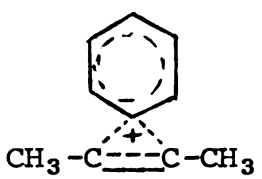
ABSTRACT

PREPARATION OF ERYTHRO-3-CYCLOPROPYL-2-BUTANOL AND A STUDY OF THE PRODUCTS OF FORMOLYSIS OF ITS TOSYLATE

By

Andrew A. Holzschuh

Cram found that the p-toluenesulfonate esters of the d and l 3-phenyl-2-butanols undergo acetolysis with retention of configuration (1). After making allowance for its rate-retarding inductive effect Winstein (2) found that the phenyl group enhances the rate of this acetolysis reaction by a factor of four over that of the unsubstituted butyl compound. The formation of an ethylenephenonium ion intermediate was offered as the best rationalization of



this unusual behavior.

The present work was undertaken to learn what might be the effect of the 3-cyclopropyl group in this molecule on the rate and products of solvolysis.

Several synthetic methods for 3-cyclopropyl-2-butanol were investigated. After the development of an improved preparatory method for cyclopropyllithium, it was reacted with trans-2,3-epoxybutane to yield about 10% of racemic

erythro-3-cyclopropyl-2-butanol (bp 82-83° at 50 mm). About 40% of the epoxide rearranged to 3-buten-2-ol and a small amount of dicyclopropyl was formed. The 3-cyclopropyl-2-butanol was found to resist purification, even by glpc. Infrared, mass, and nmr spectra were obtained on the purest material made.

Formation of a deep purple color upon mixing the tosylate (mp 52-54°) of 3-cyclopropyl-2-butanol with formic acid was an impediment to titrimetric rate determination. The formolysis product was found to be a mixture of eight to twelve components. After $LiAlH_4$ reduction, the product consisted of a mixture of olefins, and probably dimethylcyclopentanol and 2-(2-hydroxyethyl)-tetrahydrofuran.

Work directed towards the synthesis of 3-cyclopropyl-2-butanol by a multi-step route starting with a Reformatsky condensation of ethyl bromoacetate and cyclopropyl methyl ketone resulted in the preparation of the following new compounds; ethyl 3-cyclopropyl-3-hydroxybutyrate (not purified), ethyl 3-cyclopropyl crotonate, (bp 100.5° at 20 mm, $n^{25}D$ 1.4780), ethyl 3-cyclopropylbutyrate, and (bp 78° at 20 mm, $n^{25}D$ 1.4200), 3-cyclopropyl-1-butanol (bp 166° at atmos,, $n^{25}D$ 1.4350). Infrared spectra of these were obtained.

A mixture of two new 1,3-diketones (not separated, nor unequivocally identified), considered to be 1-cyclopropyl-4-chloro-1,3-pentanedione and 1-cyclopropyl-4-methoxy-1,3-

pentanedione, resulted from an attempted Darzens condensation of ethyl 2-chloropropionate with cyclopropyl methyl ketone using sodium methoxide as the base. The expected product from this condensation (followed by hydrolytic decarboxylation) was 3-cyclopropyl-2-butanone, which would then have been reduced *via* $LiAlH_4$ to yield 3-cyclopropyl-2-butanol.

In a digression from the main objective the new compounds, 6-*beta*-cyclopropylcholestan-3-*beta*-6-*alpha*-diol (mp 142.5-143.0°), and the 3-*beta*-acetate of this diol (mp 182°) were prepared.

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1. Cram, D. J., J. Amer. Chem. Soc., 74, 2129 (1952) and earlier papers.

2. Winstein, S., Morse, B. K., Grunwald, E., Schreiber, K. C., and Corse, J., J. Amer. Chem. Soc., 74, 1113 (1952).

PREPARATION OF ERYTHRO-3-CYCLOPROPYL-2-BUTANOL AND A STUDY OF THE PRODUCTS OF FORMOLYSIS OF ITS TOSYLATE

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I. INTRODUCTION

The purpose of this research was to study the solvolysis of 3-cyclopropyl-2-butyl p-toluenesulfonate. At the time (1957) this work was undertaken the rather unique solvolytic behavior of the same ester of 3-phenyl-2-butanol had been reported (1,2). As described in more detail in the following section, the nature of the solvolysis products of 3-phenyl-2-butyl tosylate was not consistent with any of the established displacement mechanisms, S_N1, S_N2, S_Ni, etc. A mechanistic scheme based on a bridged phenonium ion intermediate was proposed.

Past work (117) has shown that the cyclopropyl group strongly stabilizes a positive charge generated at an adjacent carbon atom. In this research it was hoped to determine whether the solvolysis of 3-cyclopropyl-2-butyl tosylate would exhibit evidence of a bridged ion intermediate as a consequence of its ability to stabilize a positive charge.

Some progress had been made in this laboratory (3) in the preparation of cyclopropyllithium, and 2-cyclopropylethanol had been readily prepared from it (4) by reaction with ethylene oxide. trans-2,3-Epoxybutane was readily available (5). Expectations were that

3-cyclopropyl-2-butanol could be prepared by reaction of cyclopropyllithium with 2,3-epoxybutane.

As it actually turned out, the preparation of cyclopropyllithium from cyclopropyl chloride was still quite a difficult task. (In 1962 a method for preparation of cyclopropyl bromide (36,37,38) became available, which brought considerable relief to the preparation of cyclopropyllithium.). The reaction of the lithium compound with trans-2,3-epoxybutane was found to be so unsatisfactory that it can hardly be considered useful. Yields ranging from 5 to 15% as derived from glpc graphs could be obtained, and the isolation and purification of the product proved to be very unwieldy. A number of other chemical routes to obtain this product were explored without success.

