CHAPTER IV

RESULTS AND DISCUSSION

In this research, [2-(1-propylbutyl)-1,3-dioxolan-4-yl]methyl sulfamate was synthesized. Firstly 2-propylpentanal was prepared from 2 different synthetic methods. These were:(a) the reaction of triethyl orthoformate with the corresponding Grignard reagent, and (b) the reaction of ethyl ethoxyacetate with the corresponding Grignard reagent. The latter was preferable since it gave much higher yield and proceeded more smoothly than the former. Secondly, [2-(1-propylbutyl)-1,3-dioxolan-4-yl]methanol was synthesized from the condensation of glycerol with 2-propylpentanal in the presence of p-toluenesulfonic acid monohydrate as the catalyst. Finally, [2-(1-propylbutyl)-1,3-dioxolan-4-yl]methyl sulfamate was obtained from the reaction of sodium alkoxide of [2-(1-propylbutyl)-1,3-dioxolan-4-yl]methanol and sulfamoyl chloride whice was generated *in situ* from the reaction of formic acid and chlorosulfonyl isocyanate. Since both sodium alkoxide of [2-(1-propylbutyl)-1,3-dioxolan-4-yl]methanol and sulfamoyl chloride were highly reactive, they reacted immediately.

Ethyl formate

This compound represents ester type. The mixture of formic acid and absolute ethanol was refluxed for several hours. (Figure 55-A)

This reacton is a reversible process and proceeds very slowly. In general, when equimolcular quantities of the acid and alcohol are employed, only about two-thirds of the theoretically possible yield of ester is obtained. According to the law of mass action,the equilibrium may be displaced in favour of the ester by the use of an excess of one of the components. It was frequently convenient to use an excess of the acid. Like in this case, an excess of formic acid was used. Since formic acid is a comparatively strong acid the formation of its esters does not require the use of added mineral acids such as sulfuric acid to catalyse the reaction. Sulfuric acid in any case should not be added for it causes the decomposition of formic acid to carbon monoxide.

The acid-catalysed esterification reaction usually proceeds via an acyl oxygen fission process. This involves the cleavage of the bond between the original carbonyl-carbon atom and an oxygen of an hydroxyl group in the intermediate arising from nucleophilic attack by an alcohol molecule on the protonated carboxylic acid group

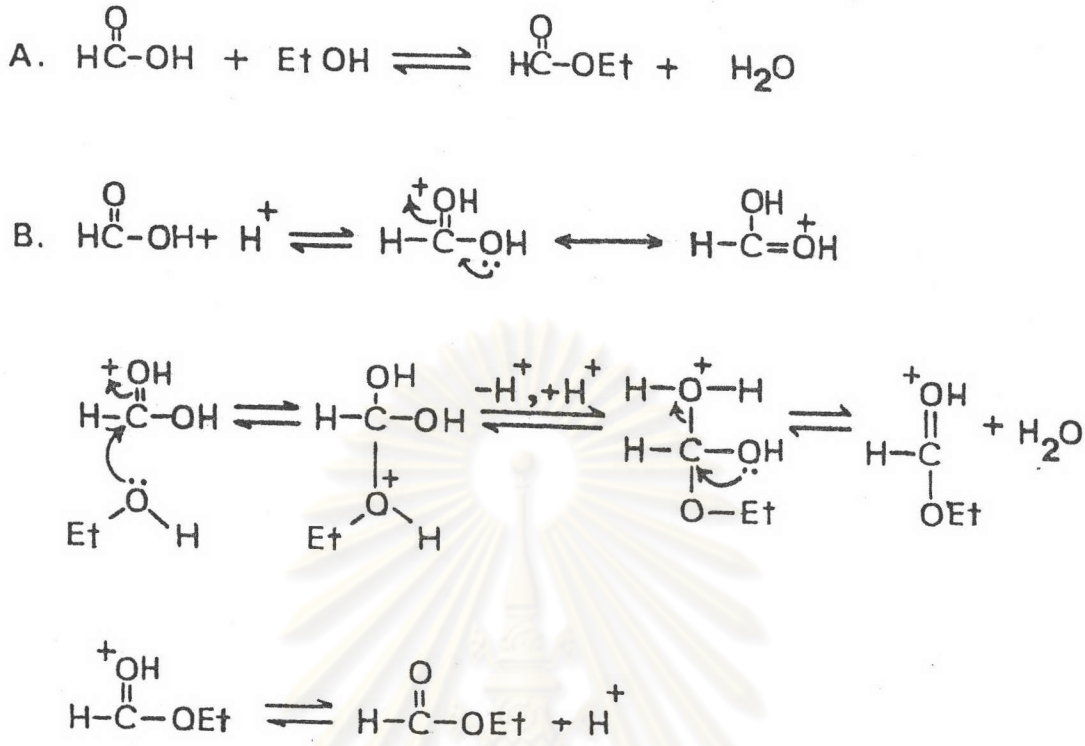


Figure 55. The mechanism of the formation of ethyl formate

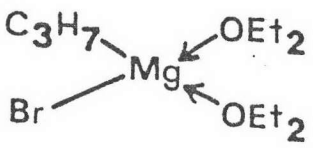
as shown in Figure 55-B (Furniss et al., 1991).

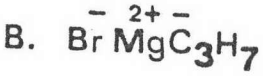
This compound was purified by fractionating distillation. Its boiling point was about 52-54°C. (lit. 53°C, Furniss et al., 1991).

4-Heptanol

This compound repesents secondary alcohol. To obtain 4-heptanol , 2 moles of Grignard reagent, propylmagnesium bromide reacted with 1 mole of ethyl formate. The solution of propylmagnesium bromide was easily obtained since propyl bromide is a reactive organic halide. Great care should be taken to assure complete dryness of solvent used (diethyl ether), magnesium turnings and apparatus to exclude moisture which reacts with Grignard reagent. The resulting alkylmagnesium halide is soluble in the ether solvent as a result of coordinate of two ether molecules onto the magnesium and may be represented as shown in Figure 56-A.

The true structural nature of the reactive species in solution is uncertain and for convenience the reagent may be represented as a polarized species as shown in Figure 56-B.

A. $C_3H_7Br + Mg \xrightarrow{Et_2O}$ 

B. 

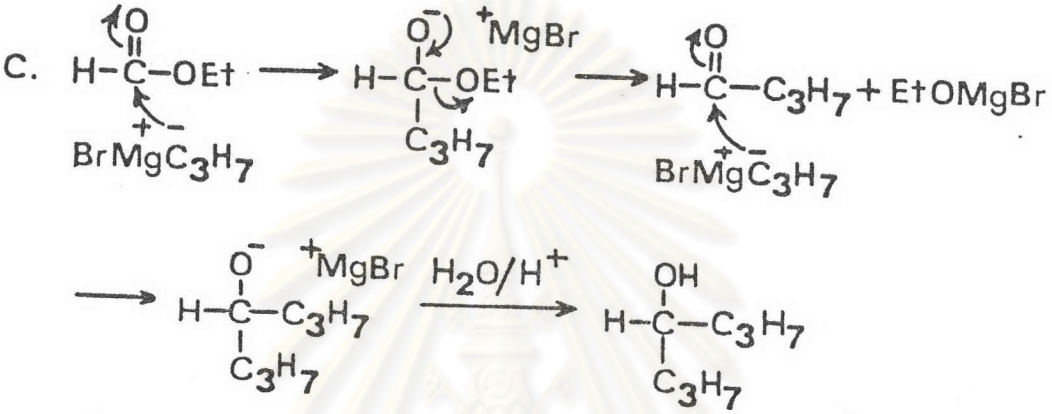
C. 

Figure 56. A. The formation of propylmagnesium bromide

B. The structure representing Grignard reagent, propylmagnesium bromide

C. The mechanism of the formation of 4-heptanol

The reaction of propylmagnesium bromide with ethyl formate followed a three-step mechanisms, namely nucleophilic addition, then β-elimination and then nucleophilic addition again. Since the product of addition elimination path was more reactive than the original substrate (ethyl formate), the second attack by propylmagnesium bromide underwent. The overall pathway may be represented as shown in Figure 56-C (Furniss et al., 1991; Scudder, 1992).

To the resulting reaction mixture, water was then added slowly to protonate the magnesium salt and followed by sufficient aqueous acid such as hydrochloric or sulfuric acid to dissolve all inorgnic salts.

This compound was purified by simple distillation. Its boiling point was about 153-155°C. (lit 156°C, Furniss et al., 1991).

The IR spectrum of 4-heptanol was compared with that of the reference compound. Its spectrum (Figure 19) showed the strong and broad band of O-H stretch vibration between 3600-3100 cm^{-1}. The broadness was due to hydrogen-bonding. The C-H stretch band appeared between 3000-2840 cm^{-1}. The C-H bending bands were between 1480-1350 cm^{-1}. The C-O stretch bands appeared between 1160-980 cm^{-1}. The broadness in this region was characteristic of secondary

alcohol.

4-Chlorotheptane

This compound represents secondary alkyl halide. To obtain 4-chloroheptane, 4-heptanol was heated with the solution of anhydrous zinc chloride in concentrated hydrochloric acid. Since chloride ion is a weak nucleophile, it will not react readily with secondary alcohol. Lewis acids such as zinc chloride must be added to the reaction mixture. Zinc chloride forms complex with alcohol through the association with unshared electrons of oxygen.

The reaction proceeded through S_n1 mechanism as shown in Figure 57-A (March, 1968 ; Solomons, 1992).

This compound was purified by simple distillation. Its boiling point was about 148-150°C. (lit 144°C/758 mmHg; Weast, 1986).

The IR spectrum of 4-chloroheptane (Figure 20) showed the strong C-H stretch band at 3000-2800 cm^{-1} and medium C-H bending bands at 1480-1360 cm^{-1}. The medium bands at 780-590 cm^{-1} represented C-Cl stretch vibration. The profusion of absorptions in the region between 1300-800 cm^{-1} was characteristic of alkyl chloride.

Ethyl chloroacetate

This compound represents ester type like ethyl formate. However in this case, concentrated sulfuric acid was used as the catalyst and an excess of absolute ethanol was used instead of chloroacetic acid.

After the reaction mixture was refluxed for some hours, an azeotropic mixture of water formed and ethanol was distilled. The removal of water formed from the reaction caused the reaction equilibrium to be displaced in favour of the ester. The mechanism of the reaction was the same as in the formation of ethyl formate which was previously described.

This compound was purified by simple distillation. Its boiling point was 144.5°C (lit. 144.2°C; Weast, 1986).

The IR spectrum of ethyl chloroacetate showed a very strong C=O stretch band at 1757 cm^{-1}. It was accompanied by the stretch bands of the carbon-oxygen single band (C(=O)-O-R) between 1313-1028 cm^{-1}. In this region the chloroacetate carbonyl-oxygen stretch vibration appeared at 1313-1098 cm^{-1} and the carbon-oxygen stretch band of the ethyl was at 1028 cm^{-1}. The C-Cl stretch bands were at 782-699 cm^{-1}.

Ethyl ethoxyacetate

This compound represents ether type. Ethyl ethoxyacetate was obtained from the reaction of sodium ethoxide and ethyl chloroacetate. This reaction was known as Williamson reaction. The reaction took place immediately and was reconized by the formation of white precipitate of sodium chloride which was one the reaction's products. The reaction involved the direct nuclophilic displacement of chloride in ethyl chloroacetate by sodium ethoxide as shown in Figure 57-B (Furniss et al., 1991).

This compound was purified by simple distillation. Its boiling point was about 156-157°C.(lit 158°C;Prager and Jacobson, 1921).

The IR-spectrum of ethyl ethoxyacetate showed very strong C=O stretch band at 1756 cm^{-1}. The carbonyl-oxygen stretch vibration appeared between 1277-1205 cm^{-1} and the carbon-oxygen stretch band of the ethyl ester was at 1034 cm^{-1}. The carbon-oxygen stretch band of the ethyl ether was at 1138 cm^{-1}.

