APPROVAL SHEET

Herman Sanders, Doctor of Philosophy, 1947

Studies In Pyrane Chemistry

Thesis and abstract approved: G. Norman Woods.
Professor in charge of thesis

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# STUDIES IN PYRANE CHEMISTRY

By

Herman Sanders

Thesis submitted to the Faculty of the Graduate School of the University of Maryland in partial fulfillment of the requirements for the degree of Doctor of Philosophy

1947





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## ACKNOWLEDGMENT

The writer wishes to express his deep appreciation to Dr. G. Forrest Woods for the suggestion of this problem and for his continuous guidance and interest during the course of the research.

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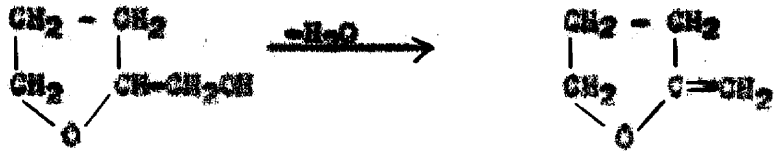
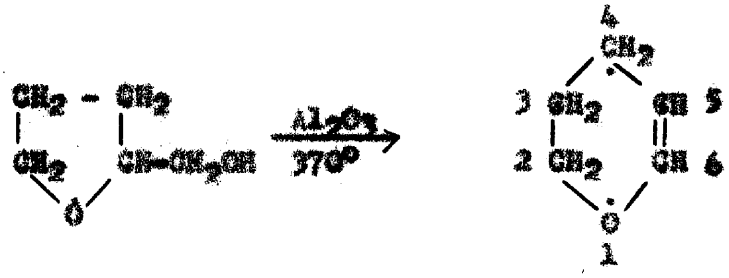
## HISTORICAL AND THEORETICAL

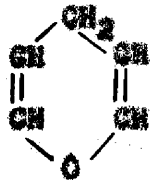
A study of the stability of the ring in tetrahydrofurfuryl derivatives was made by subjecting tetrahydrofurfuryl alcohol to catalytic dehydration over aluminum oxide at 370-380°[1]. The dehydration of this alcohol might be expected to yield 1,4-epoxypentene-4:



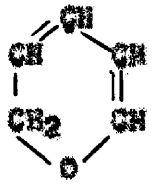

Instead, a compound was obtained which differed in chemical and physical properties from 1,4-epoxypentene-4 and subsequently proved to be 2,3-dihydropyrane. Thus, catalytic dehydration of tetrahydrofurfuryl alcohol leads to a ring enlargement with the formation of a simple dihydropyrane compound.




Although 1:4 pyrane (γ pyrane) and 1:2-pyrane (∝ pyrane) are theoretically




1:4-pyrane
or
γ pyrane




1:2-pyrane
or
∝ pyrane

capable of existence, their preparation has never been reported. However, tetrahydropyrane has long been recorded in the literature[2] and the preparation of 2,3-dihydropyrane bridges a gap between pyrane and tetrahydropyrane.

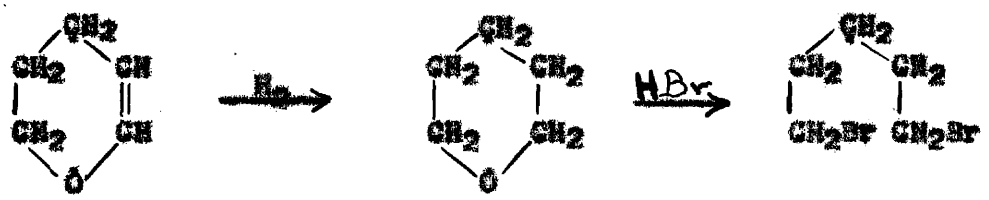
Ring enlargement resulting from the dehydration of an alcohol, although unusual, had been observed prior to the dehydration of tetrahydrofurfuryl alcohol. For example, dehydration of cyclobutylmethanol yields cyclopentene[3].

The structure of 2,3-dihydropyrane was established by Paul[1] as follows:

A - Position of the oxygen bridge

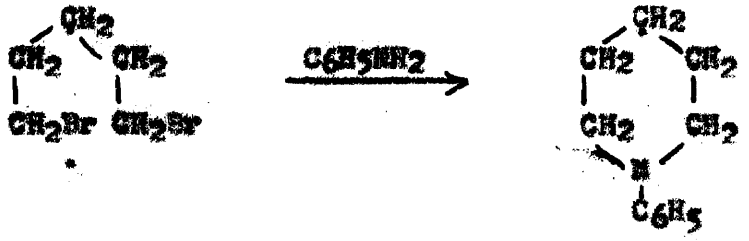
(1) Catalytic hydrogenation yielded a product with the identical physical constants reported for tetrahydropyrane.

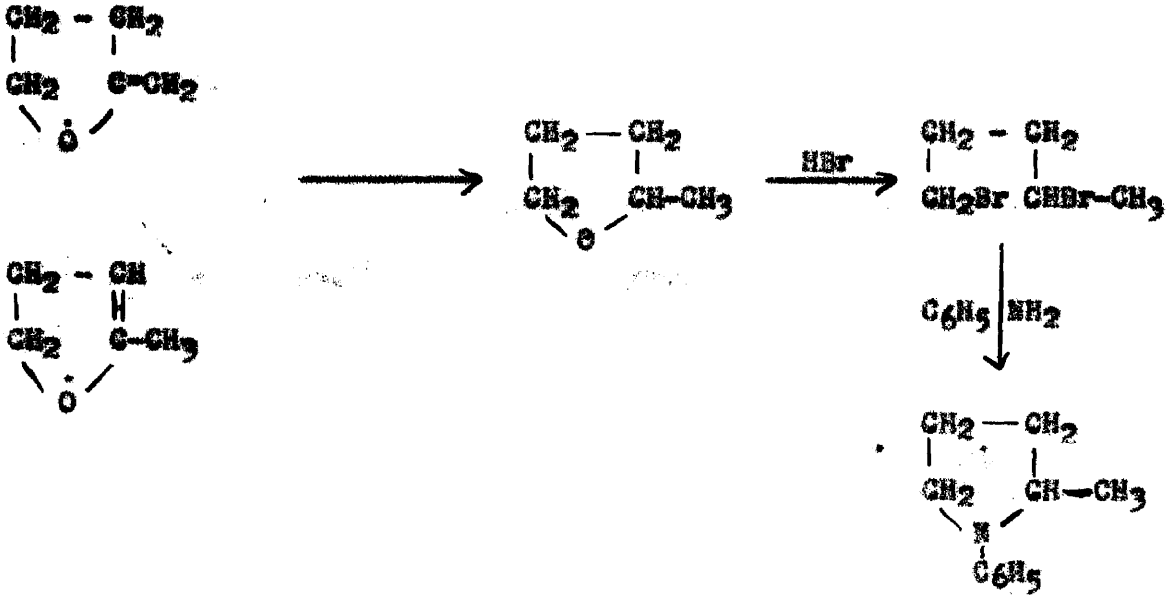
(2) This hydrogenated product reacted with hydrogen bromide to yield 1,5-pentamethylene bromide. These results are in accord with the proposed scheme:




Under these same conditions 1,4-epoxypentene-4, $CH_2-CH_2-CH_2-C=CH_2$ (O), and 1,4-epoxypentene-3, $CH_2-CH_2-CH=C-CH_3$ (O) would have yielded first 2-methyltetrahydrofurane and then 1,4-dibromopentane. The nature of the dibromide obtained from the reaction of the hydrogenated product of 2,3-dihydropyrane with hydrogen bromide was indisputably established as 1,5-pentamethylene bromide since it reacted with aniline to yield

N-phenylpiperidine. Under these conditions, 1,4-dibromopentane would have yielded ∝-methyl-N-phenylpyrrolidine. Thus, the oxygen bridge was established at the 1,5 positions



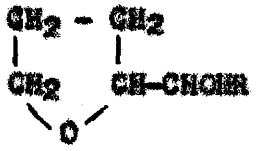


B - Position of the double bond

Once the existence of a pyrane ring was established, determination of the position of the double bond in dihydropyrane was essential. Two possibilities exist as shown by the formulae below:

Paul was led to accept structure I as correct on the basis of hydrolysis and subsequent bromination studies. Dihydropyrane was easily hydrolyzed in the presence of a trace of mineral acid to yield an aldehyde. The dibromide obtained from dihydropyrane was easily decomposed by water and showed the presence of a very labile bromine atom. These observations are not in accord with structure II but are in accord with those expected for structure I, a vinyl ether, -CH=CH-O-R. A more detailed discussion of these reactions and their significance is presented in another section of this thesis. On the basis of the observations described above, Paul assigned the structure of 2,3-dihydropyrane to the product obtained from the catalytic dehydration of tetrahydrofurfuryl alcohol.

The study of the dehydration of tetrahydrofurfuryl alcohol was extended by Paul[4] to the homologous series of tetrahydrofurfuryl alcohols of the type



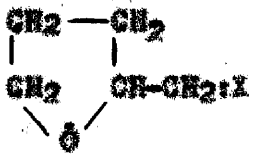
where R=$CH_3$-$C_3H_7$-$C_6H_5$

These alcohols were prepared by the catalytic hydrogenation of the corresponding substituted furfuryl alcohols. Dehydration of 1,4-epoxyhexanol-5 (R=$CH_3$) over aluminum oxide at 400° gave a 36% yield of 2-methyl - $\Delta^2$-dihydropyrane. This is similar to the ring enlargement encountered in the dehydration of tetrahydrofurfuryl alcohol. The other two substituted tetrahydrofurfuryl alcohols when subjected to catalytic dehydration gave a complex mixture of products, in which it was not

possible to determine the identity of the components ~~therein~~, with the exception of small amounts of styrene which was present in the mixture of products obtained from the dehydration of the phenyltetrahydrofurfuryl alcohol.

The possible mechanisms of the rearrangements which accompany the rupture of the ring in tetrahydrofurfuryl derivatives have been discussed in great detail by Paul[5] in terms of the electronic structures involved and with respect to the "functional influence" of neighboring groups. The following is a presentation of Paul's discussion of the possible mechanisms involved.

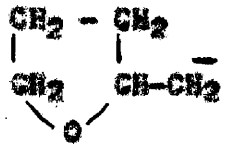
It has long been known that the characteristic properties of a group can be modified by neighboring groups to such an extent as to determine the degree of ease and the course of a reaction. The general formula of a tetrahydrofurfuryl derivative is:



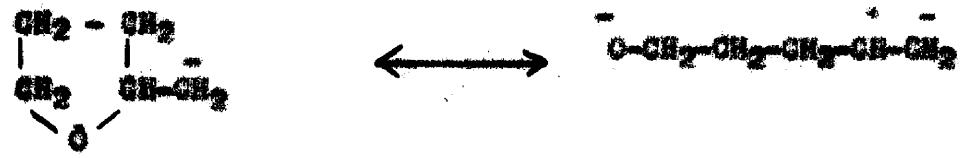
in which X tends to be negative or positive, ie. - in the rupture the bond $CH_2$:X X will retain or lose the two valence electrons binding X to $CH_2$. The two possible cases are now considered.

<u>First Case - X is positive</u>

The rupture of the bond and the departure of X will give the negative ion:

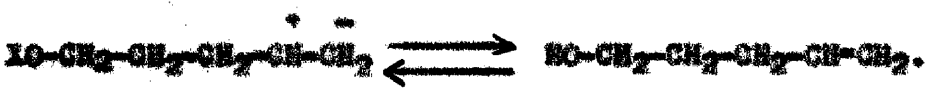


This ionization is in resonance with one which tends to lead to the rupture of the oxygen bond:

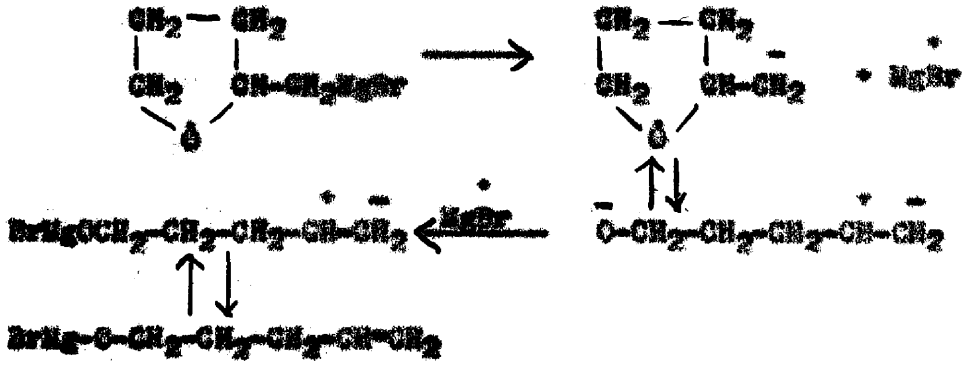


As a result, the departure of X and also the formation of this tripolar ion should be very easy. Since the oxygen is more strongly negatively charged than the terminal carbon atom, then in the rearrangement which follows, X will preferentially combine with the oxygen to yield the structure:

This is the activated form of a derivative of pentane-4-ol-1:

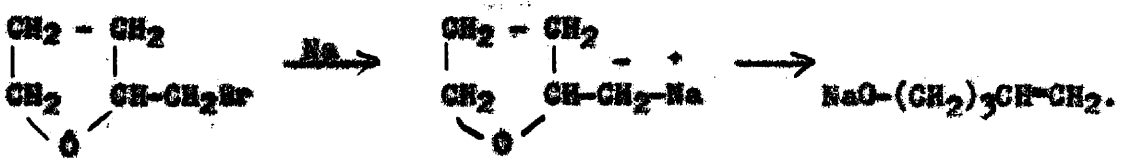


It has been found that tetrahydrofurfurylmagnesium bromide isomerises with great ease to give the bromomagnesium alcoholate of pentane-4-ol-1[6]. This reaction can be explained by the mechanism proposed above:



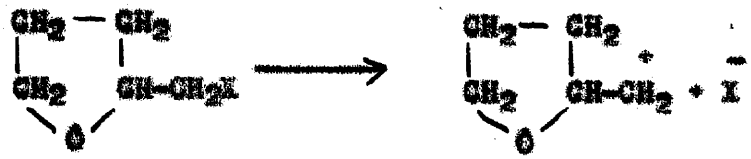
Further, if the proposals[7,8] of the existence of a metal intermediate in the reaction of sodium with an organic halogen compound are accepted, then the formation of sodium pentenolate from the reaction

of sodium and tetrahydrofurfuryl bromide can also be explained by the mechanism suggested above:

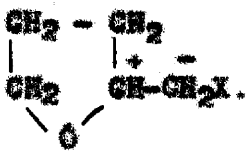


Second Case - X is negative

I. Any reaction which will proceed by the ionization:

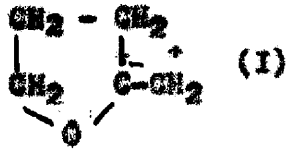


will be difficult to effect since such an ionization will be in conflict with the negative polarity which the oxygen bridge tends by induction to give to the $-CH_2$ gp:



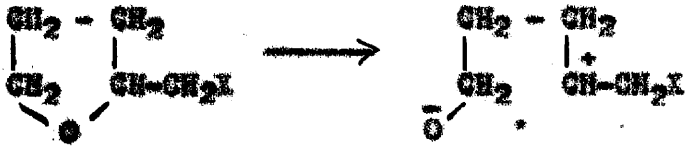
Tetrahydrofurfuryl bromide, for example, does not react with potassium acetate even at 150°; in order to effect a reaction it is necessary to use silver acetate at 160°. Similarly, no reaction was observed between tetrahydrofurfuryl bromide and potassium cyanide either in alcoholic solution or with dry potassium cyanide at 150°.

II. On the other hand, the reactions which proceed by the elimination of HX will be easy to effect since the ion which is first formed:



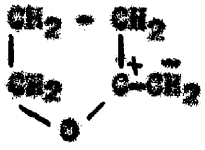
(I)

is not very stable. Its polarization is in opposition with the polarization which induces the ionization of the oxygen atom:

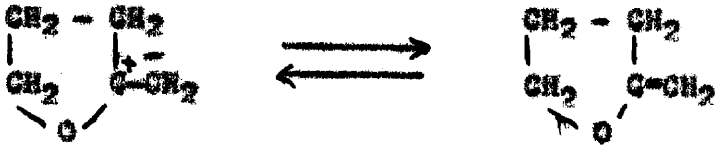


Therefore the effect will be that this ion (I) will rearrange easily to form a more stable system. This rearrangement can proceed in two different manners:

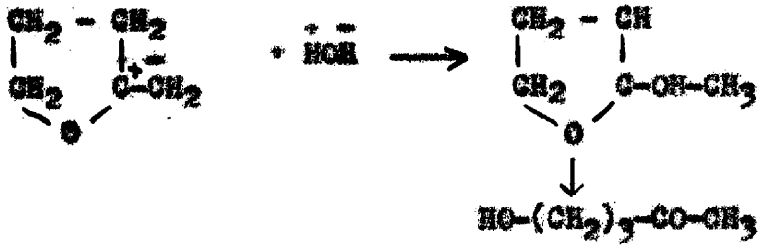
A.) The two valence electrons which originally were closer to the negatively charged carbon atom involved in the oxygen bond than to the $-\overset{+}{C}H_2$ group in ion (I) will approach the latter group. This will lead to the ion:



in which the carbon bound to the oxygen bridge is strongly positively polarised. This is a stable structure and is in effect the activated form of 1,4-epoxypentene-4:

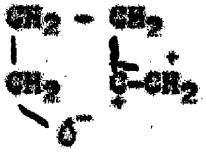


There is no ambiguity as to the direction of polarization of this compound since on hydrolysis it yields pentan-1-ol-one-4:

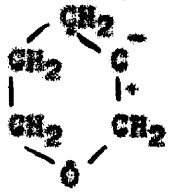


If the ion (I) were involved in the hydrolysis, then tetrahydrofurfuryl alcohol would have been obtained. This mechanism seems to be the one involved in the reaction of tetrahydrofurfuryl bromide with potassium hydroxide or sodamide since 1,4-epoxypentene-4 is the only product isolated[5].

B.) Considering the strong electron accepting character of oxygen, the departure of HX can be visualized with the simultaneous rupture of the oxygen bond. This would lead to the formation of a tetrapolar ion:



In the rearrangement which will follow this ionization, the free valence of the oxygen can associate itself either with the secondary carbon atom or with the primary carbon atom. In the latter case, the ion formed:



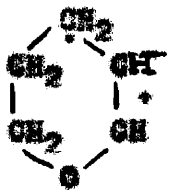
can not exist if the following rules are accepted[9]:

a) when a molecule has a methylene group $-\overset{-}{C}-$ it must undergo a migration of an atom of hydrogen or of a radical in the alpha position.

b) the atom of hydrogen attached to a positively charged carbon is more mobile than when it is attached to a neutral or negatively charged carbon atom.

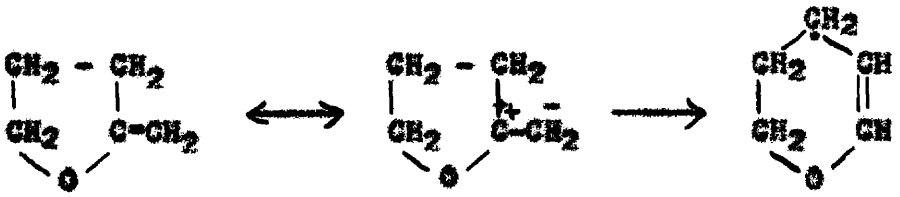
c) the charge of the migrating atom or radical is, in general, not imposed upon the carbon atom receiving it.