An improved procedure for the preparation of cyclopropyllithium from the chloride was developed. The course of the reaction of the lithium compound with 2,3-epoxybutane was elucidated to a fair degree, and enough of the desired product was ultimately obtained to get spectroscopic identification and physical properties.

The tosylate of 3-cyclopropyl-2-butanol was prepared and some information regarding the nature of its formolysis products was obtained. Several other new cyclopropyl compounds were prepared and tentatively identified.

Due to the fact that the writer was maintinaing full time employment while doing this work on Saturdays, progress

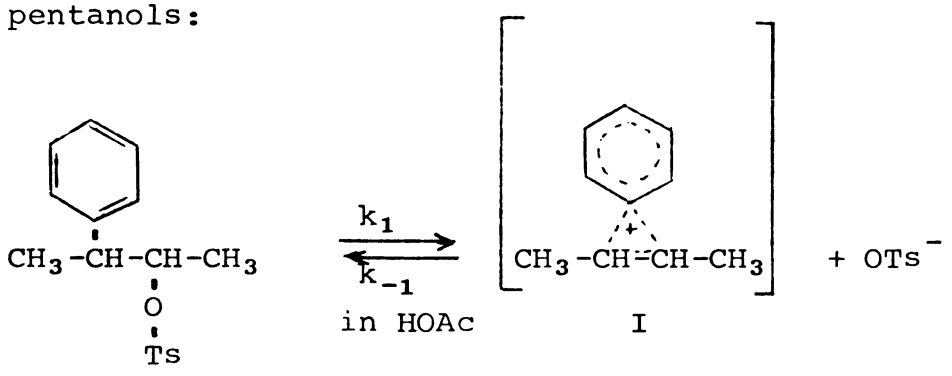
on a calendar basis was quite slow. Several papers relating to this topic were published (6a,7,8) and it seemed best not to continue to put further effort into this project.

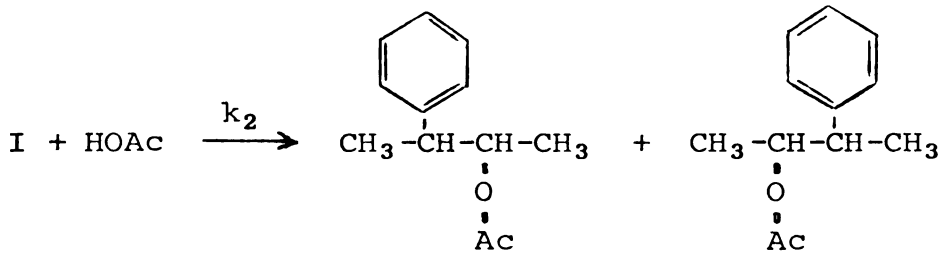
The status of the knowledge at the time of this writing is that participation by phenyl *via* a non-classical ethylenephenonium ion in solvolysis at the adjacent carbon atom may vary from essentially zero to 100% depending on the chemical structure of the compounds reacting and the physical conditions under which the reactions are performed. Much less is known about cyclopropyl but it does appear to be capable of participation *via* a bridged ion although to a considerably lesser degree than phenyl. The reactions of the cyclopropyl compounds are complicated by the fact that some ring opening occurs in the acid media.

II. REVIEW OF THE LITERATURE

A. Literature to 1957

We will first consider the five earliest papers (2,9, 10,11,12) by Cram on this subject. Based on the results reported in these papers he proposed the following mechanism involving an ethylenephenonium ion (I) for the acetolysis of the tosylates of the 3-phenyl-2-butanols and similar pentanols:





Unique to this system were the observations that (a) the optically active threo tosylate yielded a racemic threo acetate and (b) the active erythro tosylate yielded an active erythro acetate of the same configuration.

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As summarized by Hine (1a), an S_N2 mechanism would require that erythro (+) give threo (+), etc.; an S_N1 mechanism would yield a mixture of erythro and threo both of the same sign; while for an S_Ni reaction retention of configuration would be expected. He also points out that the concerted mechanism of Swain (118) would demand that threo (+) tosylate be converted to threo (-) acetate.

By comparison of the rate of loss of optical activity by the threo tosylate with the rate of acetolysis, Cram (12) concluded that k_{-1} is equal to about five times k_2. A rather tight ion pair I^+OTs^- was indicated by the fact that exchange of brosylate moiety in the ester for tosylate in the presence of a large excess of brosylate, was much slower than racemization.

Cram extended his reasearch to the study of the acetolysis of the tosylates of 3-phenyl-2-pentanol and 2-phenyl-3-pentanol (10). As the above proposed mechanism would demand, identical products were obtained from the two compounds, about seven parts of 3-phenyl-2-pentyl per three parts of 2-phenyl-3-pentyl acetate.

Up to this time the acetolyses had all been performed at 70^0 with no indication that more than one mechanism was involved. Olefin formation--about 20 to 60%-- had been noted, but not further investigated. Also no absolute rate data had been reported.

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A study of the mechanism of olefin formation, next undertaken by Cram (13,14), showed it to be of first order kinetics with respect to tosylate, as was acetate formation. It was also found that by carrying out the acetolysis at 30^0 rather than 70^0 one obtained some tertiary alcohol acetate, which was found to be unstable at 70^0. The effect of a methyl group substituent was compared to that of the phenyl. It was concluded on the basis of the results that methyl bridged ions were not important, and that the ethylenephenonium ion is 245 times as good as the ethyleneprotonium ion; also that for the threo structure the ethylenephenonium ion is somewhat less favored over the ethyleneprotonium ion than it is in the case of the erythro structure.