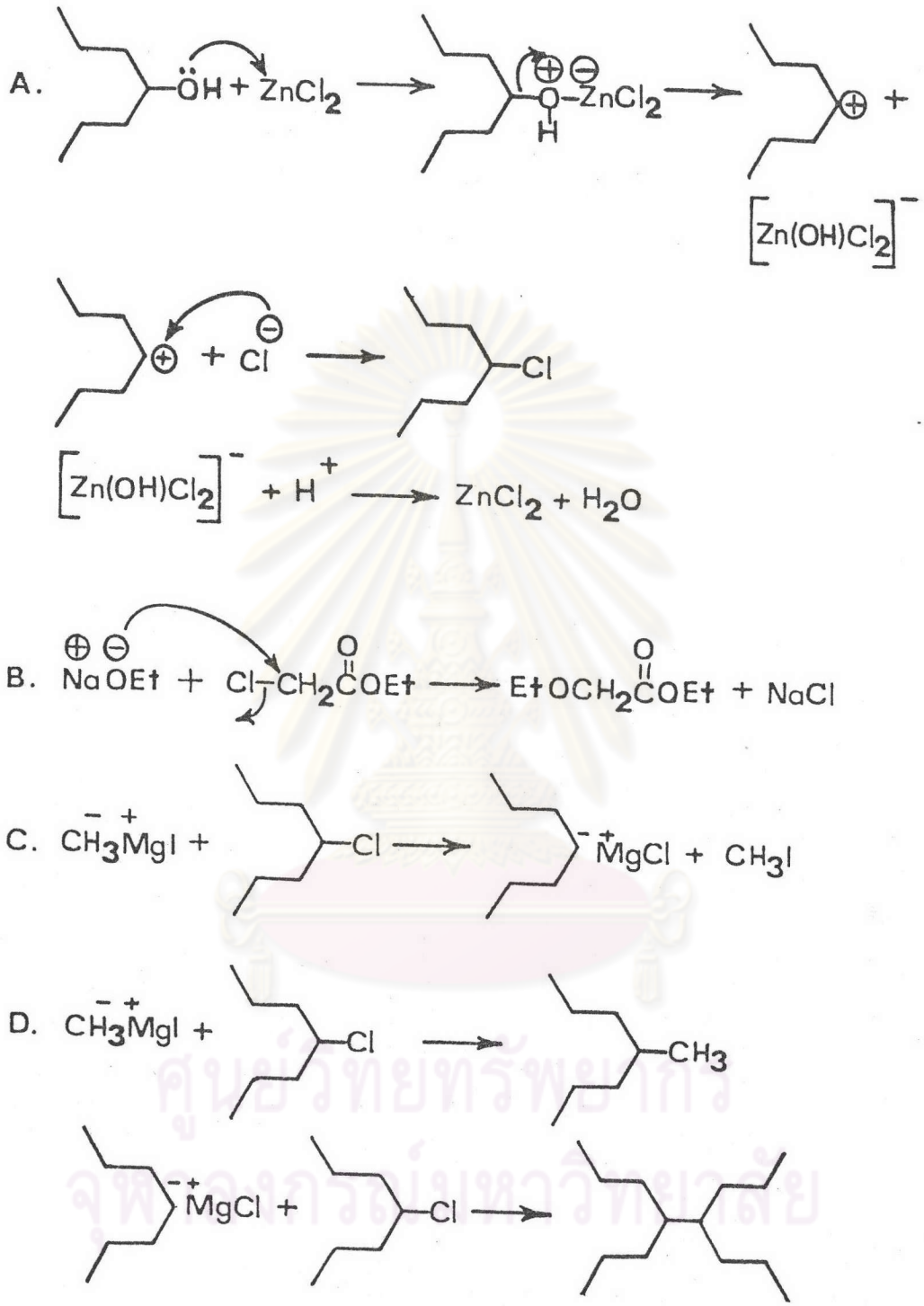


Figure 57. A. The mechanism of the formation of 4-chloroheptane

B. The mechanism of the formation of ethyl ethoxyacetate

C. The formation of 4-heptylmagnesium chloride

D. The Wurtz-Type reactions

2-Propylpentanal.

This compound represents aliphatic aldehyde. To obtain 2-propylpentanal, the 2 different methods were applied.

Firstly, it was prepared from the reaction of 4-heptylmagnesium chloride with triethyl orthoformate. It was not straightforward to generate 4-heptylmagnesium chloride since 4-chloroheptane was quite an inert halide. Stirring alone was ineffective. In this case entrainment procedure was applied to initiate the reaction. Entrainment agents used were methyl iodide and crystal of iodine. Both methyl iodide and iodine reacted so readily with magnesium that they were usually able to penetrate the oxide film and activate the magnesium. Thus inert halide could react with the active surface of magnesium. Furthermore, methyl iodide used possibly function by an exchange reaction as shown in Figure 57-C (Kirk and Othmer, 1951; Fieser and Fieser, 1967).

Moreover ,to promote the reaction, the reactive solvent, tetrahydrofuran was used instead of diethyl ether since it was a more powerful coordination solvent than diethyl ether (Pearson, Cowan and Beckler, 1959).

The chief disadvantage of the entrainment agents was that the presence of iodides tended to promote the coupling of Grignard reagent with alkyl halide (The Wurtz-type reaction) as may be shown in Figure 57-D(March, 1968).

The evidence of these side reactions was confirmed by the IR-spectrum of the product residue which was obtained after 2-propylpentanal was isolated. The spectrum showed the characteristics of aliphatic hydrocarbon.

The reaction mixture of the resulting Grignard reagent and triethyl orthoformate required to be refluxed for at least five hours. Even that such a long period of refluxing, there was no immediate evidence of a reaction. It must have been followed by cautious removal of the ether on the steam bath because during this process a point was reached at which a vigorous reaction set in (Smith and Nichols, 1941).

This reaction proceeded through the nucleophilic substitution mechanism. The Grignard reagent acted as the nucleophile which attacked triethyl orthoformate and resulted in the leaving of one of its three ethoxy groups as illustrated in Figure 58-A (Furniss et al., 1991) Scudder, 1992).

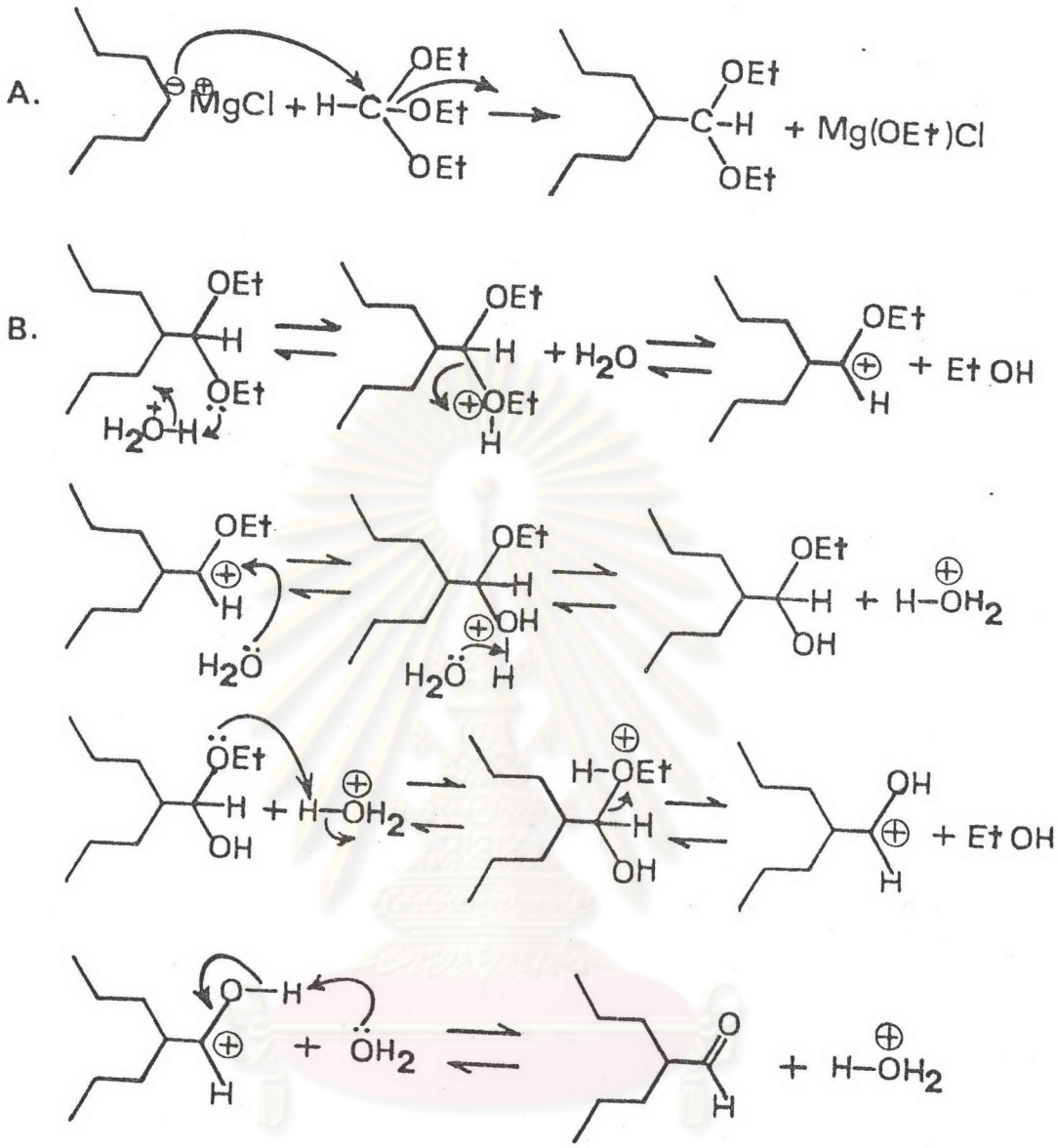


Figure 58. The mechanism of the formation of 2-propylpentanal from the reaction of 4-heptylmagnesium chloride and triethyl orthoformate

In acidic water, the acetal product was hydrolized to 2-propylpentanal. The acetal hydrolysis overview was shown in Figure 58-B (Scudder, 1992).

However, this method of aldehyde synthesis was not appreciable since it gave a very poor yield of the desired product. The incompleteness of the Grignard reagent formation due to the inertia of 4-chloroheptane and the presence of the Wurtz-type reaction as the undesired side reaction were proposed to be responsible for the unsatisfying result.

Furthermore, since tetrahydrofuran complexed with the Grignard reagent very effectively it reacted with triethyl orthoformate slowly. This may also possibly be responsible for low yield of the product (Pearson, Dorotha and Beckler, 1959).

Secondly, 2-propylpentanal was prepared from the reaction of 2 moles of propylmagnesium bromide and 1 mole of ethyl ethoxyacetate. This reaction was quite straightforward since propylmagnesium bromide was a strong nucleophile. The reaction mechanism was similar to that of 4-heptanol formation which was previously mentioned. It proceeded through a 3-step mechanism: (a). nucleophilic addition, (b). β-elimination and (c). nucleophilic addition respectively.

The first mole of propylmagnesium bromide attacked ethyl ethoxyacetate by the way of nucleophilic addition and the elimination of ethoxy anion followed, resulted in the addition-elimination product which was more reactive than ethyl ethoxyacetate. Thus it was then attacked by the second mole of propylmagnesium bromide by the way of nucleophilic addition again as illustrated in Figure 59-A (Furniss et al., 1992).

To the resulting reaction mixture, water was then added slowly to protonate the magnesium salt and followed by sufficient aqueous acid such as hydrochloric or sulfuric acid to dissolve all inorganic salts. The crude product of 1,1-dipropyl-2-ethoxyethanol was not further purified since the reaction was quite complete. The IR-spectrum (Figure 23) of the crude product showed absorptions corresponding to its chemical structure. The O-H stretch band was between 3600-3300 cm^{-1}. The C-H stretch bands appeared between 3000-2800 cm^{-1} and were accompanied by C-H bending bands which appeared at 1462-1380 cm^{-1}. The bands between 1200-878 cm^{-1} corresponded for the C-O stretch vibrations of both alcohol and ether.