By accepting the above rules, then the formation of the ion

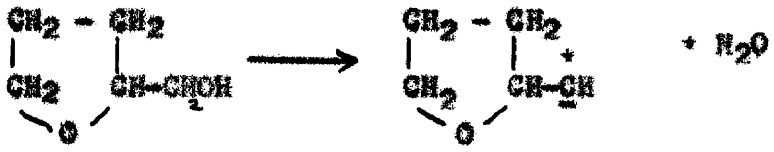


is easily visualized. This is the activated form of 2,3-dihydropyrane. Thus (8) seems to be a possible mechanism for the formation of 2,3-dihydropyrane by the catalytic dehydration of tetrahydrofurfuryl alcohol.

However, for such a mechanism to be reasonable, it must be established that the oxygen bridge in ion (I) can be opened under the conditions of the dehydration. Direct verification of the ability of the oxygen link of ion (I) to open is not possible because of the great instability of this ion. However, Paul[5] was able to show that ring opening in the ionic isomer of ion (I) can occur. He was able to convert 1,4-epoxypentene-4 into 2,3-dihydropyrane by passing the vapors of the former substance over aluminum oxide at 380°.



Since only a small amount of 2,3-dihydropyrane was obtained from the isomerization of 1,4-epoxypentene-4, Paul is unprepared to state that the sequence of reaction mechanisms which he proposed above (B), is the sole producer of 2,3-dihydropyrane in the catalytic dehydration of tetrahydrofurfuryl alcohol. It is also maintained by Paul that, it is very possible for the dehydration to be of a methylenic type:

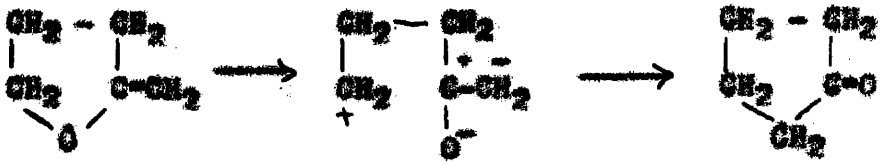


In the case of the formation of 2,3-dihydropyrane, this methylenic type of dehydration should resolve itself to a simple migration of the oxygen link if the hypotheses of Prevost and Kirrmann[9] presented above are accepted.

Finally, Paul found it impossible to reconcile the rearrangement of 1,4-epoxypentene-4 into 2,3-dihydropyrane with the results obtained by Lauer and Spielmann[10] in the rearrangements of vinyl ethers. These authors have observed the following rearrangement at a temperature of 300-350° in a number of cases:

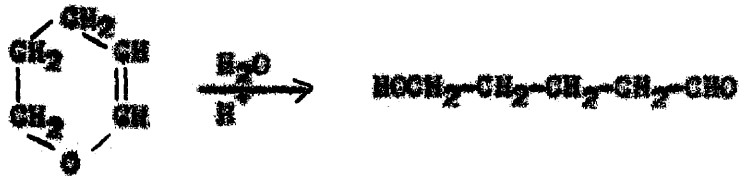


If 1,4-epoxypentene-4 were to undergo such a rearrangement cyclopentanone would be obtained according to the scheme:



Paul was unable to detect the presence of this ketone in the thermal isomerization of 1,4-epoxypentene-4 into 2,3-dihydropyrane, or in the dehydration of tetrahydrofurfuryl alcohol into 2,3-dihydropyrane. (Note 1)

Most of the reactions of 2,3-dihydropyrane are similar to those observed for other vinyl ethers. 2,3-Dihydropyrane possesses an ethylene link of marked reactivity; the hydrolysis of 2,3-dihydropyrane in a dilute acid medium occurs rapidly at 90°, or slower at room temperature, to yield 5-hydroxypentanal[12].



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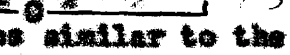
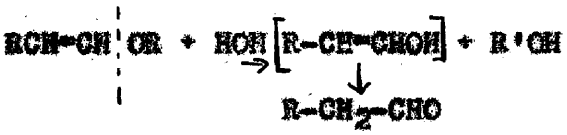
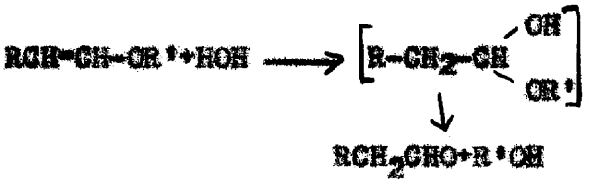
(Note 1*) In the proposed mechanism of Paul it is implicit that 1,4-epoxypentene-4 is capable of existence. Indeed, he describes the preparation of 1,4-epoxypentene-4 by the action of sodium on tetrahydrofurfuryl bromide[3]. It is interesting to note that Paul did not offer any proof of the structure of the compound to which he assigned the formula of 1,4-epoxypentene-4. In this connection, it should be observed that 1,4-epoxypentene-3[11],  would possess the chemical and physical properties similar to the substance which Paul has ascribed the structure of 1,4-epoxypentene-4. We feel that Paul's assigned structure of 1,4-epoxypentene-4 to the substance obtained from tetrahydrofurfuryl alcohol and sodium is subject to question.

The mechanisms of the hydrolysis of 2,3-dihydropyrane have been postulated by Paul[12] to be similar to those of the hydrolysis of vinyl ethers. Two mechanisms have been proposed by Paul:

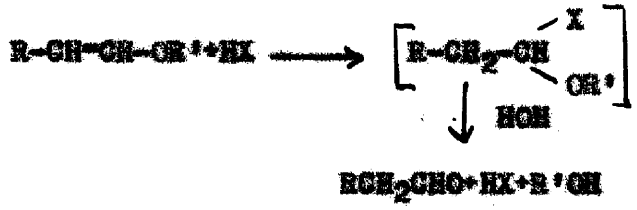
1) The rupture of the oxygen link followed by ketonization of the enol:



2) The addition of water to the ethylene link and spontaneous elimination of a molecule of alcohol from the resulting hemiacetal:

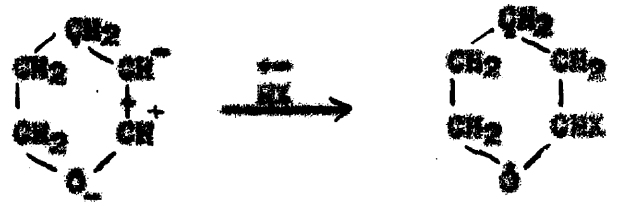


The catalytic role of the halogen acid in the hydrolysis can be explained as follows:



The intermediate is an alpha haloether, a structure which is easily capable of hydrolysis. Paul is of the opinion that the second mechanism is the most reasonable since it is the ethylene link which is very reactive in vinyl ethers rather than the oxygen linkage. Further, Paul[12] lends support to the second mechanism by observing that the oxygen bond in 2,3-dihydropyrane is rather stable since it is not ruptured even by the action of acetic anhydride at 160° and that 2,3-dihydropyrane adds anhydrous hydrogen bromide to yield a bromoether which is easily decomposable by water. In brief, the addition reactions may be represented

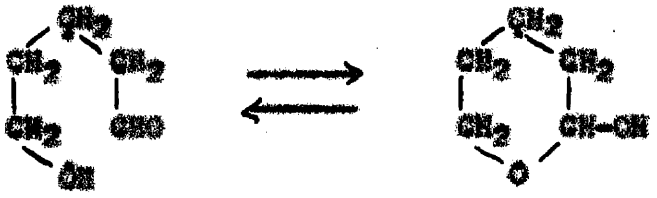
by the following scheme:



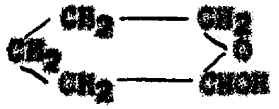
in which

HX = HCN, ROH, HBr, HOCl and $COCl_2$.

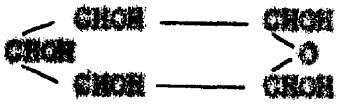
It has been stated by Paul[12] that 5-hydroxypentanal, the hydrolysis product of 2,3-dihydropyrane exists almost exclusively as its isomer, the cyclic 2-hydroxytetrahydropyrane:



The assignment by Paul of the cyclic structure to this hydroxyaldehyde was based on physical properties i.e.: boiling point and molar refractivity. Further support of the existence of this cyclic structure was presented by Schnlepp and Geller[13], who, on the basis of absorption spectra studies estimated that 5-hydroxypentanal exists as 95% in its cyclic form and 5% as the linear hydroxyaldehyde. This equilibrium between the cyclic and linear form of hydroxy aldehydes is not unique. It is well known in the sugar series. Indeed, 2-hydroxytetrahydropyrane may be regarded as an extreme form of a desoxypentose.



2-hydroxytetrahydropyrane

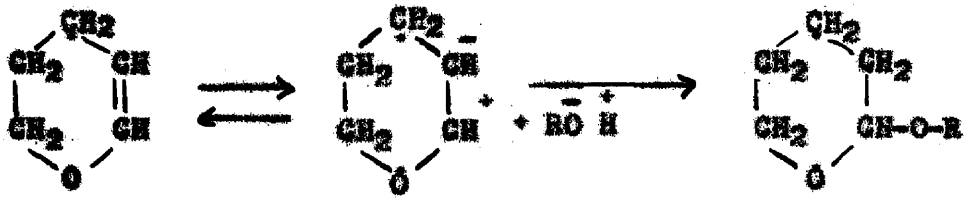


pentose

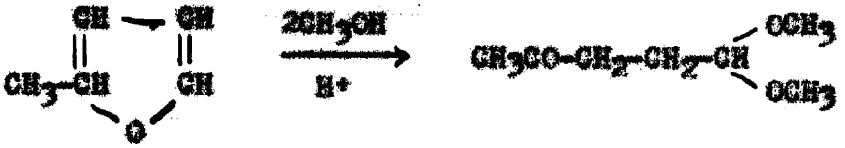
Many of the reactions of 5-hydroxypentanal[12] can be explained

on the basis of its linear, rather than its cyclic form. An aqueous solution of this substance readily yields an oxime; when subjected to the action of aluminum amalgam, an aqueous solution of 5-hydroxypentanal yields 1,5-pentamethylene glycol; oxidation of the hydroxyaldehyde with silver oxide leads to 5-hydroxyvaleric acid.

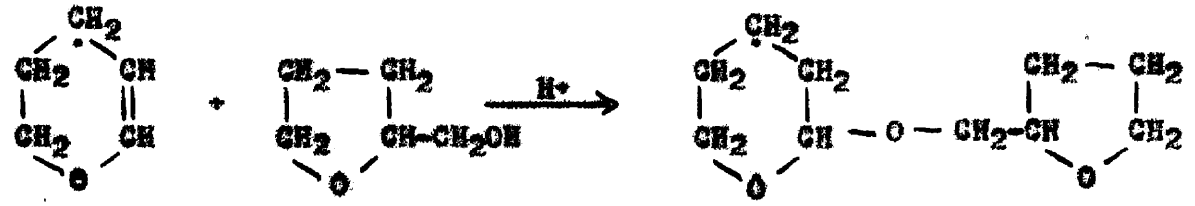
In the presence of a trace of mineral acids, alcohols add very readily to 2,3-dihydropyrane to yield cyclic acetals[12] which may be regarded as glycosides of deoxypentoses:



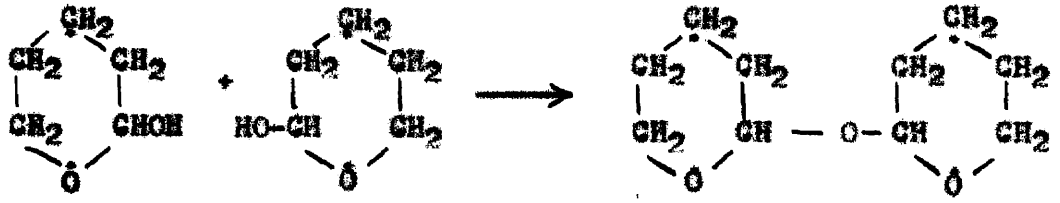
Prolonged refluxing of 2,3-dihydropyrane with alcohols containing 1% hydrochloric acid does not open the ring to produce linear acetals[12]. This is in contrast to the furane series in which 2-methylfurane under these same conditions yields the linear acetal of pentanone-4-al-1:[14]



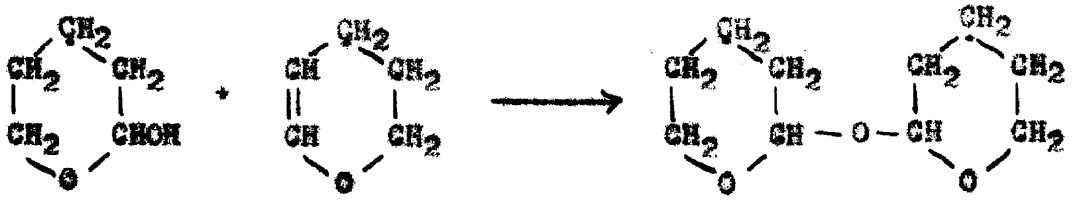
It thus appears that the pyrane ring is more stable than the furane ring. Paul[12] prepared 2-methoxytetrahydropyrane by the addition of methyl alcohol containing small quantities of hydrogen chloride to 2,3-dihydropyrane. A cyclic acetal was also prepared from 2,3-dihydropyrane and tetrahydrofurfuryl alcohol in the presence of an acid catalyst[12]:



It is interesting to note that although the main reaction product of the acid hydrolysis of 2,3-dihydropyrane is 5-hydroxypentanal, (2-hydroxytetrahydropyrane), small amounts of the symmetrical acetal of 2-hydroxytetrahydropyrane have been isolated and identified[12]. Formation of this substance could result from the condensation of two molecules of the cyclic aldehyde with the elimination of water:



or the reaction may be a result of the addition of 2-hydroxytetrahydropyrane to 2,3-dihydropyrane:

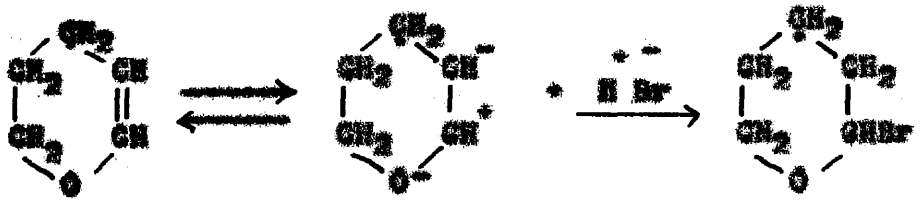


These cyclic acetals are stable in an alkaline medium but are rapidly hydrolyzed by dilute acids to 5-hydroxypentanal and the corresponding alcohols. In addition, the cyclic acetals reduce Fehling's solution and give a color with Schiff's reagent.

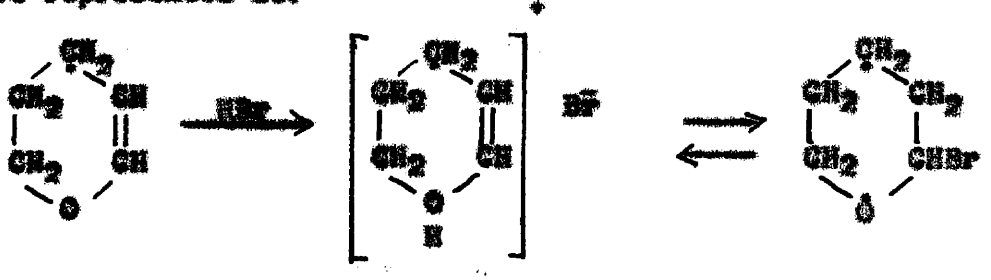
It has been shown above that the ethylene link in

2,3-dihydropyrane is very reactive and will add water and alcohols. It was also shown that bromine and hydrogen bromide added easily to 2,3-dihydropyrane[15]. The halogen derivatives of dihydro- and tetrahydropyrane are versatile and interesting substances. Moreover, they are valuable intermediates for the preparation of many pyrane compounds.

Rigorously dried hydrogen bromide reacts very readily with 2,3-dihydropyrane to yield 2-bromotetrahydropyrane:



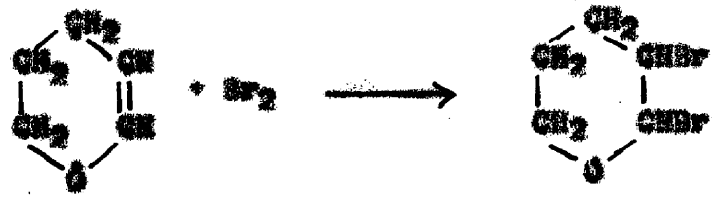
The bromine atom is alpha to an ether group and consequently possesses a high degree of lability. 2-Bromotetrahydropyrane is unstable and can not be easily purified by distillation. Schostakovskii[16] postulated the formation of an oxonium compound as an explanation of the reactions observed for vinyl ethers. He suggested that substances such as halogens and hydrogen halides are capable of addition to vinyl ethers to form an oxonium compound which subsequently rearranges to saturate the ethylene link. The halogenated ether is in equilibrium with its oxonium compound. The addition of hydrogen bromide to 2,3-dihydropyrane may be represented as:



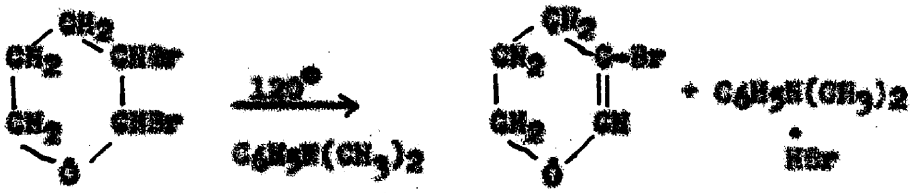
The lability of the bromine atom in 2-bromotetrahydropyrane may be

explained on the basis of the formation of its oxonium compound.

The addition of bromine to 2,3-dihydropyrane dissolved in a dry inert solvent at low temperatures yields 2,3-dibromotetrahydropyrane[15].



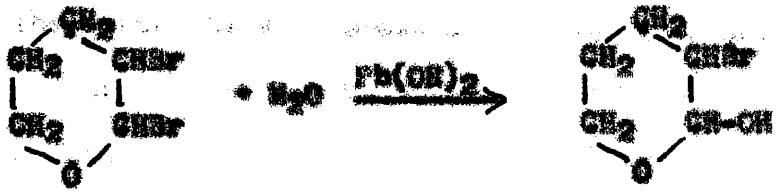
This dibromide is very unstable; at room temperature it slowly decomposes with noticeable evolution of hydrogen bromide. It can not be distilled even at reduced pressures without decomposition. At 120° the dibromide decomposes rapidly and loses a molecule of hydrogen bromide to yield, among other substances, a small amount of 3-bromo-$\Delta^2$-dihydropyrane; a larger yield of the latter compound is obtained if the dehydrohalogenation is accomplished in the presence of a tertiary amine such as dimethylaniline[15]:



This marked instability of 2,3-dibromotetrahydropyrane is not too unusual since it is a property common to all $\alpha,\beta$-dihaloethers. For example, $\alpha,\beta$-dibromoethyl ethyl ether $BrCH_2-CHBr-O-C_2H_5$[17] and the dibromoether, $(C_2H_5)_2CHBr-CHBr-O-C_2H_5$[18] can not be distilled without the loss of a molecule of hydrogen bromide. On the basis of the great reactivity of the alpha halogen atom in $\alpha,\beta$-dibromoethers,

Shostakovskii[19] postulated that the structures of these compounds may best be expressed as an equilibrium between the normal structure and the corresponding oxonium compound. He further maintained that the dissociation of the oxonium compound which results in the loss of a molecule of halogen acid may occur under the influence of (1) temperature - usually 100°, (2) water, and (3) various other reagents.