Winstein and co-workers (15) studied the kinetics of the acetolysis of the tosylates of the 3-phenyl-2-butanols and compared the rates with that for sec-butyl tosylate. They found:

	k, seconds^{-1} at 49.6^0
2-butyl brosylate	12.9×10^{-6}
2-butyl tosylate	4.3×10^{-6}*
threo-3-phenyl-2-butyl tosylate	2.38×10^{-6}
erythro-3-phenyl-2-butyl tosylate	2.72×10^{-6}

*This tosylate has not yielded to purification by crystallization. The figure listed was obtained by taking one-third of the figure for the brosylate.

By these figures the actual decrease in rate of acetolysis as caused by the replacement of hydrogen by phenyl is a

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little less than a factor of two. It is estimated on the basis of inductive effects (1b) that for this structure the phenyl group should retard the solvolysis rate by a factor of about eight compared to the corresponding unsubstituted butyl compound. By combination of the observed effect with the factor of eight a rate enhancement of four is obtained as the effect due to neighboring group participation.

At this point the present work was started.

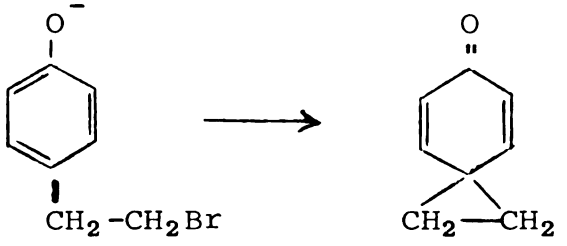
B. Literature, 1957 to 1970, Other than Cyclopropyl Compounds

During this time period thirty papers--more or less--have appeared, dealing with the mechanism of solvolytic displacement as affected by a neighboring (at the two position) carbon moiety substituent. Hammett sigma-rho reaction rate correlations, stereochemistry, migration tendency of groups sometimes recognized by isotopic labelling, effect of p-phenyl substitutents on the solvolysis rates, and effect of polarity of the solvent on the same, form a large part of the subject matter of these articles. The behavior of groups other than phenyl--including cyclopropyl--was studied. Some work was done in which the carbonium ions were generated by deamination. Direct observation of the ethylenephenonium ion by nmr was reported.

No doubt a significant contribution to the incentive for this intense activity was a polemic which arose--and still continues--as a result of the proposal by Brown (119)

of an alternate mechanism based on rapidly equilibrating classical ions, and claimed by him to offer a better rationalization of the observed facts than that of the non-classical bridged ion proposed by Cram. Brown's argument is not limited to the ethylenephenonium ion but includes all cases in which sigma bonded non-classical carbon skeleton ions have been proposed as intermediates.

By working under very mild conditions, Winstein and Baird (16) were able to isolate spiro-(2,5)-octa-1,4-diene-3-one which was formed by alkaline solvolysis of 2-p-hydroxyphenyl-1-ethyl bromide. While this structure is



quite far removed from those of present interest it does constitute an example of extreme phenyl group participation.

Cram and McCarty (17) subjected 3-phenyl-2-butylamines to deaminative acetolysis by nitrous acid. As in the case of the earlier work with the alcohols, optically pure stereoisomers were used. Novel to this method of generation of the carbonium ions were the much greater degree of migration of neighboring hydrogen, and the substantial migration of methyl which was not found at all in the case of the tosylate solvolysis. The relative amounts of migration observed were as follows:

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	Methyl	Phenyl	Hydrogen
threo	32	24	24
erythro	6	68	20

It was postulated that bridged non-classical ions of all three types played a part. The steric requirements of the diazonium ion and lack of ion pair formation were invoked to rationalize the results. A much more complex reaction scheme is required than that suggested for solvolysis of the tosylate.

The four optically active 3-cyclohexyl-2-butanols were prepared by Cram and Tadanier (18). The rates of solvolysis of their tosylates in several solvents were measured, and the products of solvolysis were identified. A number of mechanisms operating simultaneously were required to explain the findings. Bridged ethyleneprotonium ions play a part.

Roberts and Regan (22) diazotized a number of 2-phenylethylamines having various substitutents at the para position of the ring and carbon-14 at the number one position, in water and in acetic acid. Ring substituents were methoxyl, hydrogen, and nitro. The greatest degree of phenyl migration (ca. 45%) was found in case of the methoxyphenyl compound when diazotized in acetic acid, and the lowest (ca. 5%) for the nitro compound regardless of solvent. It is pointed out that electron-donating groups in the ring would be expected to stabilize the ethylenephenonium ion.

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Lee and Finlayson (27) carried out some research on the acetolysis and formolysis of 3-methyl-2-butyl tosylate. Conditions were chosen such that olefins were the only products. From the product composition they concluded that hydrogen participation, methyl participation and unassisted solvolysis were all occurring, and that in formolysis methyl participation played a greater part--at the expense of unassisted solvolysis--than it did in acetolysis. Acetic acid, a stronger nucleophile, should be able to compete against neighboring group assistance better than formic acid.

Lee and co-workers (28) investigated the solvolysis of 2-(α-naphthyl)- and 2-(β-naphthyl)ethyl tosylates with a carbon label at the one position. The reactions were carried to 50% completion and the unreacted tosylates and the products were examined for carbon atom rearrangement. The results follow, and are compared with those reported in the literature for the corresponding phenyl compound.