1,1-Dipropyl-2-ethoxyethanol was then transformed to 2-propylpentanal by being heated in the presence of anhydrous oxalic acid. The transformation proceeded through 2 phases. Firstly , one molecule of water was

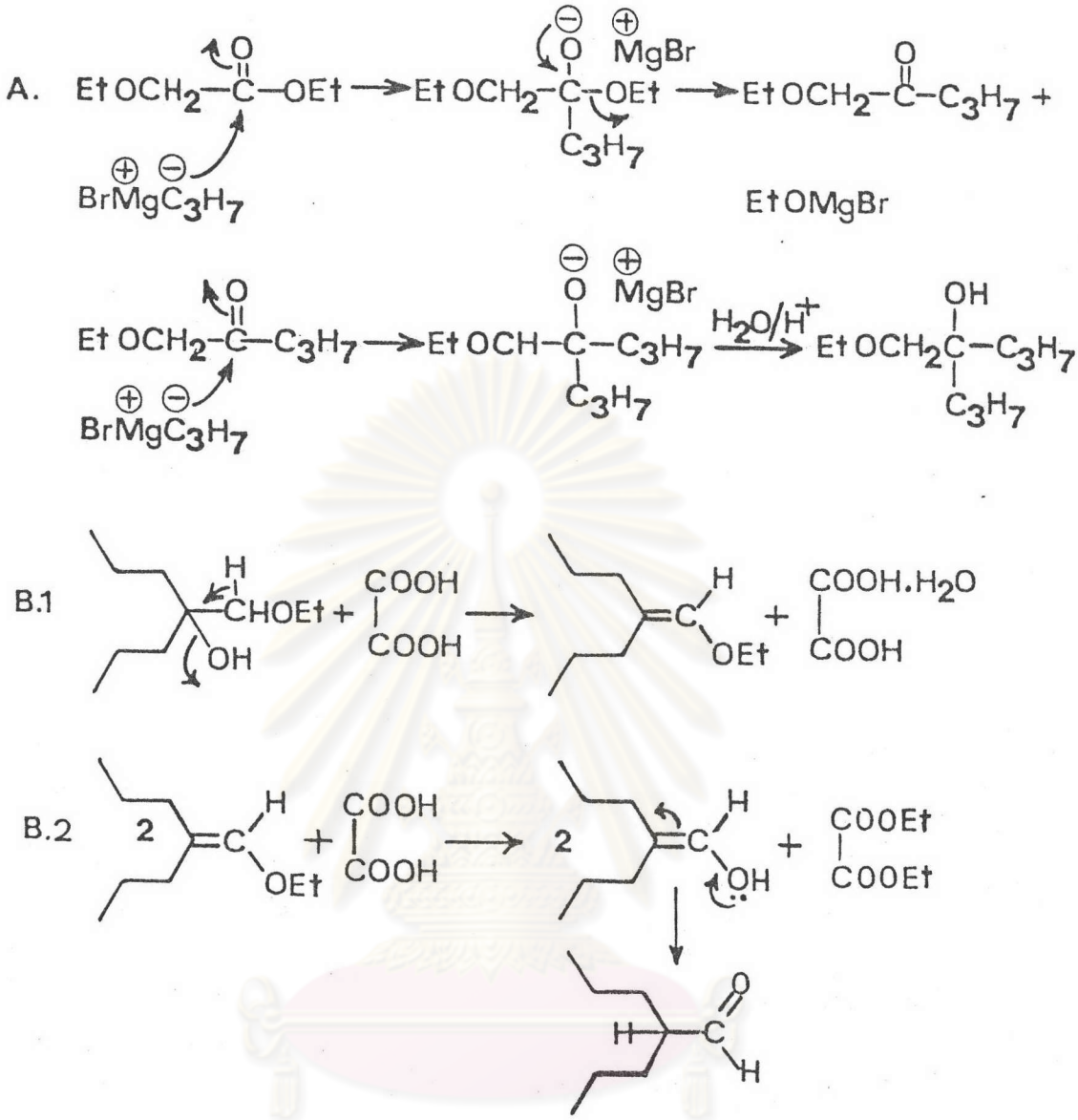


Figure 59. The mechanism of the formation of 2-propylpentanal from the reaction of propylmagnesium bromide and ethyl ethoxyacetate

eliminated from 1,1-dipropyl-2-ethoxyethanol and was then absorbed by anhydrous oxalic acid which acted as a dehydrating agent as illustrated in Figure 59-(B.1). Secondly, oxalic acid acted as a saponifying agent which resulted in the desired aldehyde and diethyl oxalate as illustrated in Figure 59-(B.2) (Behal and Sommelet, 1904).

2-Propylpentanal was isolated by steam distillation.

The IR-spectrum of 2-propylpentanal (Figure 24) showed the two characteristic carbon-aldehydic hydrogen stretch bands at 2810 and 2696 cm^{-1}. The former almost superimposed on the alkyl C-H stretch bands. Only the shoulder appearance was observed. The strong C=O stretch band of aldehyde was at 1728 cm^{-1}. The C-H bending bands appeared between 1463-1305 cm^{-1}. The bands between 1183-1071 cm^{-1} represented C-O stretch vibration.

The ^{1}H-NMR spectrum of 2-propylpentanal in $CDCL_3$ (Figure 25) showed the peak at 0.8-0.9 ppm. (triplet, 6H) for 2 methyl groups of alkyl chain, the peak at 1.15-1.65 ppm. (complex, 8H) for 2 ethylene groups of alkyl chain. The broad peak at 2.10-2.25 ppm (multiplet, 1H) represented methine proton. The methine proton resonated at lower field than other protons of alkyl chain since it was adjacent to aldehydic carbonyl group. The aldehydic proton resonated at 9.48-9.50 ppm. The doublet appearance

was caused by the coupling with adjacent methine proton. The observed coupling constant of aldehydic proton signal was 3.1 Hz. which was in the normal range (0-3 Hz.) for aliphatic aldehydes (Fresenius et al.,1989).

[2-(1-Propylbutyl)-1,3-dioxolan-4-yl]methanol

This compound represents cyclic acetal. It was prepared from the condensation of glycerol and 2-propylpentanal in the presence of p-toluenesulfonic acid monohydrate as catalyst as illustrated in Figure 60-A.

Since this reaction was reversible, the removal of water formed from the reaction was found necessary to improve the yield of acetal. It could be effectively achieved by azeotropic distillation.

The reaction mechanism involved initial formation of hemiacetal. Hemiacetal reacted rapidly by the unimolecular nucleophilic substitution (S_n1) mechanism to give acetal as shown in Figure 60-B (March, 1968; Scudder, 1992).

Since glycerol contained 3 hydroxyl groups, its condensation with 2-propylpentanal gave not only five-membered cyclic acetal (2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane) but also six-membered cyclic acetal (2-(1

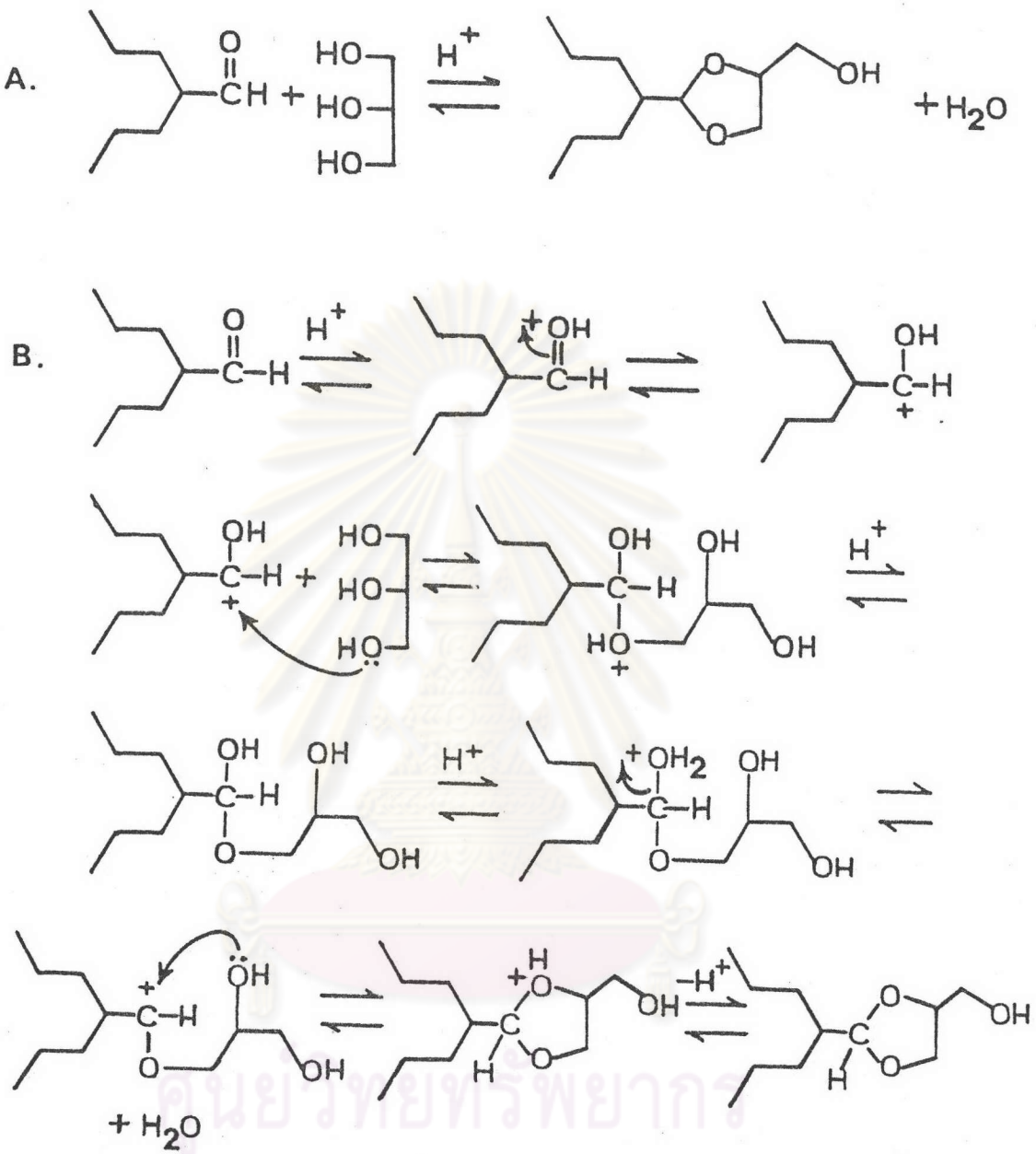


Figure 60. The mechanism of the formation of 2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane

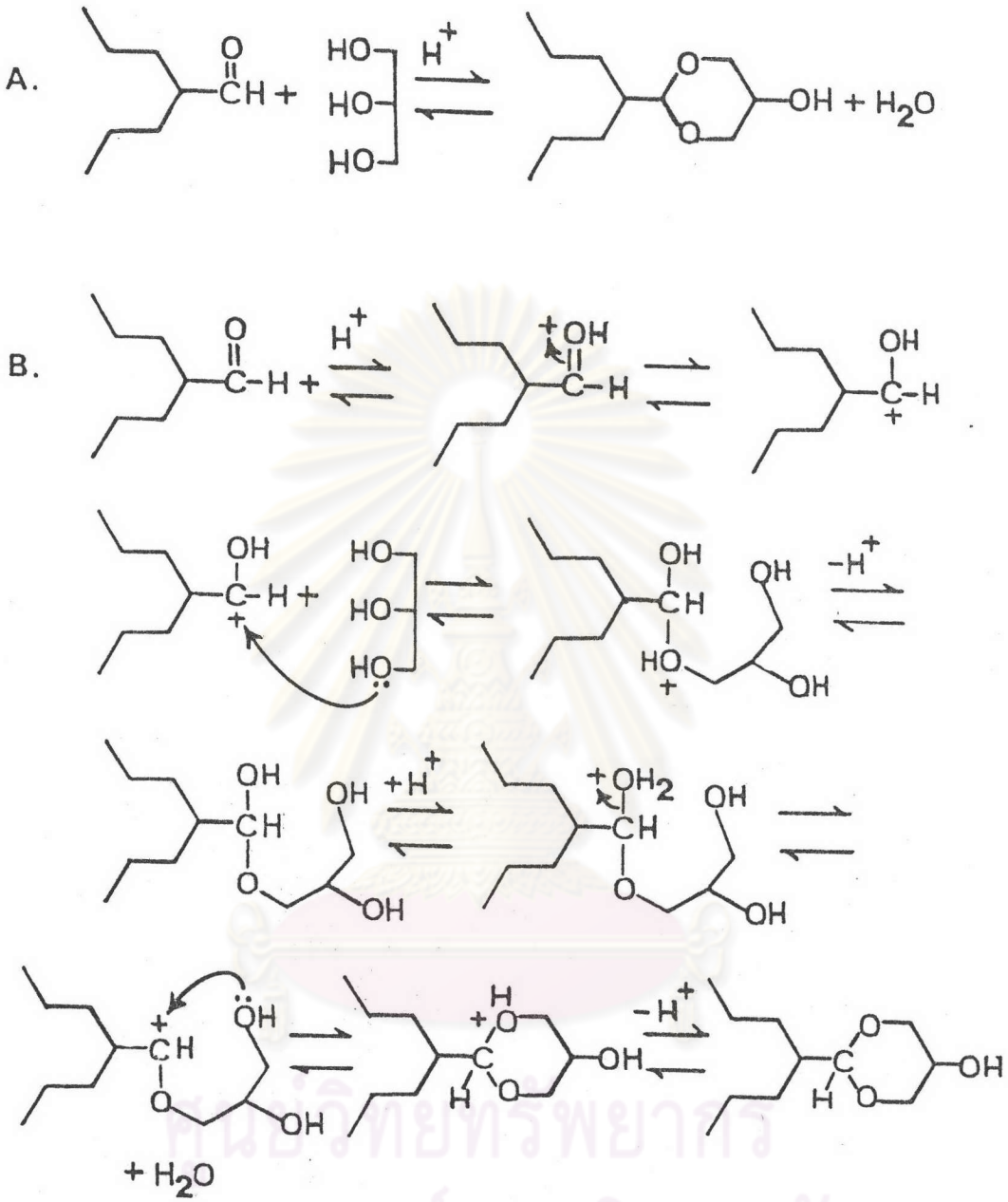


Figure 61. The mechanism of the formation of 2-(1-propylbutyl)-5-hydroxy-1,3-dioxane

-propylbutyl)-5-hydroxy-1,3-dioxane) as shown in Figure 61 (Boekelheide et al., 1949; showler and Darley, 1967).