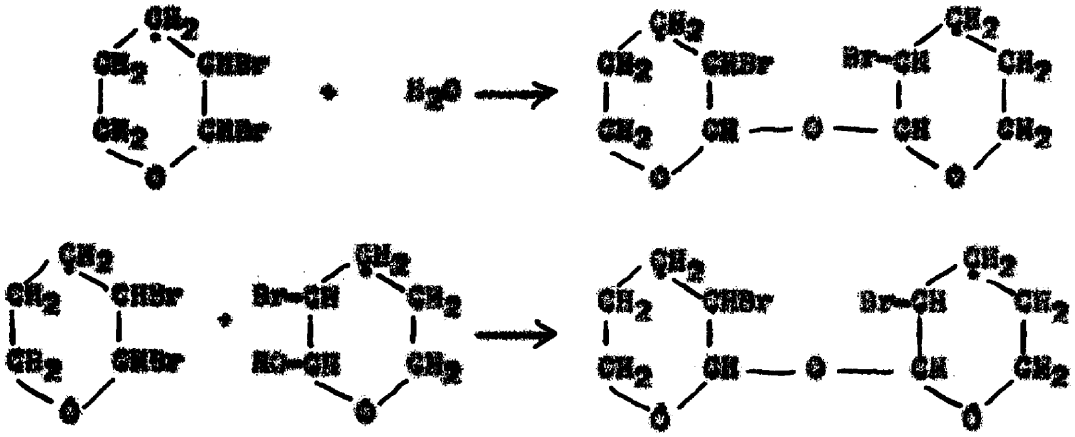
The alpha bromine atom in 2,3-dibromotetrahydropyrane is replaceable by a hydroxyl group but the nature of the products obtained vary with the hydrolysis conditions[15]. If the hydrolysis of 2,3-dibromotetrahydropyrane is conducted in the presence of a base such as lead hydroxide, the product is 2-hydroxy-3-bromotetrahydropyrane:



This latter compound reduces ammoniacal silver nitrate and Fehling's reagent when warmed but gives no coloration with Schiff's reagent. It does not react with the usual carbonyl reagents. This in contrast to the behavior of 2-hydroxytetrahydrohydropyrane which forms both an oxime and a 2,4-dinitrophenylhydrazone.

The hydrolysis of 2,3-dibromotetrahydropyrane yields another product if the hydrogen bromide which is produced in the reaction is allowed to remain unneutralized. The product obtained is the symmetrical acetal of 2-hydroxy-3-bromotetrahydropyrane[15]. This same product is obtained when equi-molar quantities of 2-hydroxy-3-bromotetrahydropyrane and 2,3-dibromotetrahydropyrane are mixed and allowed to remain

in a desiccator over soda-lime for ten days[15]:



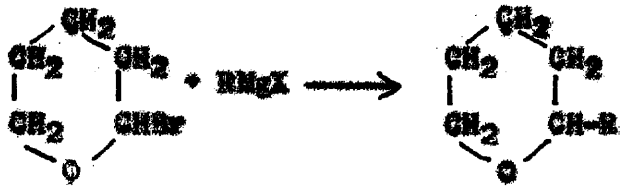
This symmetrical acetal does not reduce ammoniacal silver nitrate and reduces Fehling's solution only after it has been hydrolyzed with hydrochloric acid.

The preparation of 2-alkyl or arylotetrahydropyrans by the dehydration of the corresponding 1,5-diols has been investigated by Paul[20]. The yields were found to be poor and the nature of the cyclic oxides obtained were in doubt. In this connection, a convenient method of the preparation of substituted 1,5-diols was developed by reacting 5-hydroxypentanal (2-hydroxytetrahydropyrans) with an excess of the corresponding Grignard reagent[20]:

$HOCH_2(CH_2)_3CHO + 2\ RMgX \longrightarrow HOCH_2-(CH_2)_3CHOH-R$. The overall yields of the various substituted 1,5-diols are about 33%.

The 2-alkyl or arylotetrahydropyrans are most conveniently prepared in excellent yields by the reaction between 2-bromotetrahydropyrans and the corresponding Grignard reagent[20,21]. Since 2-bromotetrahydropyrans is unstable and incapable of purification by distillation, the crude product obtained from the reaction between 2,3-dihydropyrans and anhydrous hydrogen bromide is dissolved in anhydrous ether and

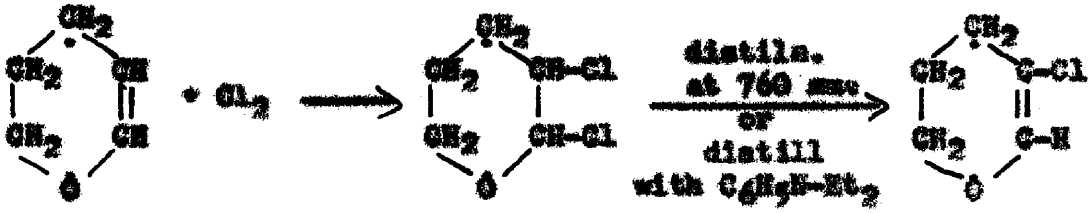
reacted with an excess of the Grignard reagents.



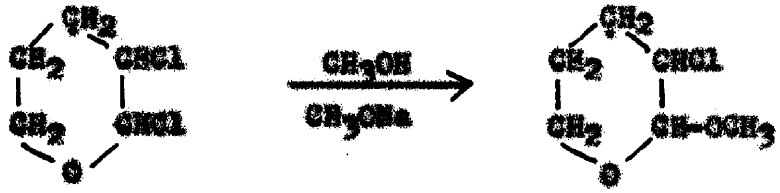
R=$CH_3$-$C_2H_5$-$C_3H_7$-$C_4H_9$-$C_6H_5$

The yields of these alkyl and aryltetrahydropyranes, based on 2,3-dihydropyrane are 75-80%. In a similar manner, the 2-alkyl or aryl-3-bromotetrahydropyranes are prepared. The $\alpha$-bromine atom is inert to the Grignard reagent; nevertheless, the yields of the 2-alkyl or aryl-3-bromotetrahydropyranes are much lower (26-44%) than those obtained in the preparation of the 2-alkyl or aryltetrahydropyranes.

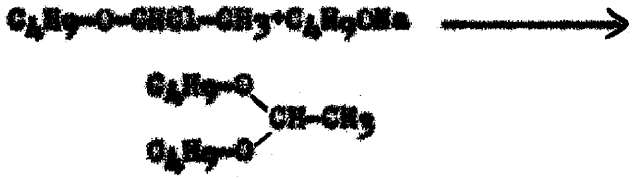
In some recent work which has come to hand, Paul[22] has reported the chlorination of 2,3-dihydropyrane and the products derivable from the resulting 2,3-dichlorotetrahydropyrane. It is evident that this dichloro compound has less tendency to lose a molecule of halogen acid than does 2,3-dibromotetrahydropyrane, since the former substance can be purified by distillation under reduced pressures, whereas the latter can not. On the other hand, distillation of 2,3-dichlorotetrahydropyrane at atmospheric pressure or in the presence of diethylaniline gives excellent yields of 3-chloro-$\Delta^2$-dihydropyrane[22,23].



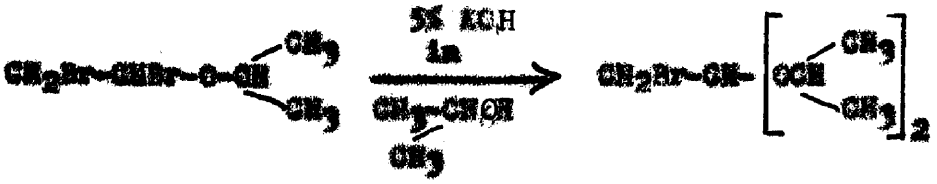

The marked reactivity of the alpha chlorine atom and the unreactivity of the beta chlorine atom is observed in the reaction between 2,3-dichlorotetrahydropyrane and methyl alcohol in the presence of sodium methoxide[22]. The product thus obtained is 2-methoxy-3-chlorotetrahydropyrane, which is a cyclic acetal.



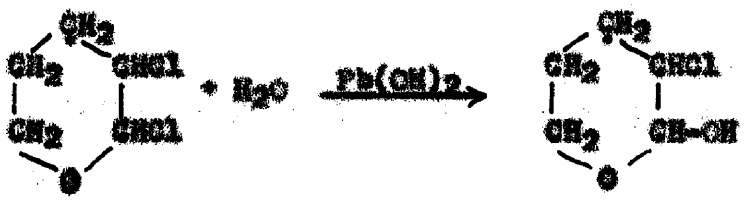

This reaction which appears to be of a solvolysis nature is not new and has been observed for a number of $\alpha$-halo and $\alpha,\beta$-dihaloethers and has been employed in the preparation of acetals. Rense and Marchisen[24] reacted $\alpha$-chloroethyl-n-butyl ether with sodium-n-butoxide to obtain di-n-butyl acetal of acetaldehyde:

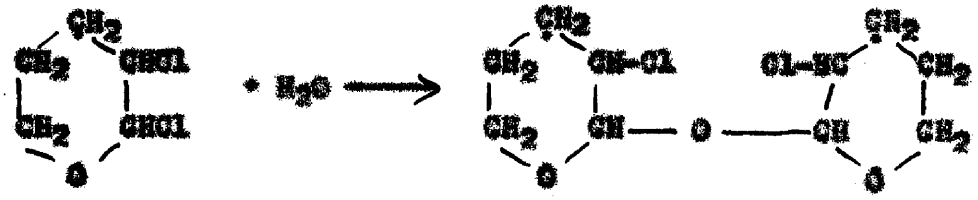



The relative degrees of reactivity of the halogens in $\alpha,\beta$-haloethers is further illustrated by the following two reactions[16,25]:

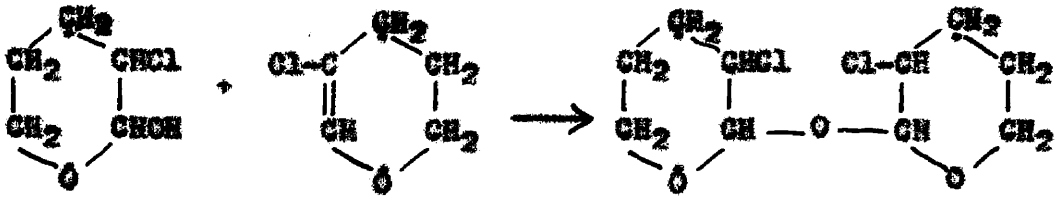


The reaction between 2,3-dichlorotetrahydropyrane and alkyl or aryl Grignard reagents yields the 2-alkyl or aryl-3-chlorotetrahydropyranes. The reaction of 2,3-dichlorotetrahydropyrane with water is similar to that of the 2,3-dibromotetrahydropyrane and water. Thus, the following reactions occur according to the conditions of operation:

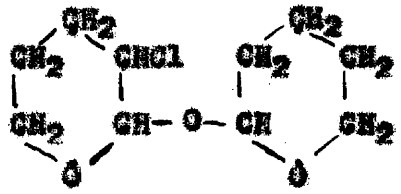




In a continuation of the study of the products obtainable from the chlorine derivatives of tetrahydropyrane, Hawkins and Bennett[26] reacted 3-chloro-$\Delta^2$-dihydropyrane with 2-hydroxy-3-chlorotetrahydropyrane to 3-chloro-$\Delta^2$-dihydropyrane acetal:

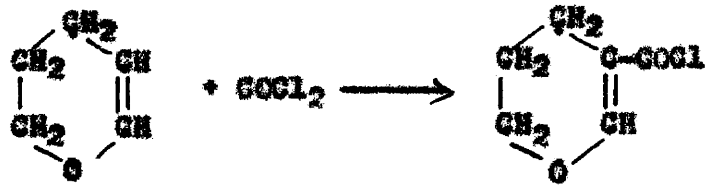


Further, 2-hydroxy-3-chlorotetrahydropyrane was added to 2,3-dihydropyrane to yield the unsymmetrical acetal shown below[26]:



The addition reactions of 2,3-dihydropyrane are not limited to water, alcohols, chlorine, bromine and hydrogen bromide. Hypochlorous acid adds to 2,3-dihydropyrane to yield 2-hydroxy-3-chlorotetrahydropyrane. An emulsification of 2,3-dihydropyrane in water is treated with a stream of chlorine until the separated phase disappears. The product is isolated by extraction with ether and then removal of the solvent[27].

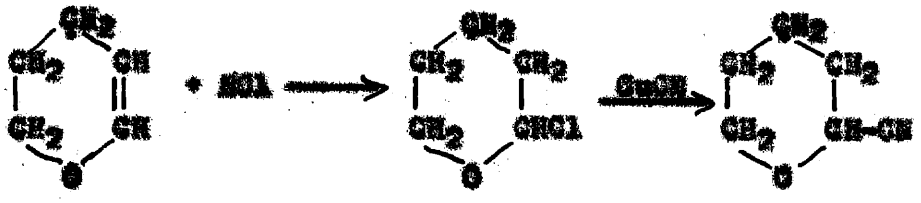
According to Hawkins and Bennett[28], when an excess of gaseous phosgene is dissolved in 2,3-dihydropyrane at room temperature and the solution allowed to remain at room temperature for three days, the product isolated is 5,6-dihydro-3-pyranecarbonyl chloride:



This acid chloride was used to prepare 5,6-dihydro-3-pyranecarboxylic

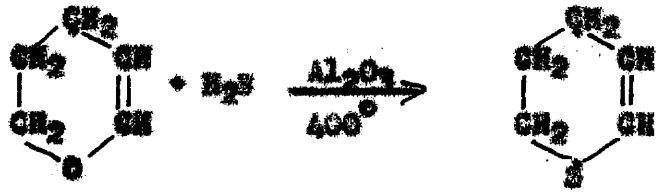
amid and a variety of the amid derivatives, a few of which are: anilide, p-toluide, amide, amid anhydride, ethyl ester, diethylene glycol ester, etc.

In an attempt to prepare 2-cyanotetrahydropyrane by the addition of gaseous hydrogen cyanide to 2,3-dihydropyrane, a clear resin was the only product obtained[29]. This cyano compound was obtained, however, by the following sequence of reactions[29]:



When 2,3-dihydropyrane and ammonia are passed over a chromic oxide-aluminum oxide catalyst at 400°, addition of ammonia to 2,3-dihydropyrane was not observed. Instead, the oxygen was replaced by nitrogen to give a 1% yield of pyridine and a 9% yield of piperidine[30].

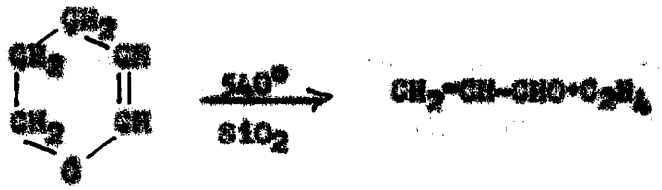
The reaction of 2,3-dihydropyrane and hydrogen sulfide at 400° over aluminum oxide does not lead to an addition to the ethylenic bond. A replacement of the oxygen by sulfur occurs and there is obtained a 60% yield of 2,3-dihydrothiapyrane.[31]



Still other reactions which involve the replacement of the oxygen in the pyrane ring have been observed. For example, when tetrahydropyrane and hydrogen selenide are passed over aluminum oxide at 400°, a 50% yield of pentamethylene selenide is obtained[32]. A 20%

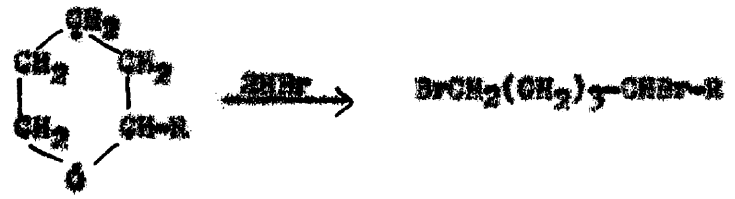
yield of piperidine is obtained by the reaction of tetrahydropyrane and ammonia at elevated temperatures in the presence of a catalyst; with ethylamine, a 17% yield of N-ethylpiperidine is obtained[33].

It is interesting to note that 2,3-dihydropyrane which apparently is stable up to 400° in the presence of aluminum oxide[1,34] and gives resinous products at 500° in the presence of this same catalyst, behaves differently at this (500°) and higher temperatures in the presence of silica. An 85% yield of acrolein can be obtained by the pyrolysis of 2,3-dihydropyrane over silica catalyst at a temperature of 340°. Higher temperatures result in decreased yields of acrolein[35].



The oxide ring in tetrahydropyrane and its alkyl or aryl derivatives is fairly stable. No hydrogenolysis has been observed in the vapor phase hydrogenation of 2,3-dihydropyrane up to temperatures of 300°[36].

The action of hydrogen bromide on tetrahydropyrane and its 2-alkyl or aryl derivatives yields the corresponding 1,5-dibromides[20].

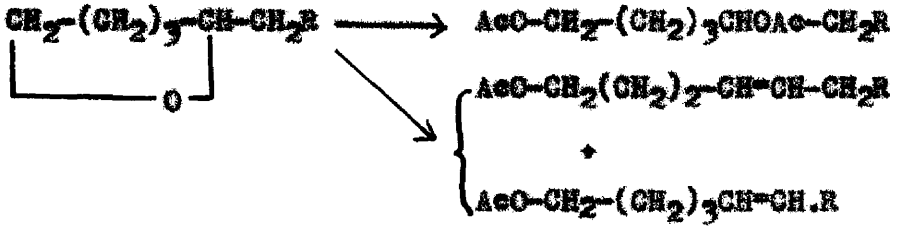


R=H-$CH_3$-$C_2H_5$-$C_3H_7$-$C_4H_9$-$C_6H_5$

The ease with which the oxide ring is opened depends upon the nature

of the substituent in the alpha position. Tetrahydropyrane when dissolved in acetic acid and saturated with dry hydrogen bromide reacts at 110° in a sealed tube. The 2-alkyltetrahydropyranes react in a similar manner at 150°. In contrast, is the ease of the reaction of the phenyl-homologue which occurs at room temperature.

The tetrahydropyrane ring is stable to the action of acetic anhydride up to a temperature of 190°. At this temperature acetic anhydride reacts with tetrahydropyrane and its alpha-alkyl or aryl substituted derivatives in the presence of zinc chloride as catalyst to yield diacetates and ethylenic acetates according to the general equation:



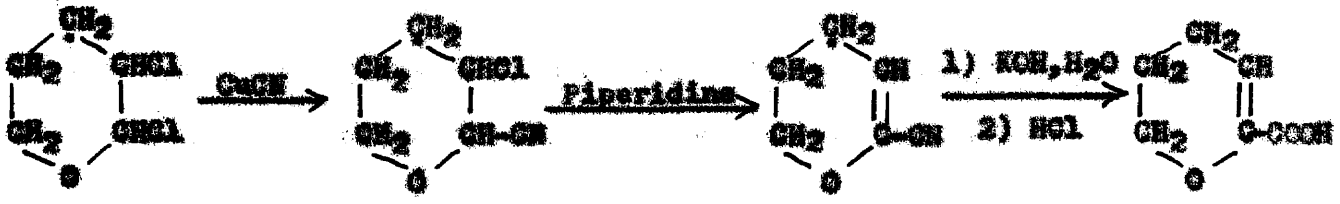

The yields of the products vary according to the tetrahydropyrane compounds used and are tabulated below[37]:

| $CH_2-(CH_2)_3-CH-R$ (O) | Amount of rupture occuring | % Yield of Diacetate | % Yield of ethylenic acetates |
|---|---|---|---|
| R = H | 15% | 15% | 0% |
| $CH_3$ | 94 | 24 | 70 |
| $C_2H_5$ | 94 | 10 | 84 |
| $C_4H_9$ | 94 | 11 | 83 |
| $C_6H_5$ | resins | | |

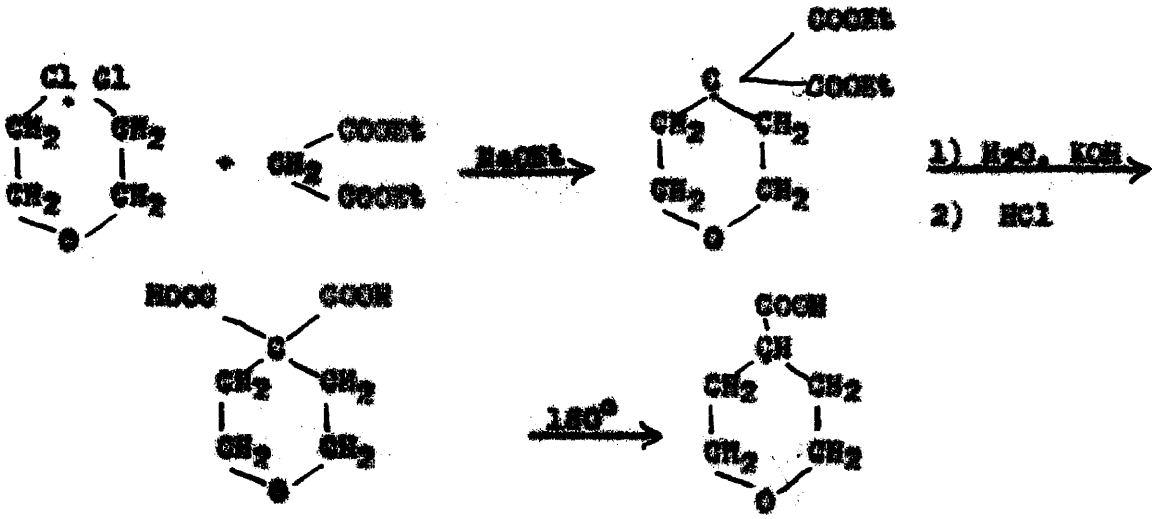
Although no exhaustive survey of pyrans compounds and pyrane chemistry has been attempted in this thesis, the following miscellaneous work is presented in order to illustrate some simple pyrane derivatives that are reported in the literature and the chemistry involved in their preparation. The benzopyranes, pyrones, etc. will not be considered in this work; only some of the more interesting and simple pyrane derivatives are discussed in the sections to follow.