	Acetolysis		Formolysis	
	Product	Recovered Tosylate	Product	Recovered Tosylate
Phenyl	5	2	45	3
α-Naphthyl	46	38	50	~1
β-Naphthyl	34	31	43	0.7

(The numbers are in percent rearrangement and 50 would indicate complete equilibration of the aryl group over the two carbon atoms of the ethylene moiety.)

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Lee points out that these results are consistent with the order of the capability of the several aryl groups to stabilize positive charge, and with the fact that ion pair formation becomes less important as the dielectric constant of the solvent is increased.

Brown finds it difficult to accept the ethylenephenonium ion concept (119) on two counts. Firstly, the formation of a stable intermediate should lower the activation energy which in turn should lead to a very significant rate enhancement, much greater than has been observed. Secondly, during a change in the reaction coordinate diagram from that representing a classical carbonium ion mechanism to one which represents the bridged ion one must pass through a range of conditions which would be characterized by a pair of equilibrating classical ions. It does not appear credible to him that nature would leave such a gap when one consideres the very wide range of molecular structures available. Brown believes that stereospecificity does not have to be lost if the rate of equilibration of the pair of classical carbonium ions is sufficiently great.

Cram (19) counters that rationalization of the research results on the basis of Brown's proposed mechanism becomes complex to the point of being untenable and, also that it is inconsistent with known effects of solvent on stereospecificity. A "blow by blow" review of this polemic is not attempted in this thesis. In the last paragraph of this section some comments are given on the matter by the

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writer. A forthcoming book for which, so far only the table of contents has been published, will contain two chapters covering the two sides of the question, these authored by Brown and Cram (123).

Collins and associates entered the fray (20,122) with a long series of kinetic expressions dealt with by computer processing, through which I did not attempt to find my way. They conclude that Brown's model is not successfully refuted by Cram's arguments.

Coke (21) deaminated carbon-labelled 1-phenylethylamine in acetic acid with sodium nitrite. Eighteen percent of 1-phenylethyl alcohol (after $LiAlH_4$ reduction of the acetates) and 82% of 2-phenylethyl alcohol were obtained. (Diazotization of 1-phenylethylamine yielded only the secondary alcohol.) Of the 2-phenylethyl alcohol 27% was found by carbon labelling to have rearranged, i.e. 54% was formed by a mechanism involving a phenyl-bridged intermediate or transition state. The fact that the 1-phenylethyl alcohol product showed practically no rearrangement was used as evidence that stable intermediate rather than a transition state was participating. It is concluded tentatively that 46% of the primary alcohol and all but a trace of the secondary alcohol are formed by the classical carbonium ion (or diazonium ion) mechanism. It is presumed that there is no leakage between the two mechanisms; k_Δ mechanism for that involving the bridged intermediate, and k_s for classical ion mode. (Note: These literature citations are given

here approximately in chronological order. More work by Coke will come later.)

Lee and Tewari (124) hydrolyzed several 2-phenylethyl-1-^{14}C compounds in aqueous dioxane. With the bromide no scrambling of carbon occurred. With the mercury perchlorate two or three times as much rearrangement occurred as did with the tosylate. Scrambling increased considerably with the water content of the solvent.

Winstein (125) undertook to provide an answer to the question of expected rate enhancement due to formation of the proposed intermediate ethylenephenonium ion, which was raised by Brown (119). The rate constant k_{Δ} is assigned to the phenyl-assisted reaction and k_s to the direct reaction of the substrate with solvent. It is pointed out that the ratio of k_{Δ} to k_s should be lowest in the most nucleophilic solvent and should increase with a change in solvent in the order; ethanol, acetic acid, formic acid, trifluoroacetic acid. He also states that it is pretty well agreed that neophyl tosylate is solvolyzed completely by the k_{Δ} route, and that for it k_{Δ} should correlate with k_t (total rate as measured). In the same manner solvolysis of ethyl tosylate should show correlation of k_s with k_t. The rates of solvolysis and the degree of carbon scrambling for ethyl, 2-phenylethyl, and neophyl tosylates in trifluoroacetic acid were measured. Corresponding data for the other three above-mentioned solvents were taken from the literature.

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From the k_t values the k_Δ and k_s values were determined. A logarithmic plot of the k_Δ values for phenylethyl tosylate (in the four solvents) versus the k_t values for neophyl tosylate yielded a straight line, whereas when k_t's for the phenyl were used a straight line was not obtained. For plots of the phenylethyl tosylate data versus those for ethyl tosylate, a straight line was obtained when the k_s figures for phenylethyl were plotted against the k_t figures for ethyl tosylate. Again a straight line was not obtained when the k_t figures for the two were plotted against each other. The data also show that as k_Δ becomes more important the rate enhancement increases. In CF_3COOH 2-phenylethyl tosylate solvolyzes 1700 times as fast as ethyl tosylate. Winstein states that these results show quite conclusively that an ethylenephenonium ion intermediate is involved in the k_Δ route.

Nordlander (126) and co-workers also studied the solvolysis of ethyl tosylate and 2-phenylethyl tosylate in trifluoroacetic acid and using their data along with data taken from the literature they show that rate enhancement due to phenyl increases as the nucleophilicity of the solvent decreases. Only total rate constants are used. They find a 3040 rate enhancement in trifluoroacetic acid. Work in 1-phenyl-2-propyl tosylate gave results which were consistent with those of the ethyl compound.