Formation of the five-membered cyclic acetal is faster than that of six-membered cyclic acetal because the five-membered ring is easier to close,even though the five-membered ring is less stable than the six-membered ring. The formation of cyclic acetal is reversible, and if the reaction is allowed to continue for a long period, equilibrium of all three sets of species will be established as shown in Figure 62 (Eliel, 1962).

It has been investigated that the five-membered cyclic acetal was definitely favoured over six-membered derivative. However the ratio was a variable one since it depended on experimental conditions such as temperature, concentration of acid, etc (Hibbert and Carter, 1928; Hill, Hill and Hibbert , 1928). Furthermore , it had been investigated that, at the equilibrium of the acid-catalyzed glycerol-aldehyde reaction the proportion of five-membered cyclic acetal always exceeded that of six-membered analogues providing that the reaction mixture remained liquid (Brimacombe et al., 1960).

Since 2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane and 2-(1-propylbutyl)-5-hydroxy-1,3-dioxane were cyclic compounds and there were 2 carbons on the ring,

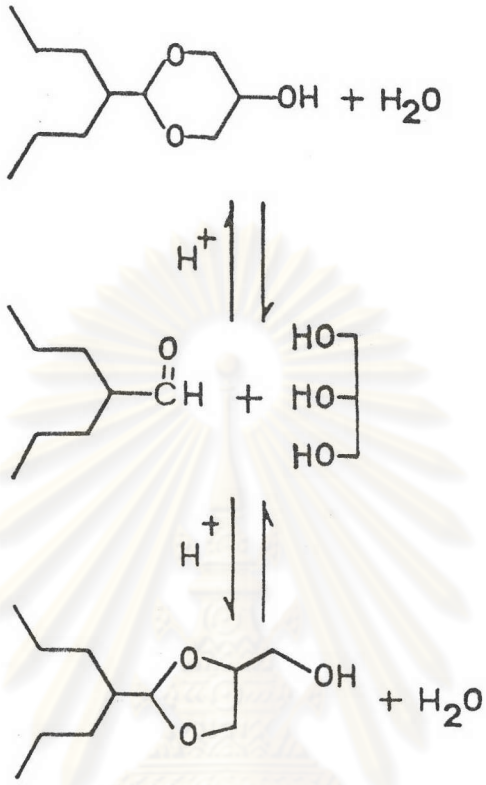


Figure 62. The condensation of glycerol with 2-propylpentanal

each of which was substituted by 2 different groups, geometrical isomerism existed. This meaned that there were 2 geometrical isomers, namely *cis*-and *trans*-isomers for each of the cyclic acetals.

The conformation of 2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane may be puckered. However, the degree of puckering was so slight since there had been an investigation indicated that 1,3-dioxolane ring was almost planar (Bakker et al., 1959; Showler and Darley, 1967).

Until recently, it had been considered that "envelope" and "half-chair" forms (Figure 63-A) were adequate models for a description of the conformation of a given five-membered ring system since these two forms were postutated as the most stable forms in much of the pioneering work on five-membered ring (cyclopentane and its derivatives).

In cyclopentane, there is little if any energy difference between the envelope and half-chair so that molecule is in a rapid state of conformational flux through what is known as "pseudorotation". In case of 1,3-dioxolane ring, since there is internal substitution of the five-membered ring with heteroatom, oxygen atom, it seems to introduce smaller energy barriers for the ring to undergo pseudorotation. So the five-membered ring found

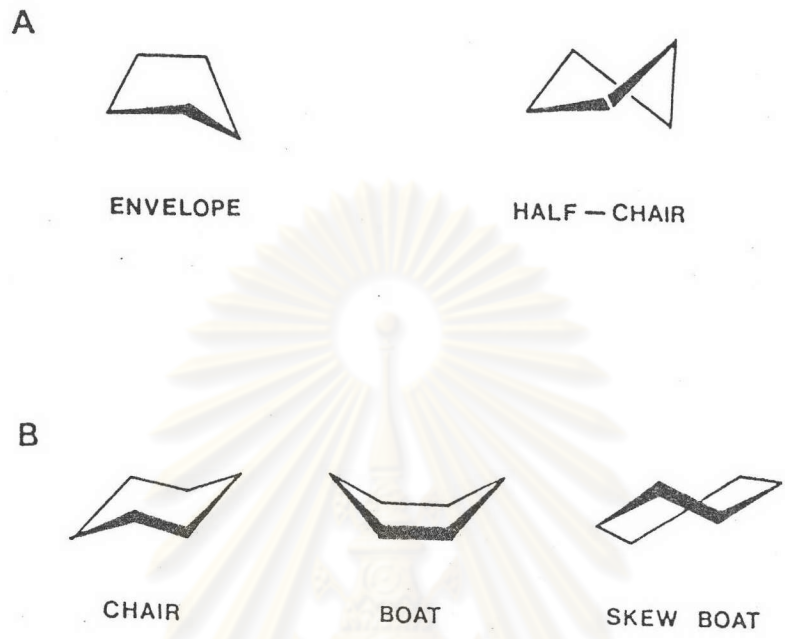


Figure 63. A. The conformations of five-membered ring
B. The conformations of six-membered ring

in 1,3-dioxolane is highly flexible and whose conformation adjusts itself easily to the steric requirements of the substituents (Willey, Binsch, and Eliel, 1970).

It has been confirmed that 1,3-dioxolane rings undergo pseudorotation with favoured (pseudo) equatorial substitution. The different possible conformation of 1,3-dioxolane is shown in Figure 64 (Aldereweireldt and Anteunis, 1965).

Furthermore, it has been confirmed that in both *cis*-and *trans*-isomers of 2-substituted-4-hydroxymethyl-1,3-dioxolane, hydrogen bonding occurs either with oxygen-1 to give a six-membered ring or with oxygen-3 to give a five-membered one. However the bonding is not complete (Brimacombe, Foster and Haines, 1960; Showler and Darley, 1967).

The comformation of *cis*-and *trans*-isomers of 2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane may be illustrated as in Figure 65. The dotted lines in the figure represent the proposed hydrogen bonding.

In all 1,3-dioxolanes , *cis*-isomers are thermodynamically favoured over the corresponding *trans*-isomers. So at the equilibrium *cis*-isomers are more abundant. This has been explained on the basis of an

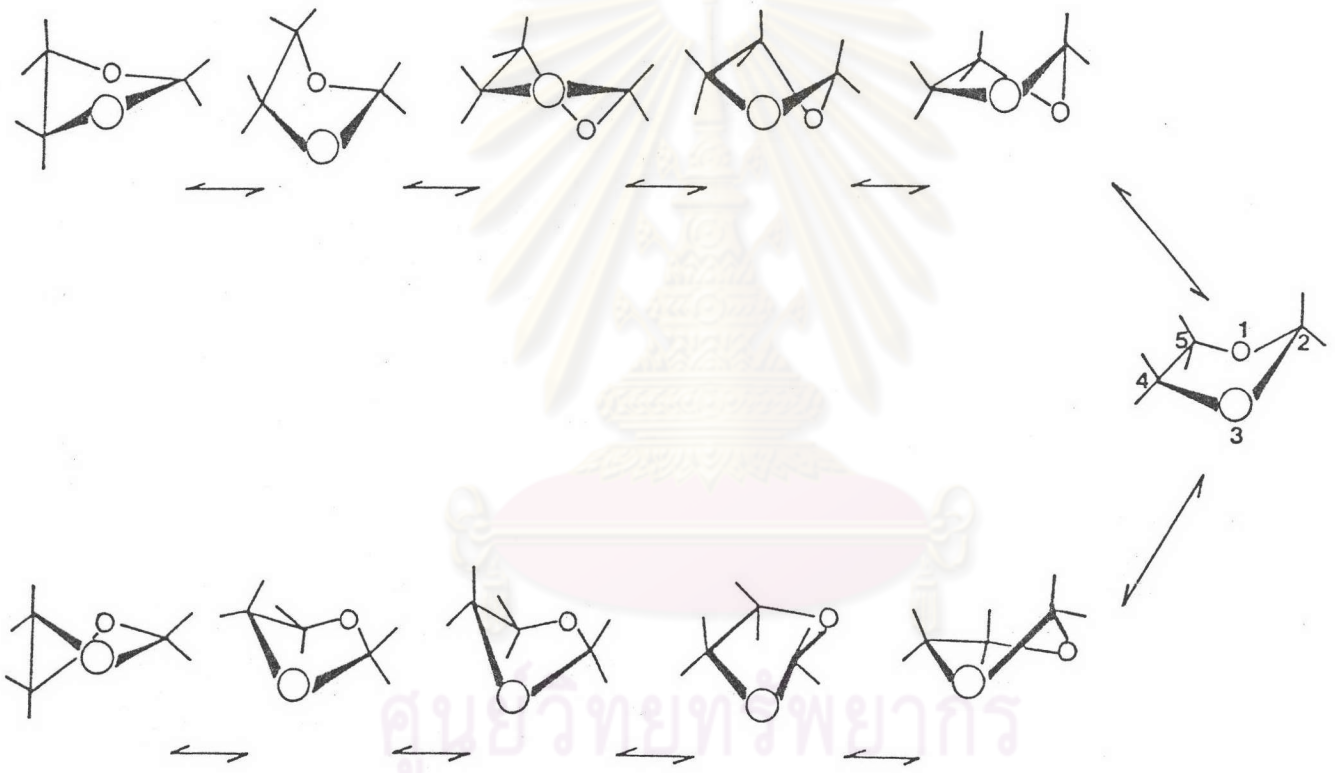


Figure 64. The pseudo rotation showing different possible conformation of 1,3-dioxolane

unfavourable steric interaction of pseudoaxial substituent at C-2 with a pseudoaxial hydrogen at C-4 (envelope-conformation) in *trans*-isomer, so it would rather suggest that in the predominant conformation the substituent at C-4 is pseudoaxial and that at C-2 pseudoequatorial so that the salient interaction is between the C-4 subsituent and H-2 (Boekelheide et al., 1949; Eliel and Willey, 1969; Showler and Darley, 1967; Rommelaere and Anteunis, 1970; Willey et al., 1970).

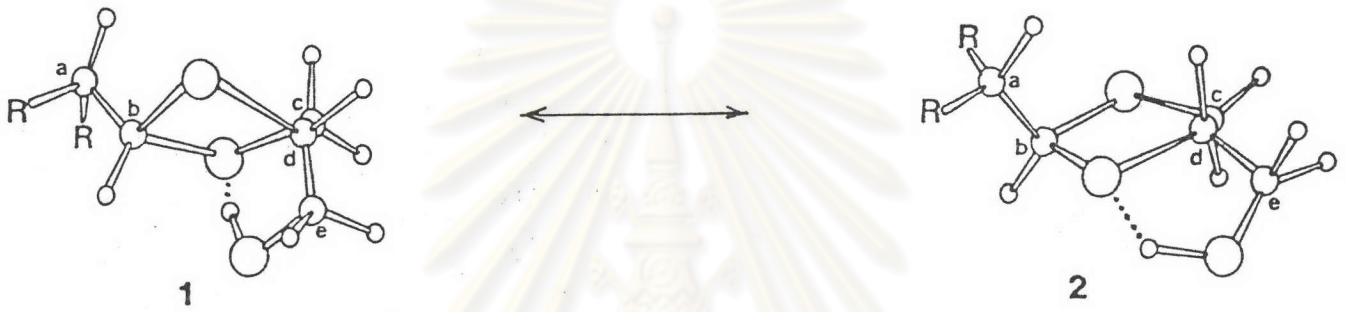
So in Figure 65, conformation A-1 would represent the more stable conformation for *trans*-isomer, and conformation B-2 would represent the more stable conformation for *cis*-isomer which both substituents at C-2 and C-4 were pseudequatorial.

The conformation of 2-(1-propylbutyl)-5-hydroxy-1,3-dioxane may also be puckered.

There are three possible conformations in six-membered ring, namely chair, boat and skew-boat as shown in Figure 63-B.

For cyclohexane, the chair form is the most stable. Thus, at room temperature, cyclohexane is predominantly in the chair form. Similarly, the 1,3-dioxolane ring exists in a chair conformation which is substantially more stable

A. TRANS



B. CIS

(R= C_3H_7 : ◯ = OXYGEN : ○ = CARBON : ○ = HYDROGEN)

Figure 65. The proposed conformations of 2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane of (A) trans-, and (B)cis-forms

than any of the boat forms. (Riddell, 1970; Eliel and Banks, 1972).

2-(1-propylbutyl)-5-hydroxy-1,3-dioxane also existed in both *cis*-and *trans*-forms as found in 2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane.