2,3-Dichlorotetrahydropyrane can be employed as the precursor of 5,6-dihydro-2-pyranylcarboxylic acid[29]. The dichloride is reacted with cuprous cyanide to obtain 2-cyano-3-chlorotetrahydropyrane. Dehydrohalogenation of this latter substance by means of piperidine yields 2-cyano-5,6-dihydropyrane.

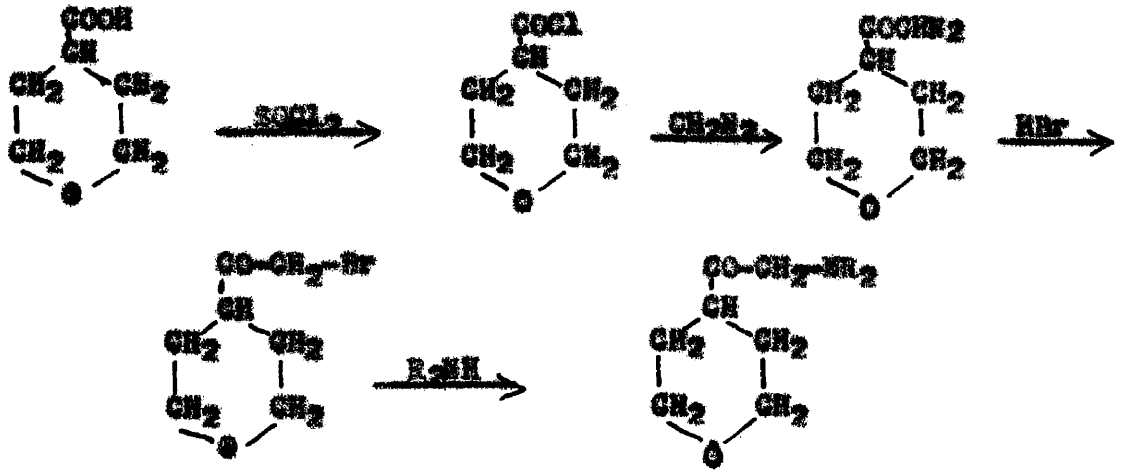
Alkaline hydrolysis of the cyano compound followed by careful acidification results in 5,6-dihydro-2-pyranylcarboxylic acid.




The preparation of tetrahydropyrane-4-carboxylic acid has been reported by several different workers[30]. A β-dihalodiethyl ether is condensed with ethyl malonate in the presence of sodium ethoxide. The resulting product, diethyl tetrahydropyrane-4,4-dicarboxylate is hydrolyzed with potassium hydroxide and after acidification yields tetrahydropyrane-4,4-dicarboxylic acid. This latter substance is easily decarboxylated at 190° to tetrahydropyrane-4-carboxylic acid.

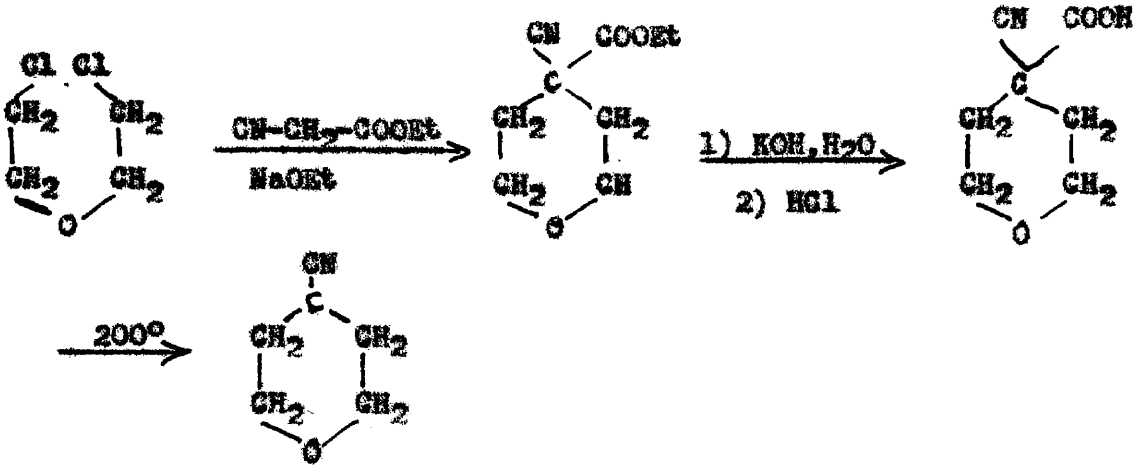


In an attempt to prepare new analgesic substances, Harnest and Burger[38c] prepared 4-tetrahydropyranoyl chloride by the action of thionyl chloride on tetrahydropyrane-4-carboxylic acid. Upon treatment of the acid chloride with diazomethane, there was obtained 4-diazoacetyltetrahydropyrane. The action of hydrobromic acid upon the diazoketone yielded 4-bromoacetyltetrahydropyrane. From the reaction of this latter substance with secondary amines, a host of substituted derivatives of 4-aminoacetyltetrahydropyrane were obtained.

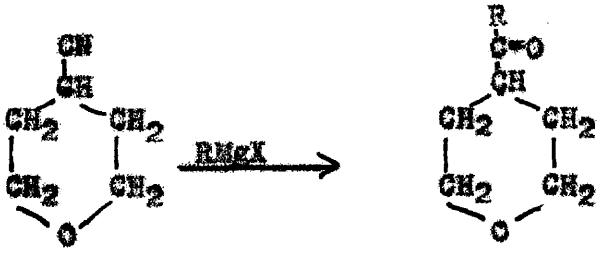


Gibson and Johnson[38b] condensed β-dichlorodiethyl ether with

ethyl cyanoacetate in the presence of sodium ethylate. The product, ethyl-4-cyanotetrahydropyrane-4-carboxylate was carefully hydrolyzed with alkali; acidification of the hydrolysis reaction mixture yielded 4-cyanotetrahydropyrane-4-carboxylic acid. Decarboxylation of this acid to 4-cyanotetrahydropyrane occured at 200°.




The reaction of Grignard reagents with 4-cyanotetrahydropyrane proceeds on the regular manner and 4-ketotetrahydropyranes are obtained[39].



## DISCUSSION

Recently, 5-hydroxypentanal has become of importance in organic synthetic work and it was deemed advisable to modify Paul's procedure[12] to improve the yield of this substance. The modification consisted of the hydrolysis of 2,3-dihydropyrane in 1 N hydrochloric acid at room temperature. The carefully neutralized reaction mixture was subjected to continuous extraction with ether; after removal of the solvent and distillation of the product a 79% yield of 5-hydroxypentanal was obtained. The product was identified by the preparation of its 2,4-dinitrophenylhydrazone[40] which melted at 109°.

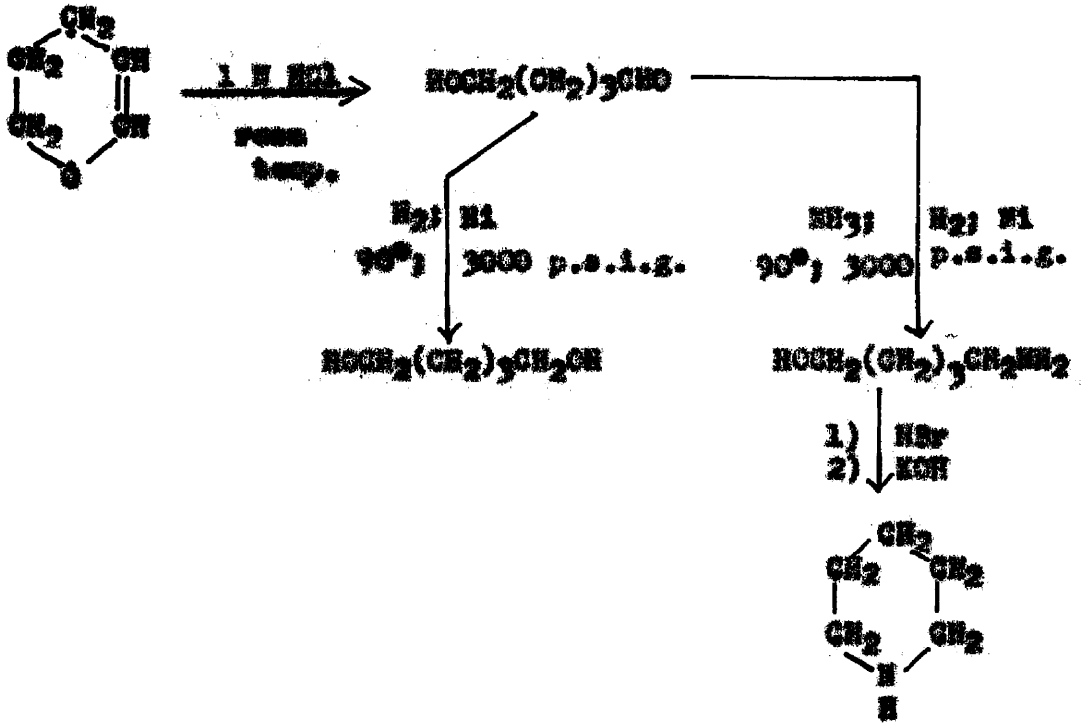
Paul was unable to reduce 5-hydroxypentanal with hydrogen and platinum catalyst; he effected reduction to 1,5-pentamethylene glycol in 50% yield with aluminum amalgam. In the present work, it was found that reduction of 5-hydroxypentanal with hydrogen and Raney nickel catalyst at 90° and 3000 p.s.i.g. of hydrogen is a convenient and rapid method for the preparation of 1,5-pentamethylene glycol of excellent quality in 96% yield.

5-aminopentanol-1 has been obtained by several different procedures,[41] all of which are time consuming and give a product in low yields and of doubtful purity. Reductive amination of 5-hydroxypentanal is a more convenient and satisfactory method of preparing this otherwise difficultly obtainable compound. The reaction of 5-hydroxypentanal with liquid ammonia and hydrogen with Raney nickel as catalyst was allowed to continue at 90° and 3000 p.s.i.g. of hydrogen until absorption of hydrogen had ceased. The crude 5-aminopentanol-1 obtained was contaminated with small amounts of 1,5-pentamethylene glycol which could

not be removed by fractional distillation. Attempts to prepare a crystalline hydrochloride of 5-aminopentanol-1 by passing dry hydrogen chloride into an ethereal solution of the amino-alcohol yielded only oily products. It was found that a crystalline bisulfate of 5-amino-pentanol-1 could be obtained by adding a solution of concentrated sulfuric acid in absolute alcohol to an alcoholic solution of the amino-alcohol and then diluting with anhydrous ether. This derivative has the advantage of being a stable, white crystalline solid with a sharp melting point and capable of recrystallization from alcohol-ether. The bisulfate of 5-aminopentanol-1 can be titrated for one hydrogen ion with sodium hydroxide using methyl red as the indicator; the titration for the second hydrogen ion can be performed in the presence of formaldehyde with phenolphthalein as the indicator.

Pure 5-aminopentanol-1 was obtained from its bisulfate salt by making its aqueous solution alkaline and subjecting the alkaline solution of the amino-alcohol to continuous extraction with ether. 5-Aminopentanol-1 was thus obtained in a very high degree of purity.

5-Aminopentanol-1 bisulfate was refluxed with a 75% excess of 48% aqueous hydrobromic acid for three hours. The reaction mixture was made alkaline and then subjected to steam distillation. The steam distillate was made strongly alkaline with sodium hydroxide and extracted with ether; after removal of the solvent, a 61% yield of piperidine was obtained.



The bromination of 2,3-dihydropyrane in carbon tetrachloride afforded a 92% yield of crude 2,3-dibromotetrahydropyrane(I). This latter substance could not be purified by distillation because of its instability; it was therefore used in the crude state.

The difference in the reactivity of the two bromine atoms in 2,3-dibromotetrahydropyrane was most noticeable. The addition of this substance to methyl or ethyl alcohol saturated with dry ammonia or to cold alcoholic solutions of the sodium alcoholates resulted in a solvolysis reaction in which the alpha bromine atom was replaced with an alkoxy group to yield 2-alkoxy-3-bromotetrahydropyrane(II). Under these conditions the second bromine atom is inert.

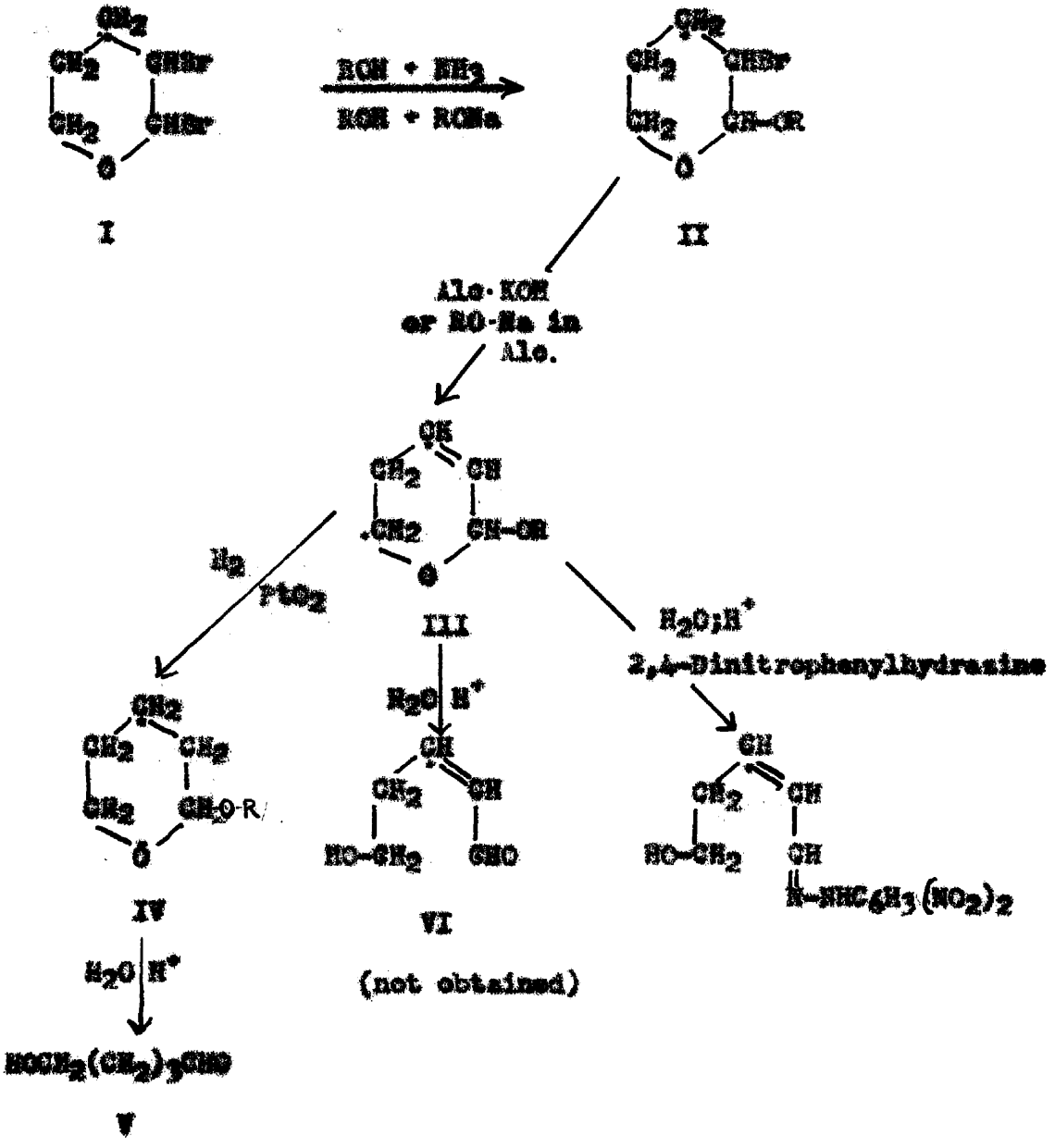
Although Paul[22] made the statement that the β-chlorine atom in tetrahydropyrane derivatives is inert, it was found that the more drastic treatment of refluxing 2-alkoxy-3-bromotetrahydropyrane

with alcoholic potassium hydroxide or with alcoholic solutions of sodium alcoholates led to the elimination of a molecule of hydrogen bromide with the formation of 2-alkoxy-$\Delta^3$-dihydropyrans (III). These cyclic acetals are stable to alkaline reagents and to sodium but are rapidly decomposed by acids.

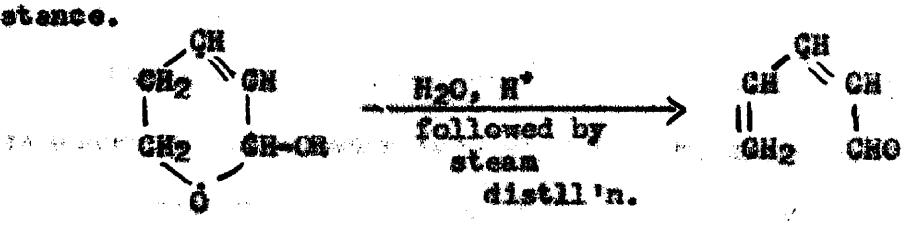
Reduction of 2-ethoxy-$\Delta^3$-dihydropyrans with Adams' catalyst at room temperature and 2-3 atmospheres of hydrogen afforded 2-ethoxytetrahydropyrans (IV), which, since it is an acetal was readily cleaved by mild acid hydrolysis at room temperature. That the above structures were correct was shown by the identity of the 2,4-dinitrophenylhydrazone of the hydrolysis product of 2-ethoxytetrahydropyrans with the 2,4-dinitrophenylhydrazone of 5-hydroxypentanal[40](V).

All attempts to isolate 5-hydroxy-$\Delta^2$-pentenal (VI) by mild acid hydrolysis of 2-ethoxy-$\Delta^3$-dihydropyrans were without success. The properties of the material obtained were those of a polymeric substance which did not form a 2,4-dinitrophenylhydrazone or a semicarbazone. Attempts at hydrogenation of the material isolated from the acid hydrolysis reaction mixture of 2-ethoxy-$\Delta^3$-dihydropyrans were also unsuccessful although absorption of hydrogen was observed. No pure product could be isolated, and no substance obtained could be identified. However, if the hydrolysis was carried out in the presence of 2,4-dinitrophenylhydrazine, a 2,4-dinitrophenylhydrazone of 5-hydroxy-$\Delta^2$-pentenal was obtained.