Coke and co-workers (127) further pursued the study of the solvolysis rate enhancement due to substitution of phenyl

moiety in ethyl tosylate. Total rate constants k_t were separated into k_Δ and k_s. Substitution of p-methoxy group in the phenyl ring increased the k_Δ for acetolysis at 75^0 109 fold over that of the unsubstituted 2-phenylethyl tosylate. They prepared 2-phenylethyl tosylates with the phenyl groups substituted at the para position with hydrogen, chlorine, methyl, and methoxy and also labelled with carbon-14 in the side chain. Rates of acetolysis at several temperatures were measured along with rates of carbon scrambling in the unsolvolyzed tosylate and degree of scrambling in the product. From these data k_s (unassisted solvolysis) and k_Δ values were calculated, the latter including the scrambling which occurs in the unsolvolyzed tosylate. Total rate constants of acetolysis were measured for neophyl tosylates carrying the same phenyl group substituents. A straight line was obtained when logarithms of these total rate constants of acetolysis of the neophyl compounds were plotted against the logarithms of the k_Δ of the like-substituted phenylethyl tosylates. The consensus that neophyl tosylate is solvolyzed exclusively by the mechanism involving phenyl group participation is assumed. The straight line Hammett plot is considered strong evidence that a like mechanism is occurring in the acetolysis of the 2-phenylethyl tosylates to a degree characterized by the magnitude of k_Δ. The final statement by Coke is worth repeating here.

> For the type of solvolysis shown the competing k_Δ and k_s concept enjoys overwhelming success in explaining all the known data including rate constants, scrambling data, kinetic isotope effects, stereochemistry, substituent effects, solvent effects, and entropies of activation.

Synder and Jablonski (128) suggest that it might be worthwhile to consider the ratio of stereochemical retention to carbon label rearrangement in the ethyl group as useful information in the study of the mechanism of solvolysis of 2-phenylethyl arenesulfonates. If Brown's equilibrating cation mechanism is correct then it follows that this ratio could hardly remain constant over a range of conditions of solvent and temperature. On the other hand, the concept of the ethylenephenonium ion intermediate would demand that this ratio remain constant at a value of two. Using mostly data from the literature plus some obtained in the laboratory Snyder and Jablonski find that this ratio does indeed remain constant and equal to two, and cite this as strong support for the phenonium ion mechanism.

Several papers have appeared in the literature (23,24, 25,26) which report direct observation of the ethylenephenonium ion by nmr. In the latest of these (26) Olah and coworkers prepared solutions of 2-p-anisylethyl chloride and 2-(2,4,6-trimethylphenyl)-ethyl chloride in SbF_5-SO_2 solvent at minus 60^0 and in each case found the four ethylene protons to have the same nmr chemical shift.

This part of the literature review will be concluded with the citation of the most recent papers of the key

adversaries, Brown and Cram, followed by some comments by the writer.

In his latest paper Cram (129) points out shortcomings in the kinetic model used by Collins (20) as evidence against the phenonium ion mechanism. It is suggested that the effect of a p-nitro substituent in the phenyl group of 3-phenyl-2-butyl tosylate might be quite informative. It should greatly reduce or eliminate phenyl group participation, whereas, under the equilibrating cation concept it would be expected to have little or no effect on reaction characteristics. The p-nitro compounds were prepared and solvolyzed in acetic acid, formic acid, and trifluoroacetic acid. The degrees of retention of configuration in the product esters were found to be 7%, 30%, and 95% in the respective solvents. The p-nitrophenyl group seems to have very little chance against the stronger nucleophile, but as the nucleophilicity of the solvent is decreased it is able to participate much like the unsubstituted phenyl group. The rate ratios of racemization (ionization) of the nitro tosylate compared to unsubstituted phenyl compound for the three solvents were in the order given above; 190, 560, and 36,000. The p-methoxyphenyl compound was found to racemize 15,000 times as fast as the p-nitro in acetic acid. Cram concludes,

> These results demonstrate unequivocally that aryl and solvent are in competition with one another in nucleophilically assisting ionization at the back face of the incipient carbonium ion.

At the time of this writing the latest word from Brown (130) is a report of kinetic and product data obtained by acetolysis of p-substituted 3-phenyl-2-butyl brosylates. Eight substitutents ranging from nitro to methoxy were used. When sigma plus values were plotted against the logarithms of the solvolysis rates a straight line was obtained indicating that there is considerable charge delocalization into the phenyl ring. The acetate product configuration varied from 100% retention for methoxy to only 7% for nitro. A k_{Δ} mechanism is considered as a possibility and the results are not claimed as support for the equilibrating cation concept. "These results point up the urgent need to clarify the precise processes involved in the acetolysis of secondary alkyl arenesulfonates."

At this point a few comments by the writer may not be out of order. It is obvious from the foregoing that the phenonium ion theory is rather strongly favored over that based on equilibrating classical cations with respect to the chemical evidence. It appears to the writer that the proponent of the equilibrating ion concept has taken a first step towards its abandonment as it concerns the 3-phenyl-2-butyl system (130). If the equilibrating ion pair theory is unacceptable then what about the two premises which stimulated Brown's interest in it (119)? The rate enhancement question has been answered to a fair degree at least by separation of the rate constants (125,127) into k_{Δ} (for reaction via phenonium ion route) and k_s, by including in