In case of *cis*-isomer of 2-substituted-5-hydroxy-1,3-dioxane, it has been investigated that the preferred conformation contains the substituent at C-2 in the sterically favourable equatorial position, while the hydroxyl group is in the axial position which permits efficient intramolecular bifurcated hydrogen bonding with the ring oxygens. Such intramolecular hydrogen bonding may exert a significant stabilizing effect and cause the molecule to exist almost exclusively in this conformation. (Brimacombe, Foster, and Stacey, 1958; Brimacombe et al., 1960; Dobinson and Foster, 1961; Baggett et al., 1963; Carey and Sundberg, 1977).

The conformation of *cis*-2-(1-propylbutyl)-5-hydroxy-1,3-dioxane may be illustrated as in Figure 66-B and conformation B-1 was proposed to be favouring.

For *trans*-isomer of 2-substituted-5-hydroxy-1,3-dioxane it has been investigated that the equilibrium mixture contains the molecule which exists in both

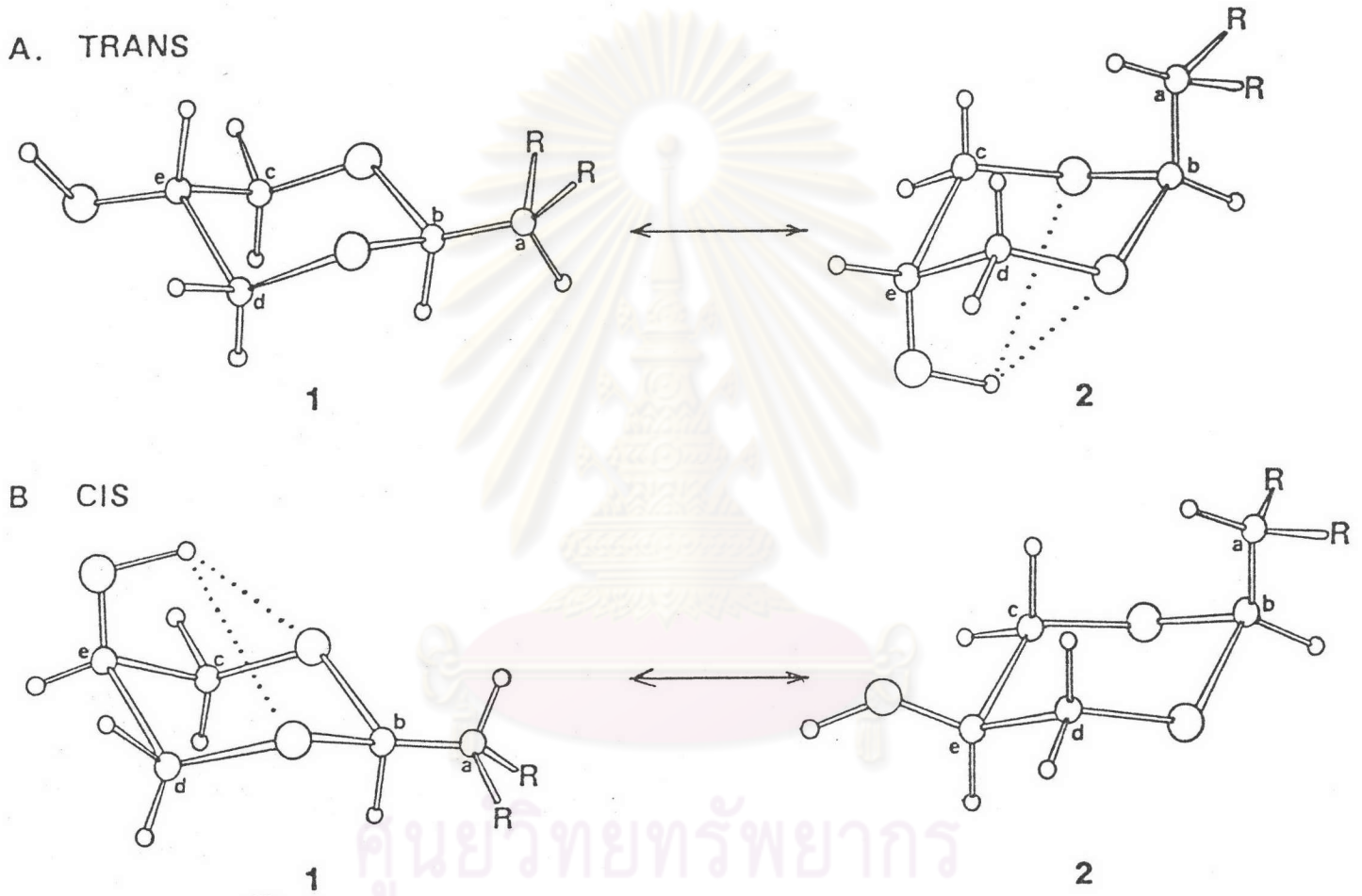


Figure 66. The proposed conformations of 2-(1-propylbutyl)-5-hydroxy-1,3-dioxane of (A) trans-, and (B)cis-forms

conformations with both substituents at C-2 and C-5 either in the equatorial or axial position. The conformation with both substituents in the sterically favourable equatorial position which hydroxyl group is not bonded is predominate while the other conformation is minor since the substituent at C-2 is in the sterically unfavourable axial position even though it has been indicated that the hydroxyl group at C-5 bonds with the ring oxygens. This result reflects that the intramolecular hydrogen bond is not complete (Brimacombe et al., 1958 ; Brimacombe et al., 1960; Dobinson and Foster, 1961; Riddell, 1967; Showler and Darley, 1967).

The conformations of *trans*-2-(1-propylbutyl)-5-hydroxy-1,3-dioxane may be presented in Figure 66-A. The diequatorial conformation (A-1) was proposed to be predominant.

Furthermore, since both C-2 and C-4 of 2-substituted -4-hydroxymethyl-1,3-dioxolane were asymmetric, both *cis*-and *trans*-isomers possessed 2 optical isomers, namely(+) and (-) forms; ie. there were altogether four stereoisomers, two *cis*-and two *trans*-isomers. While there were no optical isomers existing in 2-(1-propylbutyl)-5-hydroxy-1,3-dioxane since both *cis*-and *trans*-forms had a plane of symmetry in their molecules (Hibbert and Carter, 1928; Showler and Darley, 1967).

The product from the condensation of glycerol and 2-propylpentanal was purified by column chromatographic technique., The mobile phase used was the solution of hexane and ethyl acetate in the ratio of 2.3:1 respectively and the stationary phase was silica gel. However this purification process was not able to separate any of the proposed isomers since they were all expected to have the very close physical property. The purified mixture product was shown to be almost chromatographically homogeneous on silica gel-plate. The fractionating vacuum distillation was applied in the attempt to separate the isomers. However it was also not successful since the rise in temperature during distillation was very gradual. The observed range of temperature the product passed over was about 81-101°C at 0.75 mmHg.

In conclusion the condensation of glycerol and 2-propylpentanal was proposed to give two structural isomers namely five-and six-membered cyclic acetals, each existed in two geometrical isomers, namely *cis*-and *trans*-isomers. Only *cis*-and *trans*-isomers of five-membered cyclic acetal existed in two optical isomers, namely (+) and (-)-forms.

So all the spectroscopic data of the product should have shown the characteristics of all the proposed isomers.

The IR-spectrum of the product (Figure 26) showed the strong and broad O-H stretch band between 3650-3200 cm^{-1}. The strong C-H stretch bands of alkyl chain appeared between 3000-2800 cm^{-1}. The bands at 1480-1380 cm^{-1} characterized the C-H bendings of alkyl chain. The band at 1200-900 cm^{-1} characterized the stretch vibration of acetal. The band in this region displaying at least 2 maxima was the characteristic of acetal. The stretch band of C-O of alcohol was superimposed in that of acetal.

In this study, NMR spectroscopic techniques were applied to confirm that the product obtained from the condensation of glycerol and 2-propylpentanal was the mixture of structural isomers namely five-and six-membered cyclic acetals, each existed in both *cis*- and *trans*-form.

The NMR-spectroscopic experiments were performed at 500 MHz. and the solvent used was $CDCl_3$.

Different NMR spectroscopic techniques were performed and the spectra were shown in the following figures.

One dimensional experiments:

Figure 27	The C-13 decoupled spectrum
Figure 28	The DEPT-135 spectrum
Figure 29-30	The H-1 spectra

Two dimensional experiments:

Figure 31-32 The COSY spectra

Figure 33-38 The HETCOR spectra

The C-13 NMR spectrum of the mixture product (Figure 27) showed obviously 3 main groups of peaks. First, the group of peaks that characterized the alkyl (1-propylbutyl) chains. The methyl-carbons appeared at 14.49 and 14.52 ppm. The 2 ethylene carbons appeared at 20.28,20.33,20.35,20.39 ppm and 31.03, 31.20, 31.27, 31.33, 31.45,31.48 ppm respectively. It was not able to assign exactly which peak belonged to which carbon of its kind since each of them resonated almost at the same frequency. The propyl chain in each of the four expected isomers was expected to have very similar enviroment since it was not directly adjacent to the ring.

The peaks at 40.86, 41.28, 41.77 and 42.21 ppm. were assigned to the methine carbons (a) of alkyl chains. Since the methine carbons, each was directly adjacent to the ring, it was expected to have distinct enviroment which caused it to resonate at different frequency.

Each of the methine carbon peaks was assigned to *cis*-or *trans*-forms of either five or six-membered derivative.

According to the chemical shifts and intensity of peaks that were assigned to alkyl chains, it confirmed the presence of 1-propylbutyl chain attached at C-2 of each expected isomer.

Second, 2 pairs of the peaks appearing at 103.91, 104.62 ppm and 106.97, 107.20 ppm. were assigned to the acetal carbons (b). Since the acetal carbons, each attached to 2-oxygen atoms, it resonated at lower field than any other carbons. Each pair of the peaks was assigned to *cis,trans-* pair of either five or six-membered ring. It was not able to define exactly which pair belonged to which *cis,trans-* pair of the two expected *cis, trans-* pairs since none of the pure isomers was obtained. However it was proposed that the peaks at 106.97 and 107.20 ppm represented *cis-*, *trans*-pair of five-membered ring and the peaks at 103.91 and 104.62 ppm represented *cis-*, *trans*-pair of six-membered ring. Since the ring of five-membered derivative was more strained, its acetal carbon was proposed to resonate at lower field. This proposal would be supported by the investigation indicated that acetal carbon of unsubstituted 1,3-dioxolane resonates at lower field than that of unsubstituted 1,3-dioxane (Fresenius et al., 1989). Considering the difference in chemical shifts between peaks of both the pairs at lower field (0.23 ppm) and higher field (0.71 ppm), it was clearly seen that the pair at lower field had less marked

difference in chemical shift than the pair at higher field. There has been an investigation indicated there are less marked conformational differences between cis- and trans-isomers in five-membered rings as compared to six-membered one since five-membered rings are conformationally mobile (Levy, 1979). This supported the proposal that the peaks at 106.97 and 107.20 ppm were assigned to *cis-,trans-*pair of five-membered cyclic acetal as well.

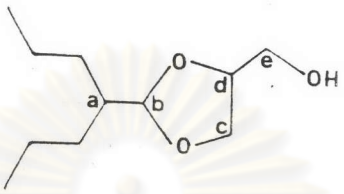
Third, the group of peaks resonated between 60-80 ppm were assigned to carbons, each attached to only one oxygen atom. The DEPT-135 spectrum (Figure 28) distinguished between methyl, methine carbons (up) and methylene carbons (down). According to the argument for the assignment of the acetal carbons, it was proposed that the peaks at 61.33 and 64.22 ppm represented six-membered ring carbons(e), and the peaks at 76.15 and 76.29 ppm represented *cis-,trans*-pair of five-membered ring carbons (d). The difference in chemical shift of *cis-,trans-*pair of six-membered ring was marked(2.89 ppm). This was in normal range since it has been investigated that *cis,trans-*differences range from 1.5 to 5.7 ppm in six-membered rings (Levy, 1979). The peaks at 71.79 and 71.87 ppm were assigned to *cis-,trans*-pair of six-membered ring carbons (c and d). Since carbons c and d of six-membered ring were magnetically equivalent, each of both peaks showed double intensity.

The 2 pairs of peaks at 62.69, 63.41 ppm and 66.42, 66.73 ppm were assigned to carbons of five-membered ring. The peaks ,at 66.42 and 66.73 ppm were assigned to five-membered ring carbons (c), and the peaks at 62.69 and 63.41 ppm were assigned to five-membered ring carbons (e). The assignment was based on the fact that the alkoxy substituent caused larger downfield shift than the hydroxy substituent (Silverstein, Bassler and Morrill, 1991).

Since the amount of each of the four expected isomers in the mixture product was proposed to be constant, the relative intensity of peak would correspond to the amount of isomer it was assigned to. Considering the acetal carbons (b), which all four isomers had in common, they resonated at difference frequency since they each had a distinct enviroment. So each peak must have shown only single intensity which corresponded to the constant amount of the isomer in the mixture product. The ratio of relative intensity of any pair of peaks represented *cis*-, *trans*-pair of either five-or six-membered ring would then be the same. This confirmed the proposal indicating that all four isomers existed in the mixture product.