The reactions discussed above are summarized diagrammatically:


KOH + NH3
KOH + RONa
I
II
Alc·KOH
or RO-Na in
Alc.
III
H2
PtO2
H2O;H+
2,4-Dinitrophenylhydrazine
IV
H2O H+
V
H2O H+
VI
(not obtained)

In the attempt to prepare 5-hydroxy-$\Delta^2$-pentenal, another reaction of 2-ethoxy-$\Delta^3$-dihydropyrane was encountered. Steam distillation of the reaction mixture from the acid hydrolysis of 2-ethoxy-$\Delta^3$-dihydropyrane yielded an aldehyde of marked acrolein-like properties. Isolation of this aldehyde was effected by "salting out" the steam distillate and extraction with ether. This aldehyde could not be distilled at atmospheric pressure since this inevitably led to rapid decomposition resulting in complete carbonization. However, the aldehyde was purified by distillation at 20 mm. at which pressure it had a boiling point of 38-40°. This aldehyde had an empirical formula of $C_5H_6O$ and formed a red 2,4-dinitrophenylhydrazone and a semicarbazone. On the basis of the analyses of the aldehyde and its derivatives, the structure of 2,4-pentadienal (VII) was assigned to this substance.

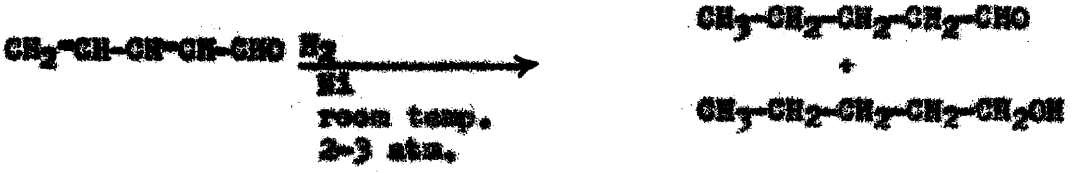



III VII

It is believed that the 2,4-pentadienal thus obtained is of cis-configuration since it was obtained from a cyclic compound.

It was recognized that the aldehyde to which was assigned the structure of 2,4-pentadienal might possibly be a cyclobutenal. Therefore, this unsaturated aldehyde (VII) was subjected to catalytic hydrogenation with Raney nickel catalyst at room temperature and 2-3 atmospheres pressure of hydrogen. The hydrogenation was interrupted

when slightly more than the hydrogen absorption calculated for two ethylene bonds had occurred. It was not possible to obtain pure products by fractional distillation. However, three fractions were obtained; (1) b.p. 85-105°, (2) b.p. 105-125°, (3) b.p. 125-130°. Fraction 1 yielded a yellow 2,4-dinitrophenylhydrazone, as did fraction 2 (although in smaller quantity) which melted at 105.5-106.5°. This derivative was identified as the 2,4-dinitrophenylhydrazone of n-valeraldehyde. An ∝-naphthylurethan was prepared from fraction 3 which proved to be the ∝-naphthylurethan of n-amyl alcohol.



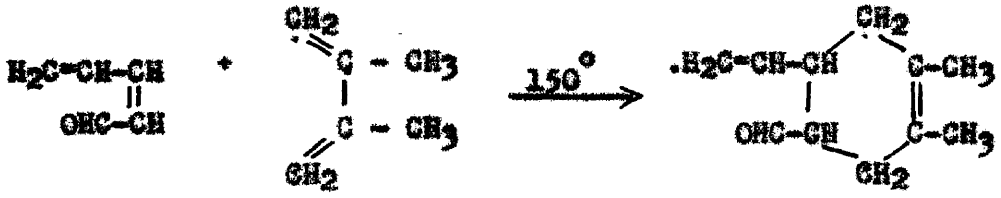
These results apparently exclude a cyclobutenal structure for the aldehyde to which was assigned the structure of 2,4-pentadienal, since under the mild conditions at which the hydrogenation was conducted, the cyclobutane ring is not opened[42].

2,4-Pentadienal is the aldehyde derivative of butadiene and therefore should react with maleic anhydride in the Diels-Alder reaction as shown below:

VIII

3-Aldehyde- $\Delta^4$-tetrahydrophthalic anhydride (VIII) was readily obtained by refluxing a solution of 2,4-pentadienal and maleic anhydride in toluene. Attempts to isolate the dicarboxylic acid by dissolving the anhydride in aqueous sodium bicarbonate and subsequent acidification with hydrochloric acid were without success. It would appear that the dicarboxylic acid is too soluble in water to be isolated. A 2,4-dinitrophenylhydrazone of 3-aldehyde- $\Delta^4$-tetrahydrophthalic anhydride was prepared. However, this derivative could not be purified sufficiently to give good results on analysis.

The versatility of 2,4-pentadienal was observed in its reaction with 2,3-dimethylbutadiene in another Diels-Alder reaction. In this case, the aldehyde molecule exhibits the behavior of a substituted ethylene link which is activated by both a carbonyl group of an aldehyde and a vinyl group. The reactants were heated in a sealed tube at 150° for six hours. Distillation of the reaction mixture gave a 35% yield of 4-aldehyde-5-vinyl-1,2-dimethyl- $\Delta^1$-cyclohexene (IX)



IX

This product formed a 2,4-dinitrophenylhydrazone and semicarbazone which was used for its characterization. Thus, 2,4-pentadienal is capable of reacting in the Diels-Alder reaction both as a diene or a dienophile.

The reaction of phenylmagnesium bromide with 2,4-pentadienal was expected to proceed by a 1,2-addition mechanism; however, the possibility of a 1,4- or a 1,6- addition mechanism was recognized:

<u>1,2-addition:</u>

$$CH_2{=}CH{-}CH{=}CH{-}CHO + C_6H_5MgBr \longrightarrow \underset{X}{C_6H_5{-}CHOH{-}CH{=}CH{-}CH{=}CH_2}$$

<u>1,4-additions:</u>

$$CH_2{=}CH{-}CH{=}CH{-}CHO + C_6H_5MgBr \longrightarrow CH_2{=}CH{-}\underset{C_6H_5}{CH}{-}CH_2{-}CHO$$

<u>1,6-addition:</u>

$$CH_2{=}CH{-}CH{=}CH{-}CHO + C_6H_5MgBr \longrightarrow C_6H_5{-}CH_2{-}CH{=}CH{-}CH_2{-}CHO$$

It is known that in many cases the products obtained from the reaction between Grignard reagents and unsaturated carbonyl compounds depend upon the order of addition of the reactants and the method in which the reaction complex is worked up[43]. Therefore, some detail is given here of the procedure for the reaction between 2,4-pentadienal and phenylmagnesium bromide. The addition of 2,4-pentadienal to phenylmagnesium bromide proceeded smoothly and the Grignard complex was decomposed with aqueous ammonium chloride. Steam distillation of the ether layer removed impurities and the viscous oil which remained in the steam distillation flask was extracted with ether. The product isolated from this extract was a white, crystalline alcohol which was unstable in air and whose maximum melting point was 78-79°. The instability in air of this alcohol will be discussed later. This alcohol readily formed a phenylurethan, under the usual conditions, which was stable. Further,

no evidence was detected for a 1,4- or a 1,6-addition since no aldehyde could be detected in the steam distillate or in the viscous oil which was not steam distillable from the reaction mixture obtained from 2,4-pentadienal and phenylmagnesium bromide.

It was anticipated that the solid alcohol obtained from the Grignard reaction would be 1-phenyl-2,4-pentadien-1-ol (X), ($C_6H_5$-CHOH-CH=CH-CH=$CH_2$). Catalytic hydrogenation of the phenylpentadienol which was believed to be (X) was accomplished at room temperature and 2-3 atmospheres of hydrogen pressure with Raney nickel as the catalyst. Isolation of the product yielded a phenylpentanol which distilled at 150-151°/14 mm. and readily formed a phenylurethan which melted at 73.5° and a 3,5-dinitrobenzoate with a melting point of 67.5°. Fourneau[44] reported that 1-phenylpentanol-1 formed a phenylurethan which melted at 74°. However, when an authentic sample of 1-phenylpentanol-1 was prepared by the reaction of benzaldehyde and n-butylmagnesium bromide, it was found that no crystalline phenylurethan could be prepared from the alcohol and phenyl isocyanate by operating under various conditions.* Moreover, no 3,5-dinitrobenzoate could be prepared from the authentic sample of 1-phenylpentanol-1. It was concluded therefore, that the phenylpentanol which was obtained by the hydrogenation of the phenylpentadienol, the reaction product from 2,4-pentadienal and phenylmagnesium bromide, was not the expected product, 1-phenylpentanol-1.

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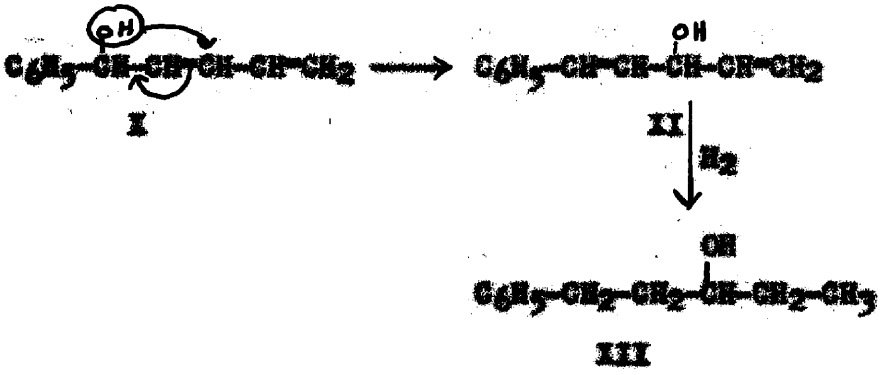
* It is interesting to note that Fourneau reported the preparation of the phenylurethan by the action of phosgene on 1-phenylpentanol-1 in the presence of dimethylaniline.

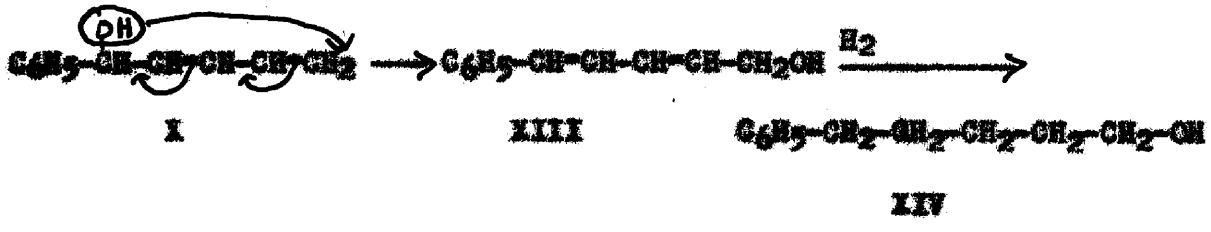
Very few instances of rearrangements in skeletal structure are known to occur during catalytic hydrogenation under mild conditions. It was concluded therefore, that the reaction between phenylmagnesium bromide and 2,4-pentadienal yielded 1-phenyl-2,4-pentadienol-1 (X) and that this product immediately rearranged to some other phenylpentadienol.

There were several possible rearrangements worthy of considerations

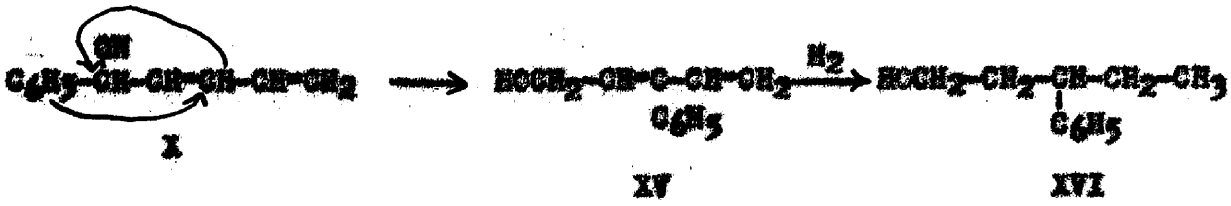
(1) a 1,3 rearrangement of the hydroxyl group to yield 1-phenyl-1,4-pentadien-3-ol, (XI) which upon hydrogenation would give 1-phenyl-pentanol-3 (XII):



(2) a 1,5 rearrangement of the hydroxyl group to yield 5-phenyl-2,4-pentadien-1-ol (XIII). This substance would give 5-phenylpentanol-1 (XIV) upon hydrogenation:



(3) a 1,3 rearrangement of the phenyl group[45] to yield 3-phenyl-2,4-pentadien-1-ol (XV) which would lead to 3-phenylpentanol-1 (XVI) upon hydrogenation:



X XV XVI

1-Phenylpentanol-3 was prepared by the reaction of ethylmagnesium bromide and hydrocinnamaldehyde[46]. This alcohol readily formed a phenylurethan which melted at 85°.

The melting point of the phenylurethan (73.5°) of the phenylpentanal obtained by the catalytic hydrogenation of the phenylpentadienol, the reaction product of 2,4-pentadienal and phenylmagnesium bromide, was lowered 20° when admixed with an authentic sample of the phenylurethan of 1-phenylpentanol-3.

Von Braun[47] reported that 5-phenylpentanol-1 would not form a crystalline phenylurethane; in view of this observation it was deemed advisable to prepare 3-phenylpentanol-1 (XVI) for comparison purposes. This substance was synthesized by the following series of reactions:

(a) preparation of ethyl 3-phenyl-3-hydroxy-n-valerate by the reaction of propiophenone, ethyl bromoacetate and zinc[48].

(b) dehydration of the ester thus formed

(c) hydrogenation of the unsaturated ester to ethyl 3-phenyl-n-valerate.

(d) reduction of the saturated ester to 3-phenylpentanol-1.

3-Phenylpentanol-1 did not form a crystalline phenylurethan with phenyl isocyanate under various conditions of operation.

In spite of Von Braun's statement that 5-phenylpentanol-1 would not form a crystalline phenylurethan, it was not unreasonable

to believe that 1-phenyl-2,4-pentadien-1-ol (X) was involved in a 1,5 rearrangement of the hydroxyl group (double allylic) to yield 5-phenyl-2,4-pentadien-1-ol (XIII) which upon hydrogenation would form 5-phenylpentanol-1 (XIV). An authentic sample of this latter substance was prepared by the following series of reactions:

(a) Friedel-Craft reaction between benzene and glutaric anhydride to yield $\gamma$-benzoylbutyric acid.

(b) Clemmensen reduction of the keto acid to phenylvaleric acid.

(c) esterification to ethyl phenylvalerate.

(d) reduction of ethyl phenylvalerate with sodium and alcohol to 5-phenylpentanol-1.

The physical constants of the 5-phenylpentanol-1 thus prepared agreed excellently with those of the phenylpentanol obtained by the hydrogenation of the phenylpentadienol which was formed by the reaction of 2,4-pentadienal and phenylmagnesium bromide. Contrary to the statement of von Braun, the authentic sample of 5-phenylpentanol-1 readily formed a phenylurethan which melted at 73.5-74° and a 3,5-dinitrobenzoate which melted at 67.5°. No melting point depression was observed in mixed melting point determinations of the phenylurethan and 3,5-dinitrobenzoate prepared from an authentic sample of 5-phenylpentanol-1 with the phenylurethan and 3,5-dinitrobenzoate prepared from the phenylpentanol which was obtained by catalytic reduction of the phenylpentadienal, the reaction product of phenylmagnesium bromide and 2,4-pentadienal.

It is considered therefore, that the reaction of phenylmagnesium

bromide and 2,4-pentadienal proceeds by a 1,2-addition mechanism to yield 1-phenyl-2,4-pentadien-1-ol (X) which immediately undergoes a 1,3-rearrangement of the hydroxyl group (double allylic) in which 5-phenyl-2,4-pentadien-1-ol (XIII) is formed see (2) under possible rearrangements.

It is not too surprising that 1-phenyl-2,4-pentadien-1-ol rearranges since rearrangements of dienols have been hitherto observed. Heilbron and co-workers[49] have reported that the dienols XVII and XVIII rearranged to yield the products XIX and XX, respectively:

$$CH_3\text{-}CH\text{=}CH\text{-}CHOH\text{-}CH\text{=}CH_2 \longrightarrow CH_3\text{-}CHOH\text{-}CH\text{=}CH\text{-}CH\text{=}CH_2$$

XVII XIX

$$CH_3\text{-}CH\text{=}CH\text{-}C(CH_3)(OH)\text{-}CH\text{=}CH_2 \longrightarrow CH_3\text{-}CHOH\text{-}CH\text{=}C(CH_3)\text{-}CH\text{=}CH_2$$

XVIII XX

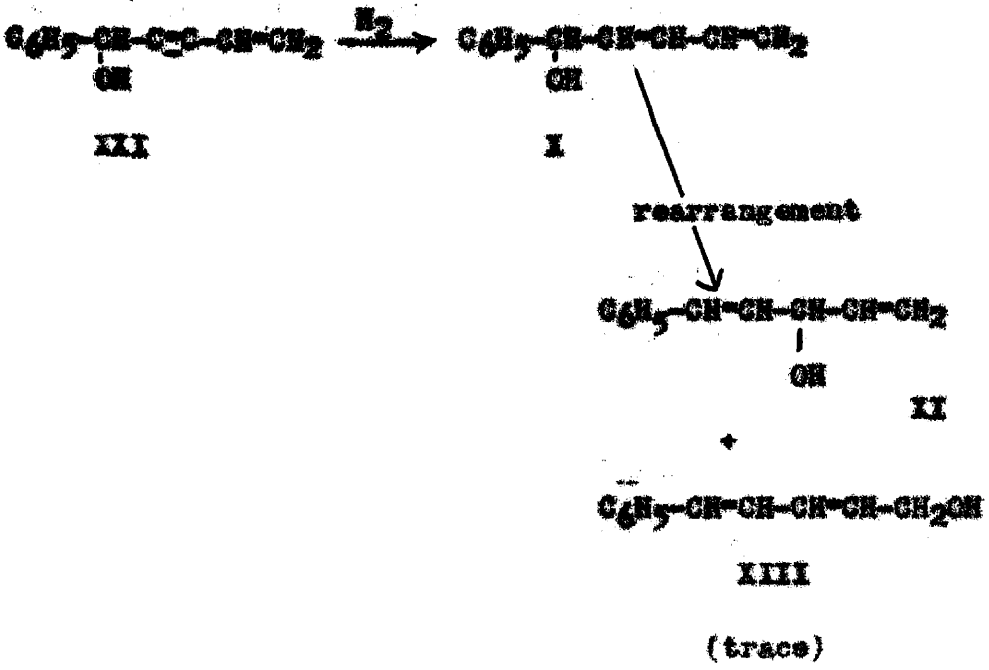
A secondary alcohol is formed in these rearrangements; the direction of the migration of the hydroxyl group is explained by the "electron repelling tendency of the methyl group"[49a]. This statement is an apparent contradiction of the facts since the hydroxyl group migrated toward the methyl group rather than away from it.

The migration of a hydroxyl group from a secondary to a primary position in a dienol has been reported by Nazarov and Fisher[50] in the equilibrium reaction:

$$(CH_3)_2\text{-}C(OH)\text{-}CH\text{=}CH\text{-}CH\text{=}CH_2 \rightleftharpoons (CH_3)_2\text{-}C\text{=}CH\text{-}CH\text{=}CH\text{-}CH_2OH$$

Zal'kind and Kulikov[51] have reported the apparent preparation

of 1-phenyl-2,4-pentadien-1-ol (X) by the reduction of 1-phenyl-2-pentyne-4-en-1-ol (XXI). They stated that their alcohol (X) rearranged to yield almost exclusively 1-phenyl-1,4-pentadien-3-ol (XI) and only a trace of 5-phenyl-2,4-pentadien-1-ol (XIII).