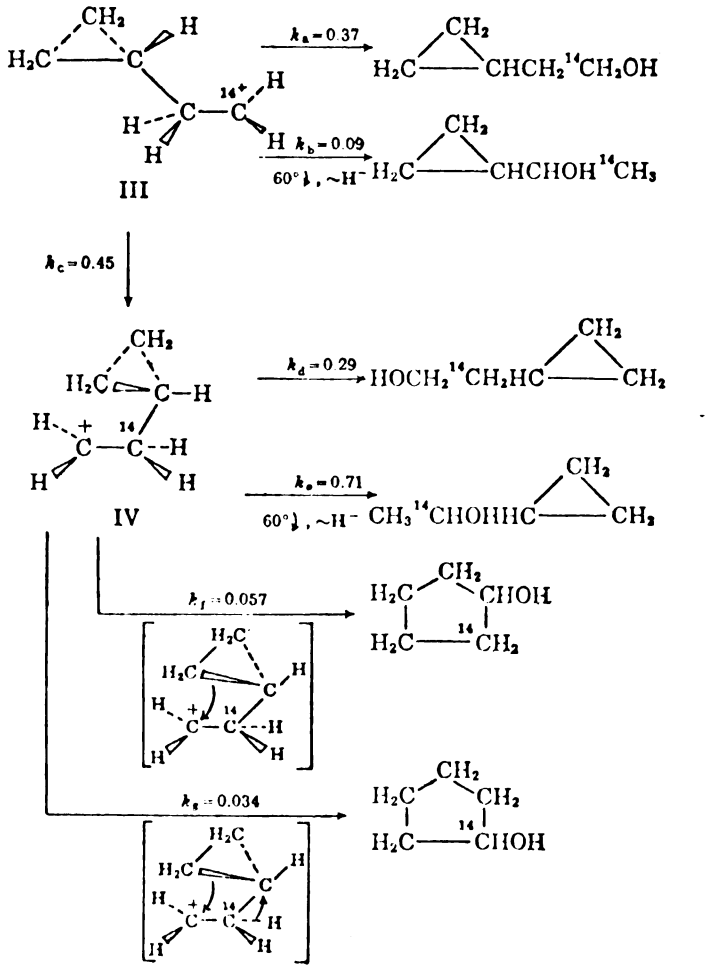
the rate constant the rate of ethyl carbon atom rearrangement in the starting tosylate (129), and by choosing less nucleophilic solvents (125,129). Rate enhancements of 100 to 36,000 were found. Brown's second premise is that between the classical ion and the bridged ion reactions the reaction coordinate for the equilibrating ion mechanism must exist. The writer should like to point out here that the classical ion--free, solvated, or ion-paired--is characteristic of the S_N1 mechanism only and not of S_N2. The reported results of the solvolysis of 2-phenylethyl tosylates are notable for retention (phenyl assisted displacement) and inversion (unassisted displacement) of configuration and for absence of racemization, which makes them of the S_N2 type. It would seem that Brown's framework could be improved. It is somewhat of a mystery to the writer that this point has not been brought up by Cram and the others on his side of the polemic. We will not do more than mention that later than any of the above cited work, Dewar (131) proposed a pi-complex intermediate as being more consistent with research results than an ethylenephenonium ion intermediate, for the solvolysis of 2-arylethyl tosylates.

C. Literature, 1957 to 1970, Cyclopropyl Compounds

Since the present work was begun in 1957, six papers have appeared in the literature which report studies of the solvolysis of 2-cyclopropylethyl tosylate or brosylate. All but one (7) of these were published after the decision to discontinue this project was made. No such studies of

the 3-cyclopropyl-2-butyl compounds have been reported. It is good to recall here that of the 2-phenylethyl compounds studied the 3-phenyl-2-butyl tosylate (or brosylate) -- also some of its para-substitution products -- exhibited the cleanest solvolysis reactions of the lot, that is, it reacted almost completely via the phenonium ion mode.

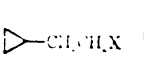
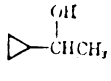
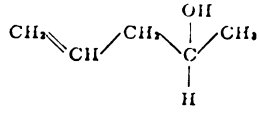
The first study of the 2-cyclopropylethyl system was done by Cartier and Bunce (7) and consisted of aqueous nitrous acid deamination of the amine. 2-Cyclopropylethanol, 1-cyclopropylethanol, and cyclopentanol were obtained in 1.00:0.76:0.18 relative amounts, respectively. The amine was carbon-14 labelled in the one position. In the primary alcohol product 74% of the label was found in the one position and the other 26% in the two position. For the secondary alcohol the corresponding values were 77 and 22, with about 0.6% of the label appearing in the cyclopropyl ring. The cyclopentanol had 37% of the label in the one position and the location of the remainder was not determined. The following mechanistic scheme (145) was proposed as being consistent with the observed data: (The numerical values shown are the solutions of simultaneous equations based on rate constants, the experimentally determined relative amounts of the three alcohols, and the position of the carbon-14 in each.)



The large fraction of unrearranged product is rationalized on the basis of the high steric requirements of the somewhat bulky diazonium ion. An ethylene-cyclopropenium ion intermediate is not postulated. It is appropriate to recall at this point that in the researches of Coke (21) and of Cram (17) on the diazotization of the 2-phenylethylamine system the reactions were much more complex than those of tosylate solvolysis (2,10).

The formolysis and acetolysis of 2-cyclopropylethyl brosylate were investigated by Sauers and Ubersax (8). The compositions of the products -- after reduction with $LiAlH_4$ -- are shown in the following table (146).