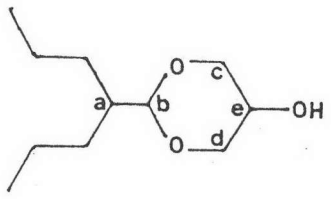
The chemical shifts of carbon-13s were shown in table 1 and 2.

Table 1. The chemical shifts of carbon-13s of *cis*-,*trans*-pair of 2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane



more abundant form		less abundant form	
carbon	chemical shift(ppm)	carbon	chemical shift (ppm)
a	40.86	a	41.28
b	107.20	b	106.97
c	66.42	c	66.73
d	76.15	d	76.29
e	63.41	e	62.69

Table 2. The chemical shifts of carbon-13s of *cis*-,*trans*-pair of 2-(1-propylbutyl)-5-hydroxy-1,3-dioxane



more abundant form		less abundant form	
carbon	chemical shift(ppm)	carbon	chemical shift (ppm)
a	42.21	a	41.77
b	104.62	b	103.91
c,d	71.87	c,d	71.79
e	64.22	e	61.33

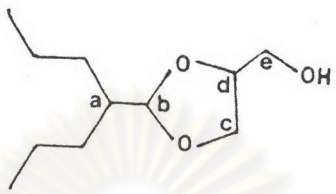
It was not able to assign the signals of protons from only H-1 spectra (Figure 29-30) since most signals were complicated from overlapping. Only signals of acetal protons were able to be assigned since they appeared at lower field than other signals.

The signals of protons would then be assigned from the HETCOR spectra (Figure 33-39). The HETCOR spectra correlated the peaks of a C-13 spectrum with the peaks of an H-1 spectrum.

The chemical shifts of protons of five and six-membered cyclic acetal were shown in table 3 and 4.

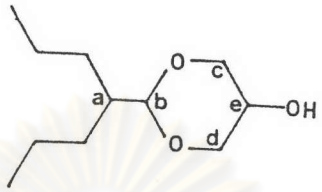
According to the NMR spectra of the mixture product, in case of *cis,trans*-pair of five-membered cyclic acetal, one form was just slightly more abundant than the other ,while for that of six-membered ring, one form was much more abundant than the other. Based on the splitting patterns and coupling constants of the signals of proton c,d and e of six-membered ring, the more abundant isomer was proposed to be *cis*-isomer.

Table 3. The chemical shifts of protons of *cis*-, *trans*-pair of 2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane.



more abundant form		less abundant form	
proton	chemical shift(ppm)	proton	chemical shift (ppm)
a	1.58 (m)	a'	1.58 (m)
b	4.825 (d,J=3.9)	b'	4.925 (d,J=4)
c	3.78 (m),3.87 (m)	c'	3.61 (m),4.1 (m)
d	4.17 (m)	d'	4.17 (m)
e	3.60 (m),3.70 (m)	e'	3.64 (m),3.69 (m)

Table 4. The chemical shifts of protons of *cis*-,*trans*-pair of 2-(1-propylbutyl)-5-hydroxy-1,3-dioxane



more abundant form		less abundant form	
proton	chemical shift(ppm)	proton	chemical shift (ppm)
a	1.58 (m)	a'	1.58 (m)
b	4.475 (d,J=4)	b'	4.315 (d,J=3.9)
c,d	3.85(dd,J=1.2,12.2)	c',d'	3.33(dd,J=9.93,10.1)
	4.01(dd,J=0.9,11.6)		4.17
e	3.50 (m)	e'	3.82 (m)

The assignment for protons of propyl chain of all isomers were not included in table 3 and 4 since they resonated at almost the same frequency. The signals of methyl protons (CH_3) appeared at 0.88-0.93 ppm. The signals of ethylene protons ($-CH_2CH_2-$) appeared at 1.23-1.49 ppm. The signal of hydroxyl protons appeared as broad band at 3.04-3.16 ppm.

[2-(1-Propylbutyl)-1,3-dioxolan-4-yl]methyl sulfamate

This compound represents aliphatic sulfamate. The sulfamate was obtained from the reaction of the corresponding alcohol and sulfamoylating agent, sulfamoyl chloride (NH_2SO_2Cl).

Sulfamoyl chloride was generated *in situ* from formic acid and chlorosulfonyl isocyanate. (Appel and Berger, 1958; Graf, 1968; Lo et al., 1992). The reaction proceeded via nucleophilic addition mechanism and the elimination of carbon dioxide and carbon monoxide respectively as shown in Figure 67-A.

Since sulfamoyl chloride was highly reactive, its generation process was to be conducted at low temperature and under nitrogen atmosphere to avoid the moisture. Sulfamoyl chloride reacted extremely vigorously with water to form amidosulfuric acid and hydrogen chloride (Graf,

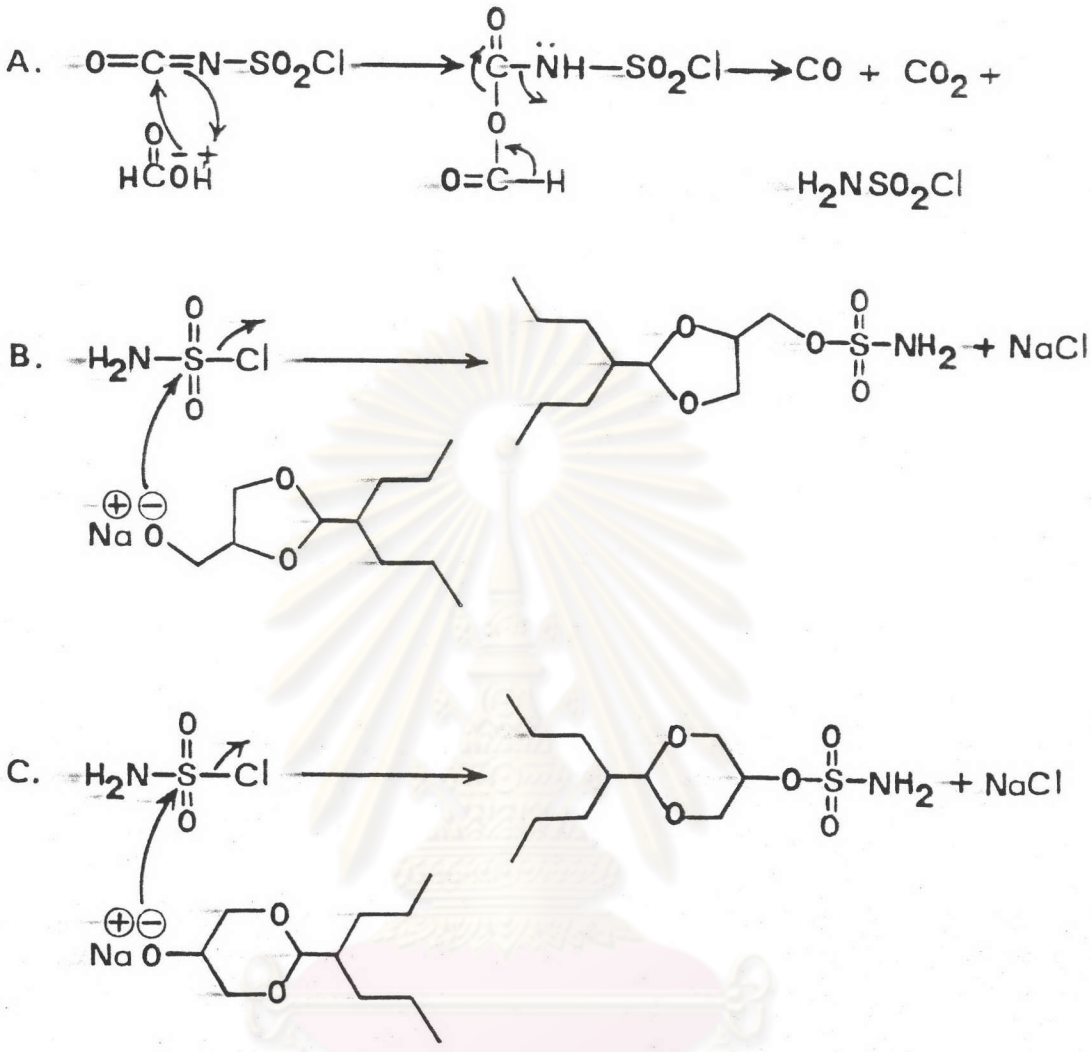


Figure 67. A. The mechanism of the formation of sulfamoyl chloride

B. The mechanism of the formation of five-membered sulfamate derivative.

C. The mechanism of the formation of six-membered sulfamate derivative.

1968).

The , sulfamoyl chloride was then allowed to react with sodium alkoxide of 2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane. The reaction proceeded through nucleophilic substitution mechanism as shown in Figure 67-B. 2-(1-Propylbutyl)-5-hydroxy-1,3-dioxane reacted with sulfamoyl chloride through the same mechanism as the 1,3-dioxolane derivative did (Figure 67-C).

The purification of product was performed by column chromatographic technique. The product obtained was the isomeric mixture. It was a waxy white solid which melted at 64-68°C.

The IR spectrum of [2-(1-propylbutyl)-1,3-dioxolan-4-yl]methyl sulfamate (Figrue 40) displayed 2 strong bands in the range of 3400-3200 cm^{-1} which were responsible for NH_2 nitrogen-hydrogen stretch vibration. The SO_2 group could be readily identified by the appearance of the two strong bands in the 1400-1350 cm^{-1} and 1180-1165 cm^{-1} regions, due to the asymmetric and symmetric stretch vibrations respectively. The C-O stretch absorption of acetal appeared between 1500-900 cm^{-1}.

Different NMR spectroscopic techniques were performed to identify the structure of product. The

experiments were performed at 500 mHz. and the solvent used was $CDCl_3$. The spectra were shown in the following figures.

One dimensional experiments:

Figure 41-42 The H-1 spectra

Figure 43 The C-13 spectrum

Figure 44 The DEPT-135 spectrum

Two dimensional experiments:

Figure 45-46 The COSY spectra

Figure 47-53 The HETCOR spectra

The same arguments for conformational analysis of the mixture product of 2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane and 2-(1-propylbutyl)-5-hydroxy-1,3-dioxane were applied to the assignment of their sulfamate derivatives (Figure 68).

The C-13 NMR spectrum (Figure 43) showed apparently 3 groups of peaks.

Firstly, peaks at 113.40 and 114.06 ppm were assigned to the acetal carbons (b) of *cis*-,*trans*-pair of five-membered sulfamate derivative. The peak at 110.57 ppm was assigned to acetal carbon (b) of six-membered sulfamate derivative. Only one form of *cis*-,*trans*-pair of the six-membered derivative existed in the mixture product.

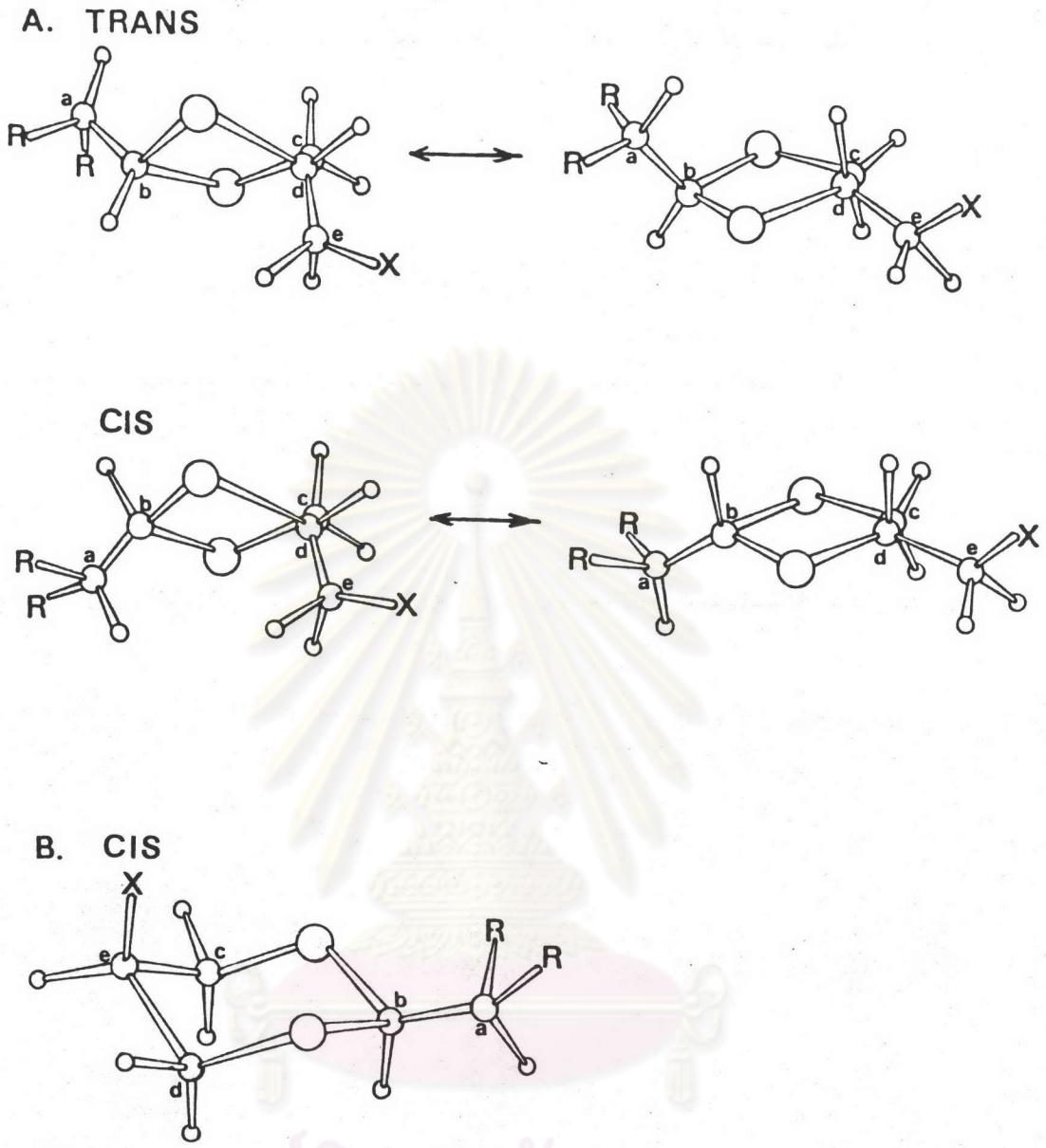


Figure 68. A. The proposed conformations of five-membered sulfamate derivative of *trans*-, and *cis*-forms