They based their conclusions on the results of ozonization studies. It would seem from the information available on this work, that no conclusive proof is presented, that a 1,3 rearrangement of the hydroxyl group had occurred and that only to a small extent did a 1,5 rearrangement occur. These workers did not hydrogenate completely the dienols XI and XIII to the corresponding phenylpentanols. They reported the absorption of one molecule of hydrogen to obtain a mixture of unidentifiable olefinic alcohols. Moreover, their alcohol to which they ascribed the structure 5-phenyl-2,4-pentadien-1-ol (XIII) was a liquid, whereas, the alcohol to which we ascribed the same structure and which upon the absorption of two molecules of hydrogen

yielded 5-phenylpentanol-1, was a solid melting at 78-79°.

5-Phenyl-2,4-pentadien-1-ol is markedly unstable in air, rapidly degenerating from a crystalline solid into a viscous mass with noticeable evolution of an aldehyde odor. A sample of the dienol was deliberately exposed to air for two days. The gummy mass which formed was triturated with alcohol and from these alcoholic washings a red 2,4-dinitrophenylhydrazone was obtained which melted at 253-254° and whose analysis corresponded to that of the 2,4-dinitrophenylhydrazone of cinnamaldehyde. An authentic sample of cinnamaldehyde-2,4-dinitrophenylhydrazone which melted at 254° was prepared; its melting point was not lowered when admixed with the 2,4-dinitrophenylhydrazone obtained from the ethanol washings of the sample of 5-phenyl-2,4-pentadien-1-ol which was allowed to decompose in air.

The nature of this decomposition of 5-phenyl-2,4-pentadien-1-ol into cinnamaldehyde has not been elucidated. It is not facilitated by acid or base. However, this decomposition can be avoided to a great extent by keeping 5-phenyl-2,4-pentadien-1-ol in an inert atmosphere.

$$C_6H_5\text{-}CH\text{=}CH\text{-}CH\text{=}CH\text{-}CH_2OH$$

exposure to air

$$C_6H_5CH\text{=}CH\text{-}CHO + \text{tar}$$

## EXPERIMENTAL *

5-Hydroxypentanal. A mixture of 300 ml. of water, 25 ml. of concentrated hydrochloric acid, and 100 g. of 2,3-dihydropyrane[52] was stirred vigorously until the mixture became homogeneous and then for an additional twenty minutes. The solution was neutralized with 20% sodium hydroxide using phenolphthalein as the indicator. The solution was extracted for twelve hours using a continuous extraction apparatus. After removal of the ether under reduced pressure, the residue was distilled. There was obtained 95 g. (79%) of 5-hydroxypentanal, b.p. 62-66° (6-8 mm.), $n_D^{18}$ 1.4534. This is in accord with the physical constants reported in the literature[12].

2,4-Dinitrophenylhydrazone of 5-Hydroxypentanal. To 100 ml. of a saturated alcoholic solution of 2,4-dinitrophenylhydrazine was added 1 ml. of concentrated hydrochloric acid and 1 ml. of 5-hydroxypentanal. The reaction mixture was heated on the steam bath for several minutes. Upon careful dilution with water and cooling, the yellow 2,4-dinitrophenylhydrazone crystallized. After recrystallization from alcohol-water, the product melted at 109°. Analysis: Calculated for $C_{11}H_{14}O_5N_4$: C, 46.81; H, 5.00. Found: C, 46.66; H, 4.67.

Pentamethylene Glycol. Catalytic reduction of 63 g. of 5-hydroxypentanal with 5 g. of Raney nickel as catalyst at 3000 p.s.i.g. at 90° required approximately one hour. The hydrogenation arrested itself when the calculated absorption of hydrogen had occurred.

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* All melting and boiling points are uncorrected. Microanalyses by Miss Eleanor Werble.

The catalyst was removed by filtration and the pentamethylene glycol distilled; b.p. 103-105° (3-4 mm.); yield, 61 g. (96%), $n_D^{20}$ 1.4498.

For purposes of further identification the di-phenylurethan of pentamethylene glycol was prepared in the usual manner and after two recrystallizations from petroleum ether (80-100°) melted at 173-174°. No depression was observed in a mixed melting point determination with the di-phenylurethan of pentamethylene glycol prepared by hydrogenolysis of tetrahydrofurfuryl alcohol.*

5-aminopentanol-1. Into a hydrogenation bomb which was immersed in a Dry Ice-acetone bath was placed in the following order, 80 g. of 5-hydroxypentanal, 10 g. of Raney nickel and 100 g. of liquid ammonia. The latter was added after the previously added contents were cooled below the boiling point of ammonia. Reductive amination was performed at 90° and 3000 p.s.i.g. and the reaction continued until it arrested itself. After cooling, the bomb was opened and the catalyst removed by filtration. The viscous crude product distilled at 85-95° (1-2 mm.); yield 70 g. (87%). This product had a neutral equivalent of 118 which corresponded to an 87% content of 5-aminopentanol-1.

To a solution of 50 g. of crude 5-amino-pentanol-1 in 200 ml. of anhydrous alcohol was added 50 g. of concentrated sulfuric acid in 200 ml. of anhydrous alcohol; the solution was cooled during the addition of the acid. After addition of 200 ml. of anhydrous ether and thorough chilling, the product was filtered and washed with ether. Recrystallization of the crude 5-aminopentanol-bisulfate from alcohol-ether yielded

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* The author wishes to thank Dr. E. Wilkins Reeve of this laboratory for the sample of pentamethylene glycol

white crystals stable in air; m.p. 102-103°; yield 85 g. (99% based on the 5-aminopentanol-1 in the crude product as indicated by its neutral equivalent). The neutral equivalent of the first hydrogen ion of 5-aminopentanol-1 bisulfate was determined by titration with sodium hydroxide using methyl red as the indicator. The second hydrogen ion titration was performed in the presence of formaldehyde with phenolphthalein as the indicator. Analysis: neutral equivalent calculated for $C_5H_{13}ON.H_2SO_4$: 201; 100.5. Found: 203,203; 103, 101.

0.5284 g. required 59.1 ml. of .08812 N NaOH to phenolphthalein end point.
0.4470 g. required 49.3 ml. " " " " " " " "
0.5284 g. required 29.5 ml. " " " to a methyl red end point
0.4470 g. required 25.0 ml. " " " " " " " "

A concentrated aqueous solution of 28 g. of 5-aminopentanol-1 bisulfate was neutralized with a 25% solution of sodium hydroxide and then subjected to continuous extraction with ether. After drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure and the residue was distilled; yield 11 g. (77%) of pure 5-aminopentanol-1, b.p. 79-81 (1 mm.); m.p. 38-39°. This value is considerably higher than that (27-28°) reported in the literature[41b]. Analysis: Calculated for $C_5H_{13}ON$: C, 58.25; H, 12.70. Neutral equivalent, 103. Found: C, 58.48; H, 12.98. Neutral equivalent, 103,103.

0.4274 g. required 42.9 ml. of 0.0950 N HCl to methyl red end point.
0.4279 g. required 43.4 ml. " " " " " " " .

Conversion of 5-Aminopentanol-1-Bisulfate to Piperidine.

5-Aminopentanol-1bisulfate (30 g.) was refluxed with a 75% excess of 48% aqueous hydrogen bromide for three hours. The reaction solution

was well cooled and neutralized with 20% sodium hydroxide and an additional 20 g. of sodium hydroxide was added. The solution was subjected to steam distillation and the distillate collected until the odor of piperidine was no longer evident. The distillate was made strongly alkaline with pellets of sodium hydroxide and extracted with ether. After drying over sodium hydroxide, the solvent was removed and the piperidine was distilled; b.p. 104-105°, $n_D^{20}$ 1.4532, yield 17 g. (81%). These physical properties agree well with those in the literature[53].

For purposes of further identification the piperidine was converted into its benzene-sulfonamide derivative in the usual manner and after several recrystallizations from alcohol melted at 93-94°. No depression was observed in a mixed melting point determination with an authentic sample of the benzenesulfonamide of piperidine.

2,3-Dibromotetrahydropyrane. The procedure used for the bromination of 2,3-dihydropyrane was a modification of that described by Paul[15]. A 2-liter, 3-neck flask was equipped with a dropping funnel, an efficient stirrer and a low range thermometer (immersed in the reaction mixture). Into this flask was added a solution of 252 g. of 2,3-dihydropyrane in 150 ml. of dry carbon tetrachloride. The dihydropyrane solution was cooled to -35-45° by means of a Dry Ice-acetone bath. A bromine solution (480 g.) in carbon tetrachloride (200 ml.) was added from the dropping funnel at such a rate that the temperature of the contents of the flask did not rise above - 10°. The bromine solution was added until decolorization was no longer evident. The solvent was removed on a steam bath under reduced pressure; yield 672 g. of crude undistilled product. Care was taken that the solvent was removed at the

lowest possible temperature, otherwise much of the 2,3-dibromotetrahydropyrane decomposed with evolution of hydrogen bromide.

Purification by distillation of a sample of the crude product yielded a straw colored oil, b.p. 80-82° (0.4 mm.). 2,3-Dibromotetrahydropyrane is not stable but darkens readily upon standing with noticeable evolution of hydrogen bromide and for this reason no analysis was performed on this product.

2-Ethoxy-3-bromotetrahydropyrane. To 450 ml. of well-cooled anhydrous alcohol which had been saturated with dry ammonia, was cautiously added with stirring, 277 g. of 2,3-dibromotetrahydropyrane. After a few minutes, precipitation of ammonium bromide occurred. In this reaction it is important that an excess of ammonia be maintained in the reaction mixture since traces of hydrogen bromide will decompose the product.

After one hour or longer at room temperature, the reaction mixture was filtered and the ammonium bromide was well washed with ether. A nearly quantitative yield of ammonium bromide was obtained. The combined filtrate and ether washings were twice washed with large quantities of water. After drying over sodium sulfate, the solvent was removed and the residue distilled; yield 205 g. of 2-ethoxy-3-bromotetrahydropyrane (86%), b.p. 94-96° (18 mm.), $n_D^{25}$ 1.4752. Analysis: Calculated for $C_7H_{13}O_2Br$: C, 40.21; H, 6.27. Found: C, 40.28, 40.40; H, 6.20, 6.32.

No 2,4-dinitrophenylhydrazone of this product could be obtained by operating in the usual manner.

2-Methoxy-3-bromotetrahydropyrane. The procedure for the

preparation of 2-ethoxy-3-bromotetrahydropyrane was followed using methyl alcohol in place of ethyl alcohol. A 50% yield (90 g.) of 2-methoxy-3-bromotetrahydropyrane was obtained from 226 g. of 2,3-dibromotetrahydropyrane; b.p. 88-89° (18 mm.), $n_D^{25}$ 1.4838. The fraction which distilled at 80-88° (18 mm.) contained substantial amounts of 2-methoxy-3-bromotetrahydropyrane. Analysis: Calculated for $C_6H_{11}O_2Br$: C, 36.94; H, 5.69. Found: C, 36.88; H, 5.99.

2-Ethoxy-$\Delta^3$-dihydropyrane. To a solution of sodium ethylate prepared from 40 g. of sodium in 600 ml. of absolute ethanol was added 170 g. of 2-ethoxy-3-bromotetrahydropyrane. This reaction mixture was refluxed for four hours, whereupon it was cooled and filtered. The sodium bromide precipitate, of which a nearly quantitative yield was obtained, was well washed with ether. The combined filtrate and ether washings were washed with water and dried over sodium sulfate. After removal of the solvent, the product was distilled; yield 64 g. (62%), b.p. 153-155°, $n_D^{25}$ 1.4475. Analysis: Calculated for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.71; H, 9.60.

Lower boiling fractions from 140-153° contained slightly less pure 2-ethoxy-$\Delta^3$-dihydropyrane and the higher boiling fractions from 160-180° contained considerable amounts of 2-ethoxy-3-bromotetrahydropyrane. This higher boiling fraction was retreated with sodium ethylate and an additional quantity of 2-ethoxy-$\Delta^3$-dihydropyrane was obtained.

If it was not desired to isolate the intermediate compound, 2-ethoxy-3-bromotetrahydropyrane, the preparation of 2-ethoxy-$\Delta^3$-dihydropyrane was considerably simplified and the yield improved if the

original ammoniacal alcoholic solution of 2-ethoxy-3-bromotetrahydropyrane obtained after filtration of the ammonium bromide was refluxed with alcoholic potassium hydroxide. A 100% excess of alkali was used. The product was isolated as above; b.p. 153-155°, $n_D^{25}$ 1.4475.

Treatment of either product by prolonged refluxing with sodium ethylate, sodium hydroxide or sodium did not alter the boiling point or refractive index.

2-Methoxy-$\Delta^3$-dihydropyrane. To a solution of 37.5 g. of commercial sodium methylate in 250 ml. of methanol was added 68 g. of 2-methoxy-3-bromotetrahydropyrane. The reaction mixture was refluxed for four hours, then cooled and filtered. The nearly quantitative yield of sodium bromide was well washed with ether. The combined filtrate and ether washings were washed with water. After drying over sodium sulfate, the solvent was removed and the residue distilled; yield 20 g. (51%) of 2-methoxy-$\Delta^3$-dihydropyrane; b.p. 136-138°, $n_D^{25}$ 1.4425. Analysis: Calculated for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found:

2-Ethoxytetrahydropyrane

2-Ethoxytetrahydropyrane. Catalytic reduction of 25.6 g. of 2-ethoxy-$\Delta^3$-dihydropyrane with 0.1 g. of Adams' platinum oxide at room temperature and 3 atmospheres of hydrogen pressure proceeded smoothly. The reduction required approximately two hours for the calculated hydrogen absorption, whereupon the hydrogenation arrested itself. The catalyst was removed by filtration and the product distilled; b.p. 145-146°, $n_D^{27}$ 1.4250. A nearly quantitative yield (23 g.) of 2-ethoxytetrahydropyrane was obtained. Analysis: Calculated for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found:

C, 64.28; H, 10.93.

The acid hydrolysis of 2-ethoxytetrahydropyrane yielded 5-hydroxypentanal which was isolated as its 2,4-dinitrophenylhydrazone. One gram of 2-ethoxytetrahydropyrane was dissolved in 10 ml. of 95% alcohol which contained a few drops of concentrated hydrochloric acid. This solution was heated on the steam bath for approximately one minute, whereupon an alcoholic solution of 2,4-dinitrophenylhydrazine which contained 7 drops of concentrated hydrochloric acid was added. Heating of the reaction mixture was continued for five minutes. The yellow 2,4-dinitrophenylhydrazone of 5-hydroxypentanal crystallized from the cooled reaction mixture after careful dilution with water. The product melted at 109° after one recrystallization from alcohol-water. There was no depression in a mixed melting point determination with an authentic sample of the 2,4-dinitrophenylhydrazone of 5-hydroxypentanal.

Attempted Preparation of 5-Hydroxy-$\Delta^2$-pentenal. Twenty grams of 2-ethoxy-$\Delta^3$-dihydropyrane was added gradually to 200 ml. of a well stirred, cold 5% hydrochloric acid solution. The time of hydrolysis was approximately two hours when only one liquid phase was observed. The hydrolysis was considered completed. The solution was carefully neutralized with 10% sodium hydroxide using phenolphthalein as the indicator and then subjected to continuous extraction with ether. The solvent was removed after drying over sodium sulfate and the liquid residue distilled. There was obtained 10 g. of a colorless liquid which boiled over a range of 105-136° (1 mm.) with a steady rise in boiling point. The boiling point was considerably higher than would

be expected by comparison with that of 5-hydroxypentanal (62-66° at 6-8 mm.) No pure product could be obtained by fractional distillation.

No semicarbazone or 2,4-dinitrophenylhydrazone of 5-hydroxy-$\Delta^2$-pentenal could be obtained from the product boiling at 105-136° (1 mm.) by operating in the usual manner.

Attempted Hydrogenation of 5-Hydroxy-$\Delta^2$-pentenal.

All efforts to prepare 5-hydroxypentanal by catalytic reduction of the product obtained from the acid hydrolysis of 2-ethoxy-$\Delta^3$-dihydropyrane were unsuccessful. A typical experiment is described below.

Twenty grams of 2-ethoxy-$\Delta^3$-dihydropyrane was hydrolyzed in dilute acid solution as described above. After removal of the ether, the residue was not distilled but used in the crude state for hydrogenation studies. A solution of 9.6 g. of the undistilled hydrolysis product in 50 ml. of absolute alcohol was subjected to hydrogenation using 0.2 g. of platinum oxide as catalyst. Room temperature and a pressure of 3 atmospheres of hydrogen were the conditions employed. At the end of four hours, the hydrogenation arrested itself when only 5.5 lbs. of the calculated 7.0 lbs. uptake of hydrogen were absorbed. Introduction of fresh catalyst did not cause any further hydrogen absorption. The catalyst was removed by filtration and the filtrate was fractionally distilled. After removal of the solvent the following fractions were obtained:

Fraction I. b.p. 94-100° (5-6mm.), $n_D^{25}$ 1.4560 - 4.0 g.

Fraction II. b.p. 110-125° (5-6mm.) $n_D^{25}$ 1.4600 - 1.0 g.

Fraction III. very high boiling fraction which was not distillable.

It was not anticipated that any homogeneity of the hydrogenated product would be observed since incomplete absorption of hydrogen had occurred. Therefore preliminary investigative tests were performed on the first 2 fractions:

Fraction I. (a) decolorized a bromine solution in carbon tetrachloride thereby indicating an ethylene link. (b) gave a positive test with Schiff's reagent after a few seconds. (c) did not form a semicarbazone. (d) formed a mixture of yellow and red 2,4-dinitrophenylhydrazones which could not be separated or purified.

Fraction II. The results of the above tests on fraction II were similar to those observed for fraction I.

Preparation of 5-Hydroxy-$\Delta^2$-pentenal-2,4-dinitrophenylhydrazone. This derivative was prepared from both 2-ethoxy- and 2-methoxy-$\Delta^3$-dihydropyrane. The dihydropyrane acetal was added to a saturated alcoholic solution of 2,4-dinitrophenylhydrazine and warmed on the steam bath. One ml. of concentrated hydrochloric acid was added and the heating was continued for five minutes. Upon partial cooling, red needles of the 2,4-dinitrophenylhydrazone precipitated and upon complete cooling the derivative gradually changed in color from red to orange. After recrystallization from alcohol, the product melted at 159-160°. The same phenomenon of change of color and crystal structure from needles to an amorphous-like substance was observed in the recrystallization and is therefore considered to be reversible. Analysis: Calculated for $C_{11}H_{12}O_5N_4$: C, 47.14; H, 4.32. Found: C, 47.36, 47.58; H, 4.41, 4.34.

Preparation of 2,4-Pentadienal. To a solution of 40 ml. of 85% phosphoric acid in 200 ml. of water was added with stirring, 40 g. of 2-ethoxy-$\Delta^3$-dihydropyrane. There was no noticeable rise in temperature upon the addition of the dihydropyrane acetal. Within a few minutes, a homogeneous solution was obtained. This solution was added dropwise to a solution of 50 ml. of 85% phosphoric acid in 200 ml. of water which was already undergoing steam distillation. Steam distillation was continued until the distillate no longer had the characteristic odor of 2,4-pentadienal.