Carbonium Ion Products from Reactions of β-Cyclopropylethyl Systems

	Relative product yields				
					CH_2—CH=CH—CH_2CH_2OH
NH_2[a]	52	9	39	0	0
OBs[b]	160	0	0	0	0
OBs[c]	35	36	0	12	17
OBs[d]	0	60	0	19	21

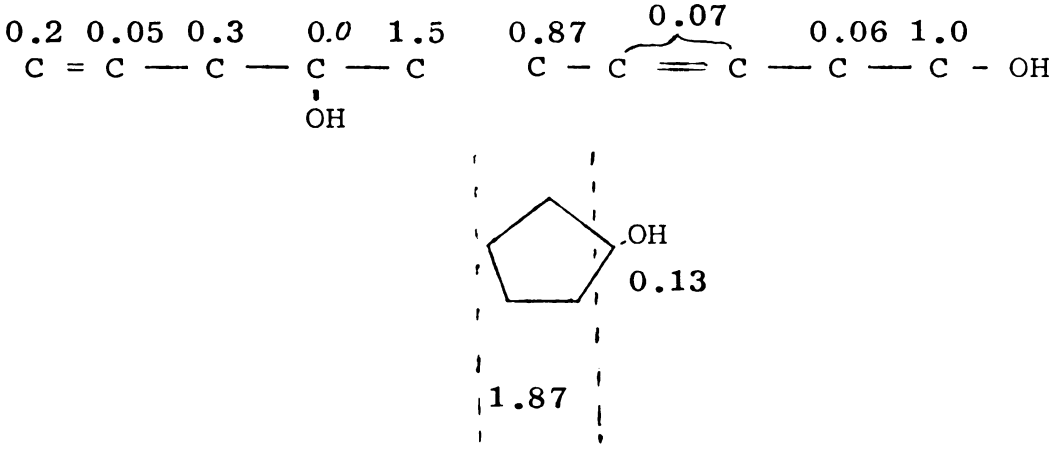
[a]From Cartier and Bunce (7).

[b]Glacial acetic acid-sodium acetate 20 hrs at reflux.

[c]Formic acid-sodium formate six hours at 100°.

[d]Formic acid-pyridine seven hours at 100°.

When the starting alcohol was deuterium labelled at the number one carbon atom no scrambling was found in the unrearranged product. In the other products the deuterium was scrambled as shown below. (Buffering with formate or pyridine did not affect the scrambling of deuterium.)



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The absence of cyclopropylmethylcarbinol among the products was explained by demonstrating that this compound under conditions used in the solvolyses is rearranged to allylmethylcarbinol. It was assumed that the product cyclopropaneethanol ester was formed by simple nucleophilic displacement. Attempts to rationalize mechanistic pathways for the formation of the remaining products left a number of alternatives which will not be detailed here. In summary it was felt that the results were not in conflict with those of Cartier and Bunce (7), and that non-classical intermediates may or may not be involved.

Hanack and Ensslin (6a) prepared a number of 2-cyclopropyl-2-R-ethyl tosylates (where R = methyl, phenyl, or cyclopropyl). Solvolyses for product study were done in aqueous acetone, water, and formic acid; for rate comparisons, in acetic acid. Rate constants x 10^6 sec^{-1} were as follows:

2,2-dicyclopropylethyl	0.64	2-phenylethyl (lit.)	0.29
2-phenyl-2-cyclopropylethyl	1.46	unsubstituted ethyl (lit.)	0.77
2,2-diphenylethyl (lit.)	2.61	neopentyl (lit.)	0.08

Fifty to seventy percent of the product was the unrearranged alcohol. The remaining hydrolysis products could all be rationalized as having been formed by migration of groups with migrating tendency decreasing in the order; phenyl, cyclopropyl, hydrogen, and methyl. Something of the order of 7% of the material was converted to olefinic hydrocarbons.

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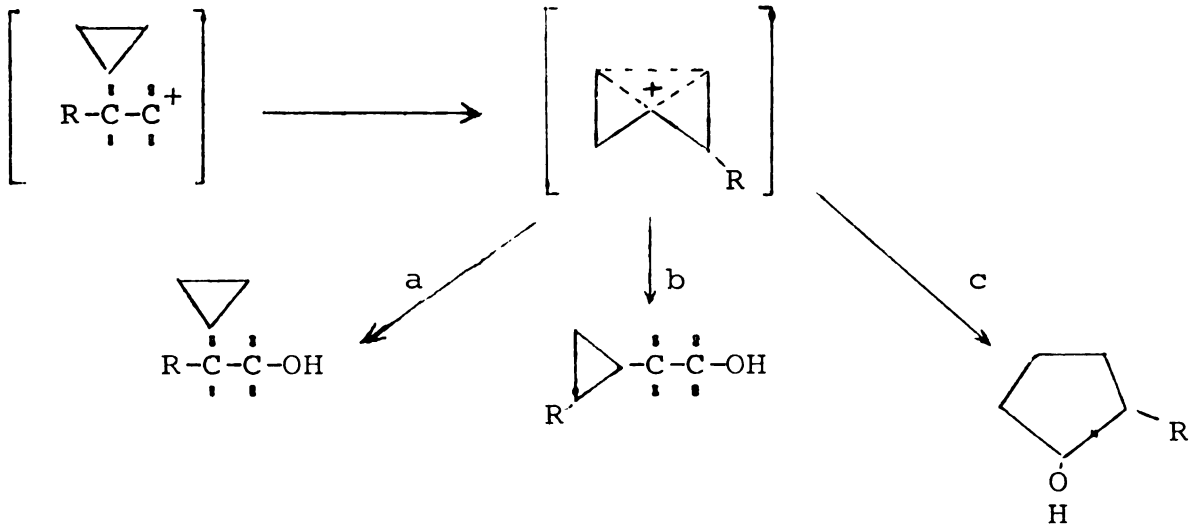
In formic acid 27% of a cyclopentanol product was formed. These results were interpreted as evidence that the cyclopropyl group enhances the solvolysis rate a little, but less than does the phenyl group; that a carbonium ion mechanism is involved which does not include the non-classical ion shown below. These same chemists recently reported research on the homologization of unsymmetrical ketones (6b) with diazomethane catalyzed by BF_3 which is reasonably presumed to proceed <u>via</u> a carbonium ion mechanism, and found the migration tendencies of phenyl, methyl, and cyclopropyl groups to be of the same order as in the above work. The argument against the participation of a symmetrical non-classical cation rests on the absence of products which would be expected from such an intermediate. Consider these reactions:



The symmetrical non-classical cation, on reaction with nucleophile (water in this case), should give rise to all three of the products shown. The fact that no product having

substituent in the cyclopropyl ring is found, is cited as evidence against the participation of this ion.