B. The proposed conformations of six-membered sulfamate derivative of *cis*-form.

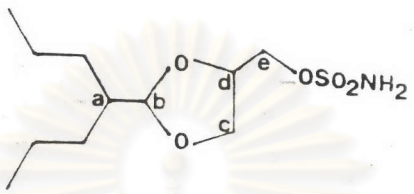
Secondly. the group of peaks resonating between 20-50 ppm. were assigned to 1-propylbutyl side chain which attached at C-2 of the acetal ring. The peaks at 46.82 and 47.10 ppm were assigned to methine carbons (a) of *cis*-, *trans*-pair of five-membered derivative and the peak at 48.17 ppm was assigned to methine carbon (a) of six-membered derivative.

Thirdly, the group of peaks resonating between 70-80 ppm were assigned to carbons, each was adjacent to one oxygen atom of either the ring or the sulfamate group. The peaks at 79.00, 79.44, and 79.90 ppm were assigned to the methine carbons. The peak at 79.90 ppm belonged to methine carbon (e) of six-membered derivative while the peaks at 79.00 and 79.44 ppm were assigned to methine carbons (d) of *cis*-,*trans*-pair of five-membered derivative. The assignment of the methine carbons was based on the fact that the sulfamate substituent which was a strong electron withdrawing group caused larger downfield shift than the ethoxy substituent. Application of the same argument to the assignment of the methylene carbons (c and e) of *cis*-,*trans*-pair of five-membered derivative indicated that the peaks at 76.48 and 76.91 ppm repesented the methylene carbons(e) while the peaks at 72.78 and 72.93 ppm represented the methylene carbon (c). The peaks at 74.98 ppm was assigned to the methylene carbons (c and d) of six-membered derivative. Since both methylene carbons

c and d of six-membered derivative were magnetically equivalent they resonated at the same frequency. So the peak at 74.9,8 ppm showed double intensity.

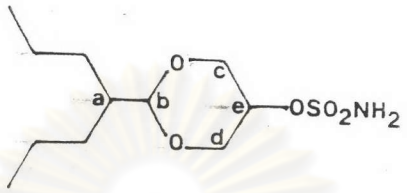
The chemical shifts of carbons of the sulfamate derivative were shown in table 5 and 6.

Table 5. The chemical shifts of carbon-13s of *cis*-,*trans*-pair of [2-(1-propylbutyl)-1,3-dioxolan-4-yl]methyl sulfamate.



more abundant form		less abundant form	
carbon	chemical shift(ppm)	carbon	chemical shift (ppm)
a	46.82	a	47.10
b	114.06	b	113.40
c	72.93	c	72.78
d	79.44	d	79.00
e	76.91	e	76.48

Table 6. The chemical shifts of carbon-13s of [2- (1-propylbutyl)-1,3-dioxan-4-yl]sulfamate

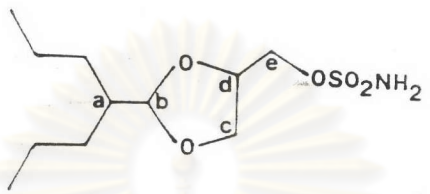


carbon	chemical shift (ppm)
a	48.71
b	110.57
c,d	74.98
e	79.90

The signals of protons of the sulfamate derivatives were assigned from the HETCOR spectra (Figure 47-53). The chemical shifts of protons were shown in table 7 and 8.

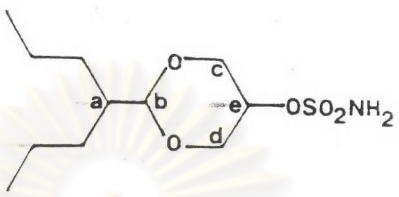
According to the NMR spectra of the mixture product, in the case of five-membered sulfamate derivative, the amount of both *cis*-, and *trans*-isomers were almost equal. The only one form of six-membered sulfamate derivative found in the mixture was proposed to be *cis*-form due to the splitting pattern and coupling constants of the signals of proton c, d, and e.

Table 7. The chemical shifts of protons of *cis*-,*trans*-pair of [2-(1-propylbutyl)-1,3-dioxolan-4-yl]methyl sulfamate.



more abundant form		less abundant form	
proton	chemical shift(ppm)	proton	chemical shift (ppm)
a	1.60 (m)	a'	1.60 (m)
b	4.83 (d,J=4.3)	b'	4.94 (d,J=4.2)
c	3.87(dd,J=4.3,9.1)	c'	3.64(dd,J=6.7,8.5)
	3.93(dd,J=6.7,8.6)		4.17(dd,J=6.7,8.55)
d	4.38 (m)	d'	4.35 (m)
e	4.14(dd,J=5.5,10.4)	e'	4.19(dd,J=4.2,10.95)
	4.23(dd,J=6.1,10.9)		4.31(dd,J=6.8,11)

Table 8. The chemical shifts of protons of [2-(1-propylbutyl)-1,3-dioxan-4-yl]sulfamate.



proton	chemical shift (ppm)
a	1.60 (m)
b	4.65 (d,J=4.9)
c,d	3.935(dd,J=1.2,14.7)
	4.34(dd,J=1.2,13.1)
e	4.437 (q,J=1.2)

The assignment for protons of propyl chain of all isomers were not included in table 7 and 8, since they resonated at almost the same frequency. The signals of methyl protons (CH_3) appeared at 0.85-1.00 ppm. The signal of ethylene protons ($-CH_2CH_2-$) appeared at 1.20-1.50 ppm. There were three broad singlet signals at 5.18, 5.23 and 5.28 ppm., each represented 2 protons of an NH_2-group. Two of these three peaks were assigned to *cis*-,*trans*-pair of five-membered sulfamate derivative and one of these three peaks was assigned to the only one form of six-membered sulfamate derivative , which was proposed to be *cis*-isomer. However it was not able to define exactly which one of these three peaks belonged to six-membered derivative.

The MS spectrum (Figure 54) was obtained at an electron beam energy of 70 eV.

The peak at 281 represented molecular ion. The peaks at 182 (base peak) and 280 were caused by the elimination of 1-propylbutyl and hydrogen respectively. The elimination of alkyl and hydrogen on acetal carbon are the characteristic fragmentation reactions which occur in ethylene acetals. The molecular ion was preferable to eliminate either 1-propylbutyl or hydrogen since either of the oxonium ions formed was proposed to be stabilized by delocalization of the positive charge between the two

equivalent oxygen atoms and the intervening sp^2 hybridized carbon atom. This resulted in the very weak molecular ion peak., The elimination of 1-propylbutyl was much greater than that of hydrogen. This was obvious since the peak at 182 was the base peak and much more intense than the peak at 280. It had been found that the ease of loss of alkyl radicals were much greater than that of hydrogen since it was proposed that alkyl radicals were more stable than hydrogen radical (Marshall and Williams, 1967).

With regard to the two principal fragmentation reactions (the loss of 1-propylbutyl and hydrogen on acetal carbon), the MS technique was not able to indicate that the product was the mixture of five and six-membered sulfamate derivatives since the both gave the peaks at 182 and 280. However, it confirmed that the desired sulfamate derivative was obtained.

The two principal fragmentation reactions of both five-and six-memberd sulfamate derivatives were shown in Figure 69.

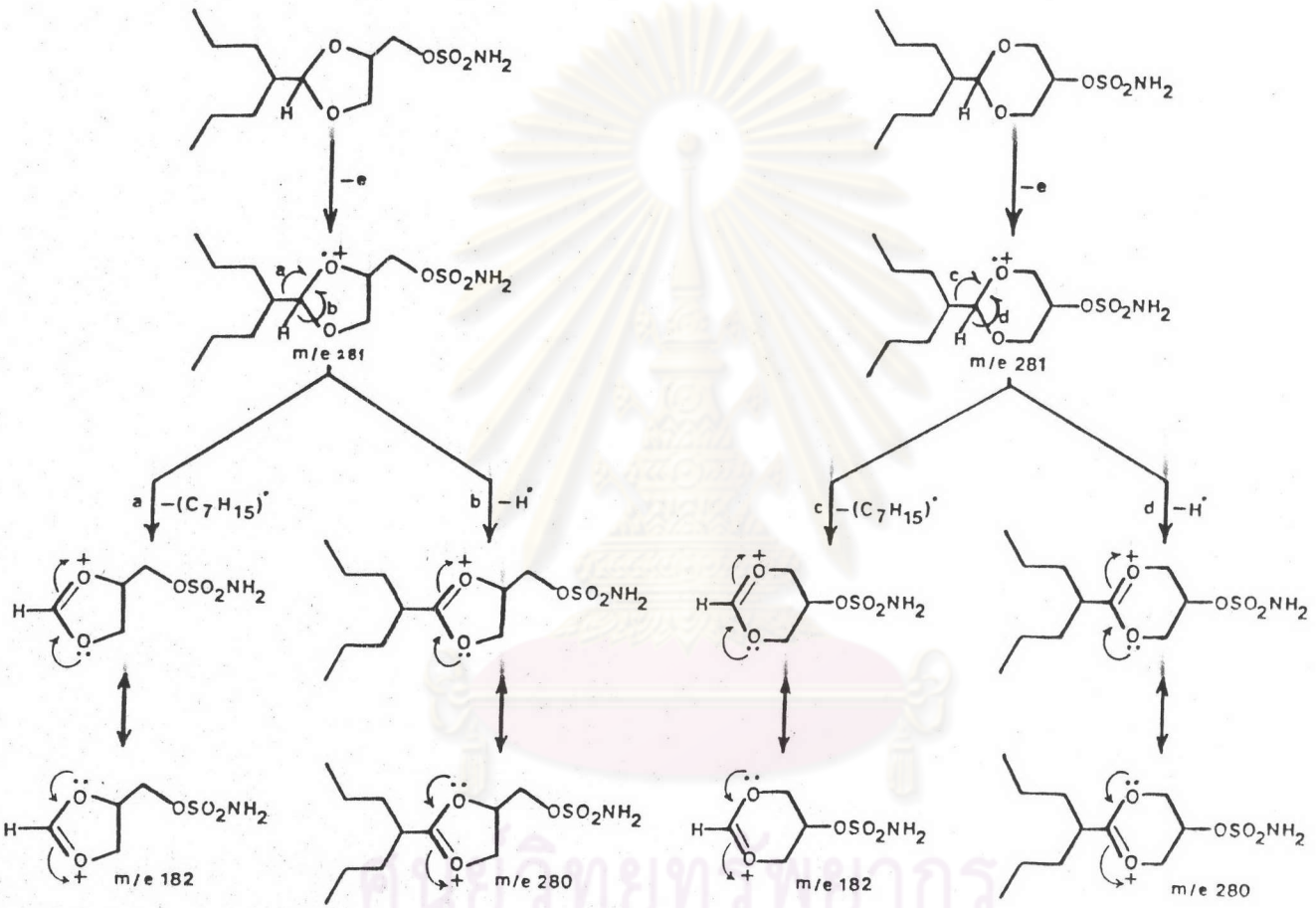


Figure 69. The mechanisms of the fragmentation reactions of both five and six-membered sulfamate derivatives which corresponded to the peaks at 182, 280, and 281 of the MS spectrum.