The steam distillate, approximately 400 ml., was saturated with potassium chloride and extracted with 3 portions of 25 ml. of ether. After drying over sodium sulfate, the solvent was removed under reduced pressure and the residue was rapidly fractionally distilled. The condenser was cooled by circulating ice-water and the receiver was cooled in a Dry Ice-acetone bath. All attempts at distillation of 2,4-pentadienal at atmospheric pressure had led to uncontrollable decomposition. 2,4-Pentadienal was therefore distilled at the pressure of 20 mm. which was found to be the most satisfactory. The following fractions were obtained.

| | | | | |
|---|---|---|---|---|
| Fraction I. | up to 21° (20 mm.) | 2 g. | $n_D^{25}$ | 1.4231 |
| Fraction II. | 21-32° (20 mm.) | 6 g. | $n_D^{25}$ | 1.4530 |
| Fraction III. | 32-36° (20 mm.) | 1 g. | $n_D^{25}$ | 1.5062 |
| Fraction IV. | 36-37° (20 mm.) | 14 g. | $n_D^{25}$ | 1.5163 |

Fraction IV was pure 2,4-pentadienal which was almost colorless and possessed a marked acrolein-like odor and was strongly lachrymatory. It was readily soluble in alcohol and ether and fairly

soluble in water. The density of 2,4-pentadienal is 0.894 at 25°. Analysis: Calculated for $C_5H_6O$: C, 73.14; H, 7.37. Found C, 73.26, 72.99; H, 7.95; 7.85.

Hydrolysis and dehydration by hydrochloric, sulfuric and oxalic acids gave lower yields of 2,4-pentadienal accompanied with a greater quantity of resinous products. The aldehyde is stable for reasonable periods of time when kept cold and in an inert atmosphere. After three days in the refrigerator, the refractive index of Fraction IV was $n_D^{25}$ 1.5149 and after ten days, it was $n_D^{25}$ 1.5200.

Preparation of 2,4-Pentadienal Semicarbazone. A solution of 0.2 g. of 2,4-pentadienal in 10 ml. of alcohol was warmed on the steam bath with a solution of 0.5 g. of semicarbazide hydrochloride and 1.5 g. of anhydrous sodium acetate in 30 ml. of water. The semicarbazone almost immediately crystallized in glistening white platelets and was recrystallized from water. This substance did not have a sharp melting point but decomposed progressively on heating to 260°. Analysis: Calculated for $C_6H_9ON_3$: C, 51.77; H, 6.52. Found C, 51.67, 51.65, 52.08; H, 6.21, 6.49, 6.67.

Preparation of 2,4-Pentadienal-2,4-dinitrophenylhydrazone. A solution of 1 g. 2,4-pentadienal in 25 ml. of alcohol was added to a solution of 2.5 g. of 2,4-dinitrophenylhydrazine in 75 ml. of alcohol which contained 1 ml. of concentrated hydrochloric acid. Immediate precipitation of the red 2,4-dinitrophenylhydrazone was observed. The reaction mixture was heated on the steam bath for ten minutes after which time it was cooled and filtered. There was obtained 3.10 g. (almost quantitative yield) of the red 2,4-dinitrophenyl-hydrazone of 2,4-pentadienal which melted at 171-172°. After several

recrystallizations from absolute alcohol, the melting point rose to 176-177°. Analysis: Calculated for $C_{11}H_{10}O_4N_4$: C, 50.38; H, 3.84. Found: C, 50.11, 50.38; H, 3.81, 3.88.

Catalytic Hydrogenation of 2,4-Pentadienal. A water suspension of 13.3 g. of 2,4-pentadienal in 150 ml. of distilled water was subjected to hydrogenation with 3 g. of Raney nickel as catalyst at room temperature and a pressure of 3 atmospheres of hydrogen. At the end of six hours, when the absorption of hydrogen was in slight excess of that calculated for the reduction of 2 ethylene links, the reaction was discontinued. The catalyst was removed by filtration and the filtrate, which consisted of 2 liquid phases, was extracted with 3 portions of 25 ml. of ether. The ether extract was dried and after removal of the solvent, the following fractions were obtained by distillation:

| | | |
|---|---|---|
| Fraction I | b.p. 85-105° | 3 g. |
| Fraction II | b.p. 105-125° | 4 g. |
| Fraction III | b.p. 125-130° | 2 g. |

There was a steady rise in boiling point during the course of the distillation and no sharp fractionation was possible. A yellow 2,4-dinitrophenylhydrazone was prepared from Fraction I by operating in the usual manner. After recrystallization from alcohol-water this derivative melted at 105.5-106.5°. This is in good agreement with the reported melting point of the 2,4-dinitrophenylhydrazone of valeraldehyde (106.5-107.5°). Analysis: Calculated for $C_{11}H_{14}O_4N_4$: C, 49.61; H, 5.30. Found: C, 49.02, 48.92; H, 5.21, 5.45. Fraction II also yielded a yellow 2,4-dinitrophenylhydrazone but in lesser

quantity than did Fraction I.

The ∝-naphthylurethan of n-amyl alcohol was prepared from Fraction III. A solution of 0.45 g. of Fraction III and 0.70 g. of ∝-naphthyl isocyanate was heated on the steam bath for several minutes. After cooling, 5 ml. of petroleum ether (60-80°) was added and the small amount of fluffy amorphous solid which soon appeared was removed by filtration. The filtrate was cooled in a Dry Ice-acetone bath. In a few minutes, white needle-like crystals of the ∝-naphthylurethan of n-amyl alcohol were deposited. After 2 recrystallizations from petroleum ether (60-80°) the derivative melted at 68°. Analysis: Calculated for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.47. Found: C, 74.71, 74.93; H, 7.43, 7.42.

The ∝-naphthylurethan of an authentic sample of n-amyl alcohol was prepared which melted at 68°[55]. There was no depression in a mixed melting point determination of the two ∝-naphthylurethans.

Reaction of 2,4-Pentadienal with Maleic Anhydride. (3-Aldehyde-$\Delta^4$-tetrahydrophthalic anhydride). A solution of 10 g. of 2,4-pentadienal and 13 g. of maleic anhydride in 60 ml. of dry toluene was refluxed for four hours. Within an hour, a dark oil settled to the bottom of the toluene reaction mixture. The reaction mixture was allowed to cool to room temperature and the toluene was decanted from the viscous oil. The toluene solution was diluted with 120 ml. of anhydrous ether and allowed to remain overnight in the refrigerator. A white crystalline precipitate (2 g.) was deposited which melted at 149-150°. After 2 recrystallizations from petroleum ether (80-100°) the melting point was elevated to 153-154°. The

anhydride obtained from the Diels-Alder reaction was sparingly soluble in the cold in acetone, ether, petroleum ether and water. It dissolved in cold dilute sodium bicarbonate with effervescence. Analysis: Calculated for $C_9H_8O_4$: C, 60.00; H, 4.47. Found: C, 60.19, 60.16; H, 4.82, 4.75.

Several attempts to prepare the dicarboxylic acid corresponding to 3-aldehydo-$\Delta^4$-tetrahydrophthalic anhydride were unsuccessful. The anhydride (0.5 g.) was suspended in 15 ml. of water and solid sodium bicarbonate was added until complete solution was evident. The reaction mixture was carefully neutralized and then made slightly acidic with dilute hydrochloric acid. After standing one week in the refrigerator no precipitate was observed. It is very likely that the dicarboxylic acid is too soluble in water to be thus isolated.

No semicarbazone of 3-aldehydo-$\Delta^4$-tetraphthalic anhydride could be obtained by operating in the usual manner.

A 2,4-dinitrophenylhydrazone was prepared by dissolving the aldehyde anhydride in a minimum of warm alcohol and then adding this solution to alcoholic 2,4-dinitrophenylhydrazine and heating for five minutes in the presence of 1 ml. of concentrated hydrochloric acid. The yellow 2,4-dinitrophenylhydrazone crystallized on cooling and melted at 228-230°. After recrystallization from dioxane-alcohol, the melting point was raised to 232-234° (decomp.). This product could not be purified sufficiently to give good results on analysis.

The viscous oil obtained in the toluene reaction mixture was insoluble in ordinary organic solvents and resisted all attempts to obtain a crystalline entity from it. It was insoluble in water but

dissolved in dilute sodium bicarbonate with effervescence. The solution was treated with charcoal, filtered and carefully acidified, whereupon a dark intractable tar was obtained. No further investigation was made of this substance.

Reaction of 2,4-Pentadienal with 2,3-Dimethylbutadiene.

(Preparation of 4-aldehydo-5-vinyl-1,2-dimethyl-$\Delta^1$-cyclohexene).

2,3-Dimethylbutadiene was prepared by catalytic dehydration of pinacol hydrate according to directions in "Organic Synthesis"[56]. Ten grams of 2,4-pentadienal and 20 g. of 2,3-dimethylbutadiene was placed in a glass Carius tube, which was then sealed. The sealed tube was placed in a high pressure hydrogenation bomb which contained 20 ml. of petroleum ether (60-80°), to minimise pressure differences between the inside and outside of the glass tube, and was then heated for six hours at 150°.

After allowing to cool to room temperature, the reaction tube was cooled in a Dry Ice-acetone bath and opened. The fragrant yellow product was fractionally distilled using a modified Vigreux column whereupon the following fractions were obtained.

| | | |
|---|---|---|
| Fraction I. | b.p. 60-70° | 8 g. |
| Fraction II. | b.p. 65-100° (12 mm.) | 0.5 g. |
| Fraction III. | b.p. 100-121° (12 mm.) | 3 g. |
| Fraction IV. | b.p. 121-128° (12 mm.) | 7 g. (35%) |
| Fraction V. | high boiling residue which was non-distillable | |

Fraction I consisted of recovered 2,3-dimethylbutadiene which was present in excess in the reaction mixture. Fraction II did not yield a 2,4-dinitrophenylhydrazone. Fraction III gave a slight yield of a

yellow 2,4-dinitrophenylhydrazone. Fraction IV was the desired product and was purified by distillation, b.p. 117-118°/8 mm., $n_D^{25}$ 1.5100. Analysis: Calculated for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.39, 80.18; H, 9.94, 9.81.

A yellow 2,4-dinitrophenylhydrazone of 4-aldehydo-5-vinyl-1,2-dimethyl-$\Delta^1$-cyclohexene was prepared by adding 0.5 g. of the aldehyde to 50 ml. of a warm saturated alcoholic solution of 2,4-dinitrophenylhydrazine to which was added 1 ml. of concentrated hydrochloric acid. After warming on the steam bath for five minutes and subsequent cooling, the 2,4-dinitrophenylhydrazone crystallized from the solution. It melted at 179-180° after two recrystallizations from alcohol-water. Analysis: Calculated for $C_{17}H_{20}O_4N_4$: C, 59.29; H, 5.85. Found: C, 59.31, 59.55; H, 5.85, 5.90.

A semicarbazone was prepared by warming an alcoholic solution of 0.5 g. of the aldehyde with an aqueous solution (30 ml.) of 1.0 g. of semicarbazide hydrochloride and 1.5 g. of anhydrous sodium acetate. The derivative formed almost immediately and after recrystallization from alcohol-water the glistening white platelets melted at 202°. Analysis: Calculated for $C_{12}H_{19}ON_3$: C, 65.09; H, 8.65. Found: C, 64.96, 64.85; H, 8.70; 8.72.

Attempted Oxidation of 2,4-Pentadienal with Silver Oxide.

Silver oxide was prepared by adding a slight excess of 20% sodium hydroxide to a solution of silver nitrate. The brown precipitate was washed by decantation 10 times with distilled water and five times with absolute alcohol, acetone and ether respectively. The silver oxide was dried in a vacuum dessicator. A suspension of 20 g. of

2,4-pentadienal and 60 g. of silver oxide in 200 ml. of water was stirred for eighteen hours at room temperature. Ten grams of sodium hydroxide and 100 ml. of concentrated ammonia was then added to the suspension which soon changed in appearance from brown to black. The stirring was continued for another four hours whereupon the reaction mixture was filtered. There was no odor of 2,4-pentadienal present.

The filtrate was acidified with dilute sulfuric acid, saturated with potassium chloride and extracted 6 times with 50 ml. portions of ether. The ether extract was dried over sodium sulfate. After removal of the solvent no product was found.

The black sludge obtained after filtration of the reaction mixture was digested on the steam bath for one-half hour with a solution of 70 g. of sodium sulfide in 800 ml. of water. The reaction mixture was cooled and filtered. The filtrate was acidified with concentrated hydrochloric acid, saturated with potassium chloride and extracted with 6 portions of 50 ml. of ether. The dried ether was evaporated to dryness; no product was obtained in the ether extract.

Reaction of 2,4-Pentadienal with Phenylmagnesium Bromide.

A solution of 14.5 g. (0.18 mole) of freshly prepared 2,4-pentadienal (b.p. 38-40°/20 mm.) in 50 ml. of ether was added dropwise and with stirring to 200 ml. of an ethereal solution of phenylmagnesium bromide prepared from 39.3 g. (0.25 mole) of bromobenzene and 6.1 g. (0.25 mole) of magnesium. The addition of the aldehyde solution was accompanied by a vigorous reaction. After the addition of the 2,4-pentadienal solution the reaction mixture was stirred for one-half hour at room temperature. The Grignard complex solution which was chilled in an

ice bath was decomposed by the cautious addition of 200 ml. of a saturated aqueous ammonium chloride solution. The ether layer was separated and washed three times with water and then subjected to steam distillation. When the solvent had been completely removed, the steam distillate was collected in a new receiver. The presence of an aldehyde in the steam distillate was not detected with Schiff's reagent or 2,4-dinitrophenylhydrazine. At the end of two hours when all the biphenyl, which was a by-product in the Grignard reaction, was removed the material in the steam distillation pot was cooled in an ice bath. The oily product settled to the bottom and formed a yellow viscous gum. The water was poured off and the gum extracted with 200 ml. of ether. After drying over sodium sulfate, the ether solution was concentrated to about 40 ml. and then cooled in a Dry Ice chest. The solution soon solidified and after three hours of cooling, the solid material was rapidly filtered. The ether filtrate was saved for hydrogenation studies. The gummy solid product on the filter was washed with 30 ml. of cold petroleum ether (30-60°). This served to remove much of the gummy impurities. There was obtained 12.0 g. (42%) of crude 5-phenyl-2,4-pentadien-1-ol. The purification of this product offered some difficulties since it decomposed progressively when exposed to the atmosphere. The best method of purification was effected by dissolving the product in boiling petroleum ether (80-100°) and treating with charcoal. After removal of the charcoal, the solution was allowed to cool somewhat, whereupon a colorless oil settled to the bottom. The warm petroleum ether solution was decanted and cooled in a refrigerator. In a few hours fluffy white crystals of the alcohol were deposited; m.p. 74-76°.

5-Phenyl-2,4-pentadien-1-ol was obtained quite pure after three recrystallizations from petroleum ether (80-100°) and melted at 78-79°. Analysis: Calculated for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.39, 82.10; C, 7.72, 7.70.

This compound is not stable when exposed to the atmosphere even for short periods of time. It should be stored in an atmosphere of nitrogen and kept in a refrigerator; under these conditions it can be kept for several weeks.

The phenylurethan of 5-phenyl-2,4-pentadien-1-ol was prepared by warming 0.68 g. of the alcohol and 0.50 g. of phenyl isocyanate for two minutes on a hot plate. The urethan crystallized after cooling, and was dissolved in a minimum of ether and treated with charcoal. The charcoal was removed by filtration, and the ether solution diluted with petroleum ether (30-60°) until a faint cloudiness was observed. The urethan crystallized in the form of stout needles after remaining overnight in the refrigerator and melted at 96-98°. The derivative was purified by two recrystallizations from petroleum ether (80-100°); m.p. 99.5-100°. Analysis: Calculated for $C_{18}H_{17}O_2N$: C, 77.39; H, 6.14. Found: C, 76.94, 77.17; H, 6.39, 6.02.

Hydrogenation of 5-Phenyl-2,4-pentadien-1-ol to 5-Phenylpentanol-1. A solution of 5.0 g. of 5-phenyl-2,4-pentadien-1-ol in 25 ml. of absolute alcohol was hydrogenated in the presence of 1 g. of Raney nickel at room temperature and a pressure of 3 atmospheres of hydrogen. Two moles were absorbed whereupon the reaction arrested itself. After removal of the catalyst by filtration the filtrate was distilled. There was obtained 3.7 g. of 5-phenylpentanol-1 boiling at 133-134° (8 mm.),

150-151° (14 mm.), $n_D^{25}$ 1.5122. Analysis: Calculated for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.09, 80.13; H, 10.04, 10.09. The physical constants reported above are in good agreement with those recorded in the literature[46,47] and with those of 5-phenylpentanol-1 prepared by a series of known reactions.

The ether filtrate obtained from the crystallization of the crude 5-phenyl-2,4-pentadien-1-ol was also subjected to catalytic hydrogenation from which was obtained 5-phenylpentanol-1 boiling at 150-152 (14 mm.) and 133-134 (8 mm.), $n_D^{25}$ 1.5126.

That the products obtained from the hydrogenation of pure 5-phenyl-2,4-pentadien-1-ol and from the hydrogenation of the ether filtrate obtained from the crystallization of 5-phenyl-2,4-pentadien-1-ol were identical, was established by the preparation of the phenylurethans of the phenylpentanols both of which melted at 73.5° and showed no depression in a mixed melting point determination.

The phenylurethans were prepared by warming 0.82 g. of the alcohol with 0.60 g. of phenyl isocyanate for one minute on a hot plate. Crystallization of the derivative was induced by cooling and scratching the inside of the flask. After two recrystallizations from petroleum ether (80-100°) the phenylurethan of 5-phenylpentanol was obtained pure and melted at 73.5°. Analysis: Calculated for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.47. Found: C, 76.43, 76.39; H, 7.64, 7.49.

There was no depression in a mixed melting point determination with the phenylurethan prepared from an authentic sample of 5-phenylpentanol-1. A 20° depression was observed in a mixed melting point determination with the phenylurethan of 1-phenylpentanol-3.

The 3,5-dinitrobenzoate of the 5-phenylpentanol-1 obtained by hydrogenation of 5-phenyl-2,4-pentadien-1-ol was prepared by warming 1 g. of the alcohol with 1.3 g. of 3,5-dinitrobenzoyl chloride. The liquid product was treated with 10 ml. of water and cooled in an ice bath until solidification had occurred. The solid product was filtered and washed with 30 ml. of 5% sodium carbonate. After two recrystallizations from petroleum ether (80-100°) the 3,5-dinitrobenzoate of 5-phenylpentanol-1 melted at 67-67.5°. Analysis: Calculated for $C_{18}H_{18}O_6N_2$: C, 60.33; H, 5.06. Found: C, 59.85; H, 4.91.

No depression in melting point was observed when admixed with the 3,5-dinitrobenzoate prepared from an authentic sample of 5-phenylpentanol-1.

Air Oxidation of 5-Phenyl-2,4-pentadien-1-ol to Cinnamaldehyde.

A sample of pure, odorless, and crystalline 5-phenyl-2,4-pentadien-1-ol was exposed to the atmosphere in a small crystallizing dish. Within a few hours the product acquired the typical odor of an aromatic aldehyde. After exposure for two days to the atmosphere, the 5-phenyl-2,4-pentadien-1-ol acquired the appearance of a gum with an occasional crystalline colony. It was dissolved in 10 ml. of alcohol and added to 25 ml. of a saturated alcoholic solution of 2,4-dinitrophenylhydrazine. One ml. of concentrated hydrochloric acid was added and the reaction mixture was heated on the steam bath for five minutes. Upon cooling, a red 2,4-dinitrophenylhydrazone precipitated; m.p. 246-247°. After three recrystallizations from ethyl acetate the melting point rose to 253-254°(decomp.). Analysis: $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.88. Found: C, 57.55, 57.57, 57.54; H, 4.05, 3.71, 3.95.

A red 2,4-dinitrophenylhydrazone was prepared from an authentic sample of cinnamaldehyde and after two recrystallizations from ethyl acetate it melted at 254°. The reported melting point is 255°[57]. When the 2,4-dinitrophenylhydrazone obtained from air oxidation product of 5-phenyl-2,4-pentadien-1-ol was admixed with the authentic 2,4-dinitrophenylhydrazone of cinnamaldehyde, the mixed sample melted at 254°, thus showing no depression.

