rotations of the corresponding acetates were $[\alpha]_D^{25} = 61.5^\circ$ and -62.6°.

2) The above resolution was effected by fractionation of the l- menthoxy acetates of the alcohol. These were prepared by mixing the alcohol and l- menthoxy acetyl chloride in benzene solution and adding excess pyridine.

3) The alcohol could not be converted into an acid phthalate, succinate, sulfate or camphorate; or into a crystalline d- camphor sulfonate or l- menthyl glycine ester. Neither could it be converted into a crystalline l- menthoxy acetate when the reaction was performed in pyridine.

4) The l- isomer was obtained as the acetate in very poor yield by fractionation of the l- menthyl urethane of the alcohol and hydrolysis by distillation from calcium hydroxide.

5) The d- bornoxy acetates of the alcohol were prepared. The product was recrystallized several times but no separation of the diastereoisomers could be obtained.

6) The synthesis of d- bornoxy acetyl chloride, and l- menthyl isocyanate was taken from the literature and improved upon.

7) Hydrolysis of some substituted acetates of the alcohol was achieved by refluxing in a solution of zinc chloride in methanol.

8) One of the optically active alcohols was converted to the diaryl ethane by condensation with benzene. This product still retained some optical activity. Theoretical deductions from this fact are drawn.

9) The separated isomers were tested for ultimate toxicity as contact insecticides on Drosophila. Over a limited range, the laevo has a relative potency twice that of the dextro.

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