An attempt to synthesize pure 2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane

An effort to prepare pure five-membered cyclic acetal, 2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane was made by the following procedures.

Firstly, α-monosodium glyceroxide was prepared from sodium ethoxide and glycerol. This preparation method was studied by Fairbourne and Toms (1921). They claimed that α-monosodium glyceroxide obtained from this method was undoubtedly pure.

Secondly, glycerol α-monobenzoate was prepared from the reaction of α-monosodium glyceroxide and benzoyl chloride. Glycerol α-monobenzoate obtained was then condensed with 2-propylpentanal in the presence of p-toluenesulfonic acid monohydrate. The product of condensation was [2-(1-propylbutyl)-1,3-dioxolan-4-yl] methyl benzoate.

Finally, the ester was subjected to alkaline hydrolysis and 2-(1-propylbutyl)-4-hydroxymethyl-1,3-dioxolane was obtained.

The overall reactions were shown in Figure 70.

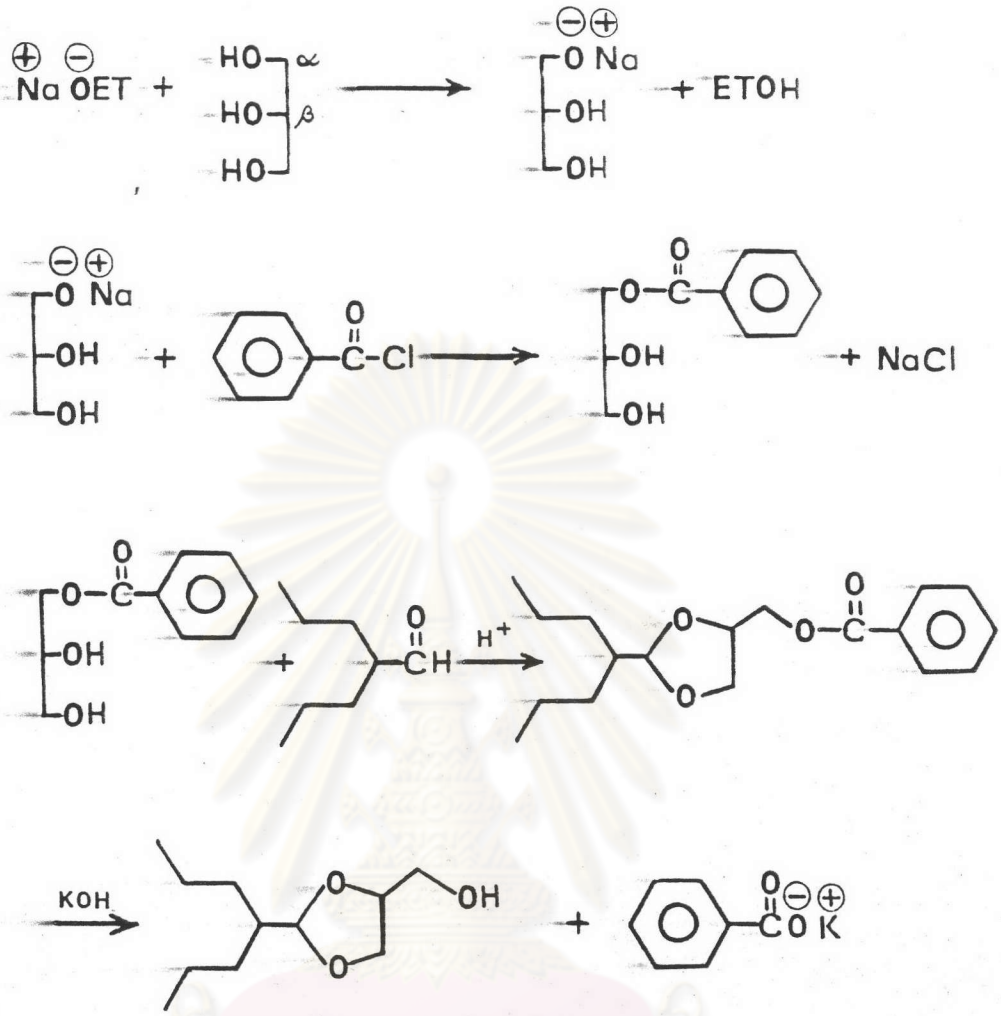


Figure 70. The overall reactions of the attempt to prepare pure [2-(1-propylbutyl)-4-hydroxymethyl-1, 3-dioxolane

The ^{1}H- and ^{13}C-NMR spectra of the product from the attempt were shown in Figure 71 and 72 respectively. The spectra, showed that the product was still a mixture of five-and six-membered cyclic acetals. However only small quantity of six-membered derivative was found in the mixture product since the relative intensity of all signals representing six-membered derivative markly reduced. It was expected that in the preparation process of α-monosodium glyceroxide, small amount of β-monosodium glyceroxide was also obtained and this, finally resulted in the formation of the six-membered derivative.

Although the attempt was not successful, it verified the assignment of the NMR signals of both protons and carbons of the mixture product which was obtained from the condensation of glycerol and 2-propylpentanal.

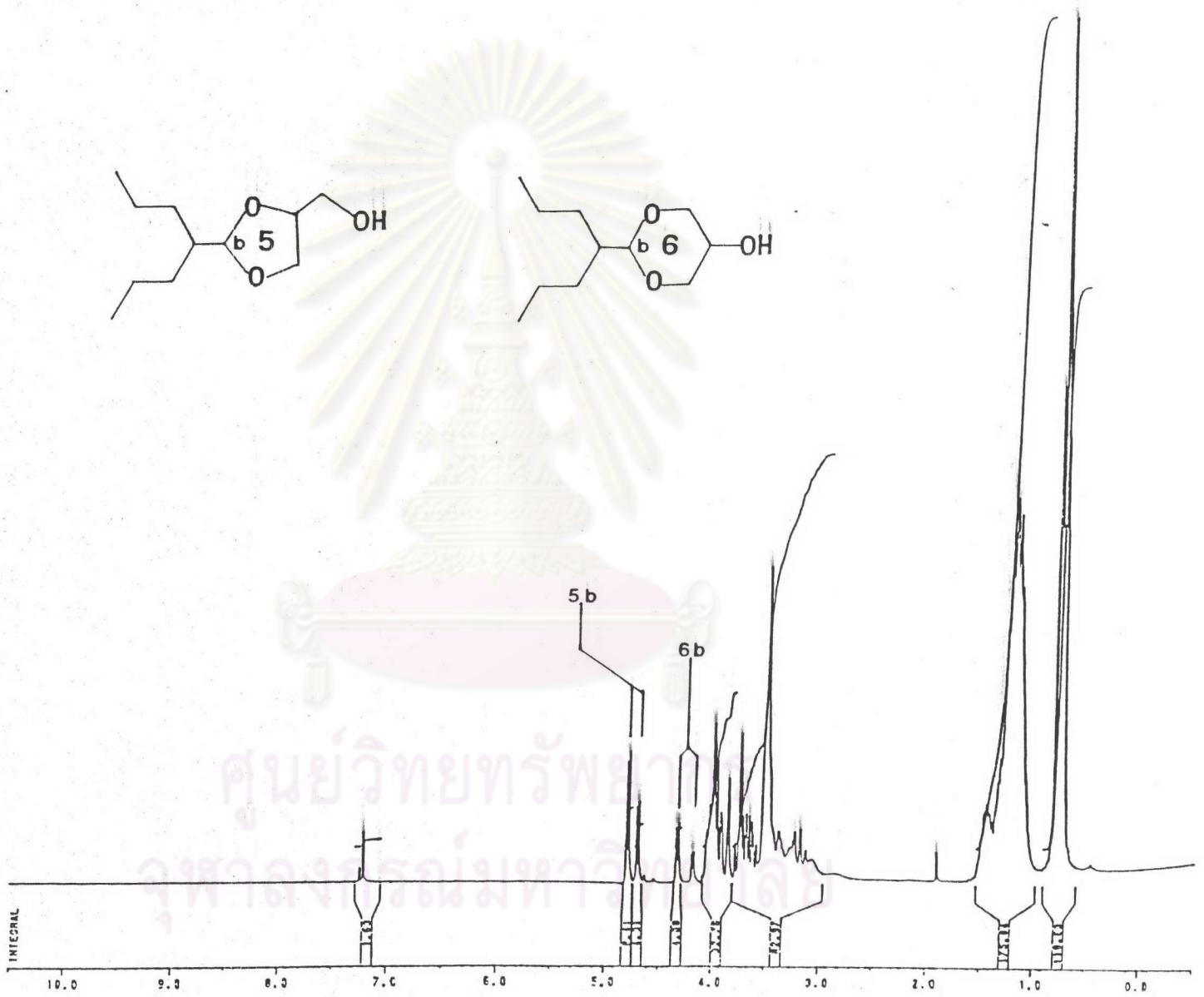


Figure 71. The H-1 spectrum of the product from the attempt

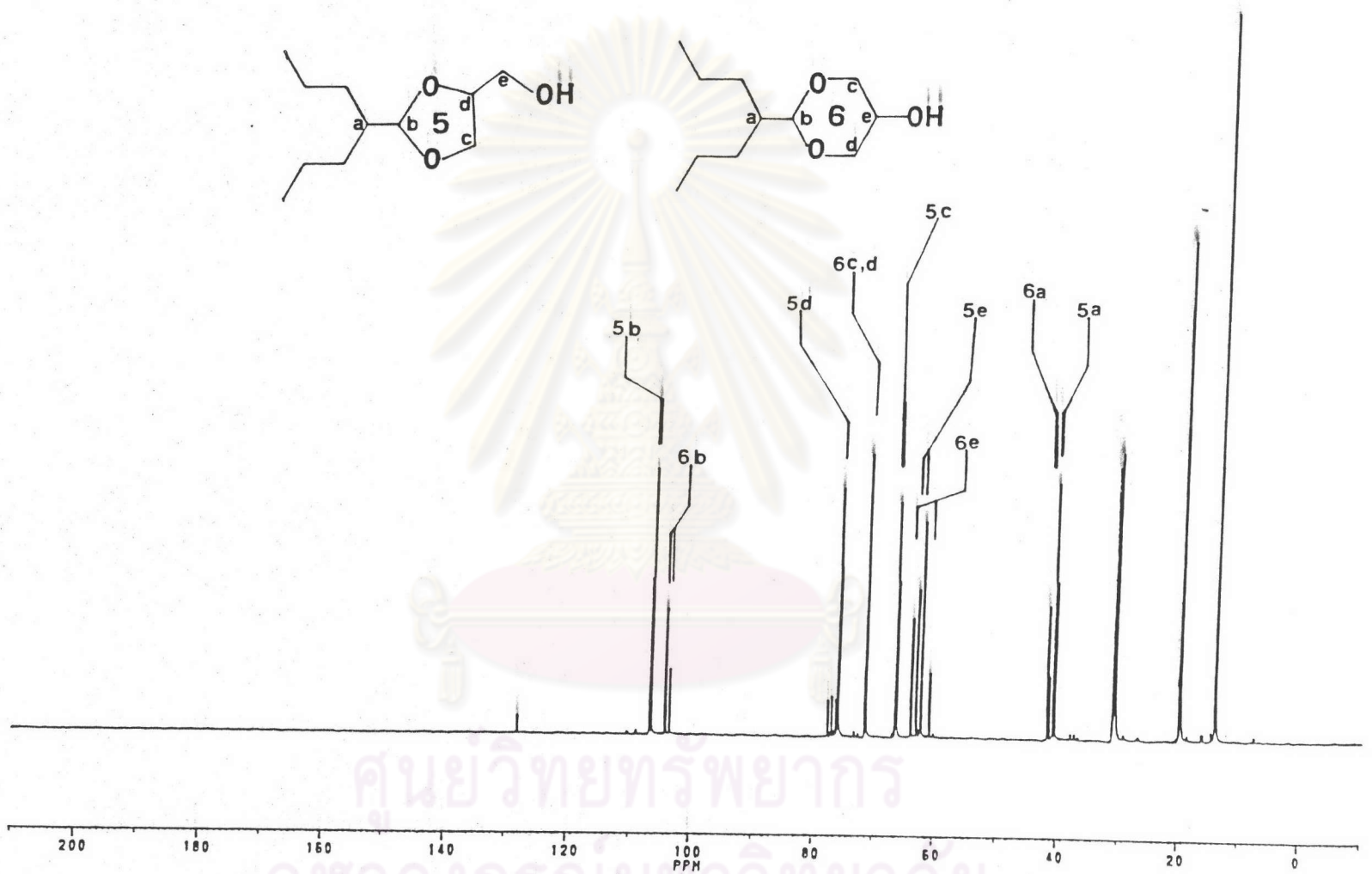


Figure 72. The C-13 decoupled spectrum of the product from the attempt.