A sample of 5-phenyl-2,4-pentadien-1-ol was placed in a 50 ml. flask and the air was displaced by oxygen. The flask was stoppered and set aside at room temperature. Only slight decomposition of the product was observed after one week. The decomposition was not catalyzed by dilute acids or bases; no 2,4-dinitrophenylhydrazone or cinnamic acid could be obtained from products so treated.

Preparation of 5-Phenylpentanol-1. This alcohol was prepared by the following series of reactions: (a) preparation of γ-benzoylbutyric acid; (b) Clemmensen reduction of γ-benzoylbutyric acid to phenylvaleric acid; (c) esterification of phenylvaleric acid with ethyl alcohol; (d) reduction of ethyl phenylvalerate in toluene with sodium and alcohol.

a) preparation of γ-benzoylbutyric acid. This substance was prepared by the procedure suggested in Organic Synthesis[58]. A cold solution of 114 g. of glutaric anhydride in 300 ml. of dry benzene was added dropwise to a well stirred suspension of 300 g. of anhydrous aluminum chloride in 300 ml. of benzene. The reaction mixture was cooled in an ice bath and the rate of addition of the anhydride solution was adjusted so that the temperature did not exceed 15°. After the

addition of the anhydride solution, the reaction mixture was allowed to remain two hours at room temperature. Water (500 ml.) was added dropwise to the well stirred reaction mixture which soon became viscous and difficult to stir. After the careful addition of 147 ml. of concentrated hydrochloric acid, the reaction mixture was steam distilled. When the benzene had been removed the γ-benzoylbutyric acid formed an upper oily layer which solidified to a crust upon cooling. This was mechanically broken and filtered. The solid material was washed on the filter with 75 ml. of concentrated hydrochloric acid in 220 ml. of water. The crude product was dissolved in a solution of 110 g. of anhydrous sodium carbonate in 750 ml. of water and the solution heated on the steam bath for fifteen minutes in order to hasten coagulation of traces of alumina. The filtered solution of the soluble sodium salt of γ-benzoylbutyric acid was decolorized with charcoal. After filtration of the charcoal, the colorless filtrate was acidified by the slow addition of concentrated hydrochloric acid. The precipitated γ-benzoylbutyric acid was filtered, well washed with water and dried at 65° "in vacuo". There was obtained 172 g. (90%) of the keto acid which melted at 126°. After one recrystallization from water the product melted at 128°. This is in agreement with the reported melting point of 127°[59].

b) <u>reduction of γ-benzoylbutyric acid to phenylvaleric acid</u>. The procedure used was the Martin modification of the Clemmensen reaction[60]. Two hundred grams of c.p. messy zinc was treated for two minutes with 5% hydrochloric acid. After decantation of the acid solution, the zinc was amalgamated by immersion in a 2% mercuric

chloride solution. The zinc was washed free of the mercury salt with distilled water. The amalgamated zinc was used immediately in the reaction. A solution of 83 g. of γ-benzoylbutyric acid in 175 ml. of toluene was added to 300 ml. of concentrated hydrochloric acid which had been diluted with 130 ml. of water. The 200 g. of amalgamated zinc was added and the reaction mixture was allowed to reflux for thirty hours. The decanted toluene layer was washed several times with water; the solvent was removed under reduced pressure and the product distilled. There was obtained 65 g. (85%) of phenylvaleric acid with a boiling point of 180-183° (12 mm.) and a melting point of 57-57.5°. This is in agreement with the physical constants reported in the literature[61].

e) preparation of ethyl phenylvalerate. A solution of 60 g. of phenylvaleric acid in 250 ml. of absolute alcohol, to which was added 8 ml. of concentrated sulfuric acid was refluxed for four hours. The cold reaction mixture was poured into 400 ml. of water and extracted with ether. After drying over sodium sulfate, the ether was removed and the crude ester distilled; yield 57 g. (82%), b.p. 141.5-142.5 (9 mm.), $n_D^{26}$ 1.4903. Von Braun and Deutsch[62] reported a boiling point of 150° (11 mm.) for this ester.

d) reduction of ethyl phenylvalerate to 5-phenylpentanol-1. The procedure used was the general Bouveault-Blanc method for the reduction of esters to alcohols. A solution of 40 g. of ethyl phenylvalerate in 350 ml. of absolute alcohol was slowly dropped into a vigorously stirred suspension of 65 g. of sodium in 500 ml. of refluxing dry toluene. The reaction mixture became viscous and difficult to

stir. When the addition of the ester solution had been completed, the excess sodium was decomposed by the cautious addition of absolute ethanol. The reaction mixture was cooled in an ice bath and 500 ml. of water was slowly added with stirring to decompose the alcoholates. After extraction with 200 ml. of ether and drying over sodium sulfate, the ether and toluene was removed under reduced pressure. The crude 5-phenylpentanol-1 was purified by distillation; yield 18 g. (56%), b.p. 138-140° (11 mm.). The product was further purified by redistillation, b.p. 132-132.5 (8 mm.), 150-151° (14 mm.), $n_D^{28}$ 1.5118. These physical constants are in agreement with those recorded in the literature[46,47]. Analysis: Calculated for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.21, 80.12; H, 9.98, 9.44.

The phenylurethan of 5-phenylpentanol-1 was prepared by the addition of 0.60 g. of phenyl isocyanate to 0.80 g. of the alcohol and heating on the hot plate for one minute. Upon cooling, the phenylurethan solidified. It was purified by recrystallization from petroleum ether (80-100°), and melted at 73.5-74°. The preparation of the phenylurethan of 5-phenylpentanol-1 is in contrast to the observation of Von Braun[47] who could not obtain a crystalline phenylurethan of 5-phenylpentanol-1. Analysis: Calculated for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.47. Found: C, 75.98, 75.93; H, 7.60, 7.66.

The 3,5-dinitrobenzoate of 5-phenylpentanol-1 was prepared by warming 1 g. of the alcohol with 1.3 g. of 3,5-dinitrobenzoyl chloride. After treatment with 10 ml. of water and thorough chilling, the derivative solidified. The solid product was washed with 25 ml. of 5% sodium carbonate and was recrystallized twice from petroleum ether

(80-100°); m.p. 67-67.5°. Analysis: Calculated for $C_{18}H_{18}O_6N_2$: C, 60.33; H, 5.06. Found: C, 60.13; H, 515.

Preparation of 1-Phenylpentanol-1. The method of Bogert and co-workers[46] was used whereby benzaldehyde was reacted with n-butyl-magnesium bromide. A Grignard reagent was prepared from 27.4 g. (0.2 mole) of n-butyl bromide and 4.9 (0.2 mole) of magnesium in 100 ml. of ether. A solution of 16 g. (0.14 mole) of freshly distilled benzaldehyde in 50 ml. of ether was slowly added with stirring, to the Grignard reagent. The reaction mixture was decomposed by the addition of aqueous ammonium chloride. The ether layer was washed several times with water and dried over sodium sulfate. After removal of the ether, the product was distilled; yield 14 g. (61%), b.p. 122 (11 mm.), $n_D^{25}$ 1.5070. The boiling point is in agreement with those reported in the literature[44,46]. Analysis: Calculated for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.21, 80.13; H, 9.91, 9.72.

Contrary to the statement of Fourneau and co-workers[44] who reported the formation of a phenylurethan by the action of phosgene and dimethylaniline on 1-phenylpentanol-1, no phenylurethan could be obtained from 1-phenylpentanol-1 using phenyl isocyanate under various conditions. It was observed that the alcohol dehydrated too readily under any of the conditions of operation. Several attempts to prepare the 3,5-dinitrobenzoate of 1-phenylpentanol-1 were also unsuccessful.

For purposes of identification, 1-phenylpentanol-1 was oxidized to valerophenone. A solution of 0.83 g. of chromic oxide in 15 ml. of water to which had been added 1 ml. of concentrated sulfuric acid, was added dropwise to a well stirred suspension of 2.0 g. of

1-phenylpentanol-1 in 5 ml. of water. The reaction mixture was kept cold during the addition of the oxidizing solution. After steam distillation of the reaction mixture, the distillate was extracted with ether. The solvent was removed after drying over sodium sulfate, and the valerophenone (1.5 g.) was used without further purification for the preparation of its semicarbazone and 2,4-dinitrophenylhydrazone. These derivatives were prepared in the usual manner. After recrystallization from water, the semicarbazone melted at 166°. The 2,4-dinitrophenylhydrazone melted at 166° after recrystallization from acetic acid. The melting points agree with those reported in the literature for these derivatives of valerophenone[63].

Preparation of 1-Phenylpentanol-3. This alcohol was prepared according to the method of Bogert and co-workers[46] by the reaction of hydrocinnamaldehyde with ethylmagnesium bromide.

The hydrocinnamaldehyde was prepared by selective catalytic hydrogenation of cinnamaldehyde contrary to a statement by Adkins[64] that olefinic links in unsaturated aldehydes cannot be selectively hydrogenated. A solution of 39.6 g. (0.3 mole) of freshly distilled cinnamaldehyde in 50 ml. of alcohol was hydrogenated at room temperature and at a pressure of 3 atmospheres of hydrogen with 3 g. of Raney nickel catalyst. After two hours, when slightly more than the amount of hydrogen calculated for one ethylene link was absorbed, the hydrogenation was discontinued. The catalyst was removed by filtration and the filtrate was fractionally distilled. There was obtained 30 g. of hydrocinnamaldehyde, b.p. 107-108° (14 mm.); literature value 104-105° (13 mm.)[65].

For purposes of identification, a semicarbazone was prepared in the usual manner and melted at 127-127.5° after recrystallization from water. The semicarbazone of hydrocinnamaldehyde is reported to melt at 127°[66].

1-Phenylpentanol-3 was prepared by the dropwise addition of a solution of 20 g. (0.15 mole) of hydrocinnamaldehyde in 50 ml. of ether to 150 ml. of an ethereal solution of ethylmagnesium bromide prepared from 4.9 g. (0.2 mole) of magnesium and 21.8 g. (0.2 mole) of ethyl bromide. After decomposition of the magnesium complex by the addition of aqueous ammonium chloride, the ether layer was separated and well washed with water. Removal of the solvent, after drying over sodium sulfate, and distillation of the product gave 17 g. (69%) of 1-phenylpentanol-3, b.p. 124-126° (12 mm.), $n_D^{28}$ 1.5090. The boiling point agrees with that reported by Bogert et al[46] for 1-phenylpentanol-3.

The phenylurethan of 1-phenylpentanol-3 prepared from 1.64 g. of the alcohol and 1.2 g. of phenyl isocyanate melted at 85° after two recrystallizations from petroleum ether (80-100°). This melting point is considerably higher than that (74°) reported in the literature[44]. Analysis: Calculated for $C_{18}H_{21}O_2N$: C, 76.29; H, 7.47. Found: C, 76.45, 76.21; H, 7.42, 7.31.

Preparation of 1-Phenyl-2-methylbutanol-1. A Grignard reagent was prepared from 41.1 g. (0.3 mole) of secondary-butyl bromide and 7.3 g. (0.3 mole) of magnesium in 150 ml. of ether. To this solution was added dropwise, a solution of 28 g. (0.26 mole of freshly distilled benzaldehyde in 50 ml. of ether. The complex was decomposed with an aqueous ammonium chloride solution. The ether extract was separated,

washed several times with water and dried over sodium sulfate. The solvent was removed and the product distilled; yield 20 g. (47%), b.p. 110-112° (9 mm.), $n_D^{28}$ 1.5087. This boiling point corresponds with that (120°/13 mm.) reported by Dumesnil[67]. Analysis: Calculated for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.25, 80.22; H, 9.47, 9.79.

No solid phenylurethan could be obtained by reacting 1-phenyl-2-methylbutanol-1 with phenyl isocyanate under various conditions.

Preparation of 3-Phenylpentanol-1. Preparation of this alcohol by catalytic hydrogenolysis of ethyl 3-phenyl-3-hydroxy-n-valerate with copper chromite at 250° was unsuccessful, therefore the following series of reactions was utilized: (a) preparation of ethyl 3-phenyl-3-hydroxy-n-valerate by the reaction between propiophenone, ethyl bromoacetate and zinc, (b) catalytic dehydration of the hydroxy-ester, (c) hydrogenation of the unsaturated ester to ethyl 3-phenyl-n-valerate (d) reduction of ethyl 3-phenyl-n-valerate with sodium and alcohol to 3-pehnylpentanol-1.

(a) preparation of ethyl 3-phenyl-3-hydroxy-n-valerate. Propiophenone was prepared according to a modification of the procedure described by Pampel and Schmidt[68]. The reaction was performed with a larger amount of aluminum chloride than used by these authors and in the absence of carbon disulfide. A solution of 300 g. of propionyl chloride in 350 ml. of dry benzene was slowly added to a well stirred suspension of 430 g. of aluminum chloride in 650 ml. of benzene. The reaction mixture was refluxed for one hour after the acid chloride had been added. After cooling, the reaction mixture was slowly poured into 1.5

liters of ice water. The benzene layer was separated and washed successively with water, dilute sodium carbonate and water. After drying over sodium sulfate, the solvent was removed under reduced pressure and the propiophenone distilled; yield 385 g. (89%), b.p. 91-93° (8 mm.) $n_D^{20}$ 1.5260. The literature value of these constants are 115-120° (21 mm.) $n_D^{20}$ 1.527[69].

The procedure of Stoermer, Grimm and Laage[49] was used to prepare ethyl 3-phenyl-3-hydroxy-n-valerate. Fifty grams of 30 mesh c.p. zinc was washed with 5% hydrobromic acid, alcohol, acetone, ether and dried in a vacuum dessicator; it was used immediately in the reaction. Forty-five grams of the treated zinc was added to a solution of 90 g. of propiophenone in 400 ml. of dry benzene. Twenty grams of ethyl bromoacetate was then added to the well stirred reaction mixture. The reaction was initiated by the addition of a few crystals of iodine and cautious warming. After the reaction had begun it continued spontaneously and an additional 92 g. of ethyl bromoacetate was added dropwise. The reaction mixture was then refluxed for two hours to complete the reaction. After cooling, it was filtered and 7 g. of unreacted zinc was recovered. The benzene filtrate was poured into 400 ml. of ice cold 10% sulfuric acid to decompose the organo-zinc complex. The benzene layer was separated and washed with water and then with a dilute sodium carbonate solution. After drying over sodium sulfate, the solvent was removed and the residue distilled. A forerun of 10 g. of propiophenone boiling at 113-120° (15 mm.) was recovered; further distillation yielded 105 g. (55% based on the zinc consumed) of ethyl 3-phenyl-3-hydroxy-n-valerate boiling at 148.5-149° (14 mm.) and melting at 35-36°. This is in agreement with the physical constants

reported by Steermar et al[49].

(b) dehydration of ethyl 3-phenyl-3-hydroxy-n-valerate. A solution of 111 g. (0.5 mole) of ethyl 3-phenyl-3-hydroxy-n-valerate in 250 ml. of dry xylene, which contained 0.1 g. of iodine, was refluxed. Provision was made for the removal and estimation of the water by using a water entrapment apparatus. At the end of four hours, when the elimination of 9 ml. of water was observed, the water entrapment apparatus was removed and the solution was distilled at atmospheric pressure. There was obtained 90 g. (88%) of the unsaturated ester which distilled at 266-272°.

(c) preparation of ethy 3-phenyl-n-valerate. A solution of 86 g. of the unsaturated ester, the dehydration product of ethyl 3-phenyl-3-hydroxy-n-valerate, in 50 ml. of alcohol was subjected to hydrogenation; room temperature, 3 atmospheres pressure of hydrogen and 3 g. of Raney nickel catalyst were the conditions employed. Within an hour, the calculated amount of hydrogen was absorbed and the reaction arrested itself. The catalyst was removed by filtration and the filtrate was fractionally distilled. There was obtained 71 g. (82%) of ethyl 3-phenyl-n-valerate; b.p. 118-120° (7 mm.), $n_D^{25}$ 1.4890. Levine and Marker[70] report a boiling point of 105° (1 mm.) for this ester which they prepared by another method.

(d) reduction of ethyl 3-phenyl-n-valerate to 3-phenylpentanol-1. The directions described by Levine and Marker[70] were followed. A solution of 71 g. of ethyl 3-phenyl-n-valerate in 350 ml. of absolute alcohol was added dropwise to a vigorously stirred suspension of 100 g. of sodium in 600 ml. of refluxing xylene. The excess sodium

was decomposed by the cautious addition of absolute alcohol. The reaction mixture which was a viscous mass, was cooled in an ice bath and 600 ml. of water was cautiously added to dissolve the sodium alcoholates. The xylene layer was separated, washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude 3-phenylpentanol-1 was purified by distillation. There was obtained 40 g. (70%) of the alcohol with a boiling point of 124-125° (9 mm.), $n_D^{28}$ 1.5140. The boiling point of this alcohol is reported by Marker and Levine to be 116° (1 mm.)[70]. Analysis: Calculated for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 79.81, 79.71; H, 9.67, 9.62.

No solid phenylurethan of this alcohol could be obtained under various conditions with phenyl isocyanate.

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# ABSTRACT

Herman Sanders, Doctor of Philosophy, 1947

B. S. College of City of New York

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Title of Thesis: "Studies in Pyrane Chemistry"

Thesis directed by Dr. G. Forrest Woods

Pages in thesis: 83 Words in abstract: 247

Major: Organic Chemistry

Minors: Physical Chemistry and Inorganic Chemistry

A literature survey has been made of the simple pyrane and dihydropyrane compounds and their chemistry.

The yield of 5-hydroxypentanal obtained by the acid hydrolysis of 2,3-dihydropyrane has been greatly improved by a modification of the original procedure. Catalytic hydrogenation of 5-hydroxypentanal led to 1,5-pentamethylene glycol. Reductive amination of 5-hydroxypentanal yielded 5-aminopentanol-1 which was purified by means of its bisulfate salt. Piperidine was obtained in good yield by treating 5-amino-pentanol-1 bisulfate with hydrobromic acid followed by alkali.

2,3-Dibromotetrahydropyrane was obtained by the bromination of 2,3-dihydropyrane. The alpha bromine atom of this substance was very labile and reacted with alcohols in the presence of ammonia or with alcoholic solutions of sodium alcoholates to yield 2-alkoxy-3-bromotetrahydropyrane. Under these conditions the second bromine atom was inert. Dehydrohalogenation of 2-alkoxy-3-bromotetrahydropyrane with alcoholic potassium hydroxide led to 2-alkoxy-$\Delta^3$-dihydropyrane.

Attempts to obtain 5-hydroxy-$\Delta^2$-pentenal by acid hydrolysis of 2-alkoxy-$\Delta^3$-dihydropyrans were unsuccessful. However, if the hydrolysis reaction mixture were steam distilled, an unsaturated aldehyde, 2,4-pentadienal was obtained. This latter substance was catalytically hydrogenated under mild conditions to n-valeraldehyde and n-amyl alcohol.

2,4-Pentadienal reacted with maleic anhydride to give 3-aldehydo-$\Delta^4$-tetrahydrophthalic anhydride; the reaction of 2,4-pentadienal with 2,3-dimethylbutadiene yielded 4-aldehydo-5-vinyl-1,2-dimethyl-$\Delta^1$-cyclohexene. Thus 2,4-pentadienal can function as a diene or a dienophile in the Diels-Alder reaction.

Phenylmagnesium bromide reacted with 2,4-pentadienal in a 1,2-addition mechanism to yield 1-phenyl-2,4-pentadien-1-ol. This latter substance immediately rearranged to 5-phenyl-2,4-pentadien-1-ol which was converted by catalytic hydrogenation to 5-phenylpentanol-1.

When exposed to air, 5-phenyl-2,4-pentadien-1-ol decomposed to cinnamaldehyde. The nature of this reaction has not been elucidated.

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