Dewar and Harris (132) carried out rate and product studies of the solvolysis of 2-cyclopropylethyl brosylate in formic acid-sodium formate at 75°. The product mix -- after reduction with $LiAlH_4$ -- was in agreement with that of Sauers and Ubersax (8). Relative to that of ethyl brosylate the first order rate constant for the formolysis of 2-cyclopropylethyl brosylate was 0.93. D. and H. conclude that participation of the cyclopropyl group in the solvolysis reaction is not significant.

Rhodes and Takino (133) compared the rates of solvolysis of 2-cyclopropylethyl brosylate with those of isoamyl brosylate in ethanol, acetic acid, and formic acid. The isoamyl compound was chosen for comparison because of its similar steric requirements. The rates were found to be very nearly the same for the two compounds over the three solvents and several temperatures. The maximum enhancement by cyclopropyl was about 8% and the minimum enhancement was a rate reduction of about 3%. It was shown that the main kinetic product is 2-cyclopropylethyl formate -- product study for the formolysis reaction only -- and the ring cleavage products are produced from it rather than directly from the brosylate.

In summary it hardly needs to be repeated that the cyclopropyl group has much less -- if indeed any -- tendency

toward formation of an ethylenecyclopropenium ion than has the phenyl group for formation of a similar species. Still somewhat tempting is the question of how cyclopropyl would behave in the secondary butyl system, since the phenyl group showed its strongest tendency for bridged ion formation when it was part of the secondary butyl system.

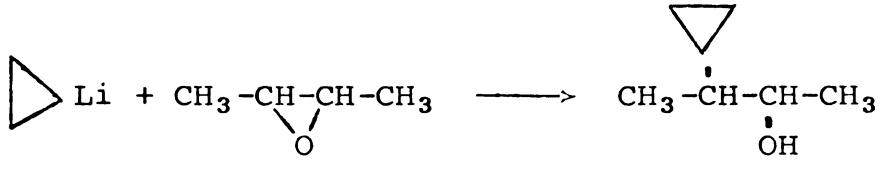
At about the time this thesis was ready for publication it was disclosed by Rhodes and associates (147) that they had studied the acetolysis of erythro- and threo-3-cyclopropyl-2-butyl tosylates. The information is in the form of an abstract of a paper to be presented at a coming meeting and few details were given. The threo isomer solvolyzed with 80% retention and 20% inversion of configuration, showing that cyclopropyl participates to a lesser extent than does phenyl and to about the same extent as p-chlorophenyl. Hydrogen migration and cyclopropyl ring opening also take place.

III. RESULTS AND DISCUSSION

A. General Discussion and Chronology

The overall chronology of planning and action is given here. Particular research results will be discussed in the subsequent sections.

As mentioned in the Introduction, when the work was first planned the outlook was that it could be expected to go through quite smoothly. An apparatus for continuous photochemical chlorination of cyclopropane to produce cyclopropyl chloride (29) was already available in this laboratory. An improved method for the preparation of cyclopropyllithium had recently been discovered (3). There was sufficient knowledge to the effect that cyclopropyllithium, as well as other organo-lithium compounds, could be successfully reacted with ethylene oxide, that it was presumed -- later found unjustifiably -- that the reaction of cyclopropyllithium with butylene oxide would be a practical method for the preparation of 3-cyclopropyl-2-butanol.

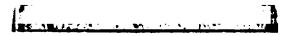


Fortuitously, trans-2,3-epoxybutane was available (5).

Preparation of tosylate esters of alcohols and solvolysis of these is a well documented field and would be expected to offer no serious difficulties.

The chlorination of cyclopropane was carried out quite satisfactorily. It was soon found that the preparation of cyclopropyllithium by the published procedure was quite unpredictable. At about this time Ramsden and co-workers (30) reported the successful preparation of vinylmagnesium chloride by working in tetrahydrofuran. The use of Ramsden's procedure for the preparation of cyclopropylmagnesium chloride was quite thoroughly investigated by the writer and by others (31,4) in this laboratory, and a degree of success was achieved. Attempts to synthesize 3-cyclopropyl-2-butanol by reaction of this Grignard reagent with butylene oxide were unsuccessful.

A completely new chemical approach was now undertaken. It consisted of a multi-step synthesis beginning with a Reformatsky condensation of cyclopropyl methyl ketone and ethyl bromoacetate. It is analogous in part to procedures used in this laboratory by Hart and Wyman (32,44). A number of experiments in the synthetic sequence were carried out. Some steps went very well, whereas others ranged from mediocre to poor. It was at about this time that some success was forthcoming with the preparation of cyclopropylmagnesium chloride in the hands of Cipriani (31) in this laboratory. The work on the Reformatsky sequence was tabled in favor of additional attempts at preparation of



3-cyclopropyl-2-butanol by means of Grignard reagent plus butylene oxide reaction. However, even with the Grignard reagent being accessible, it was still not possible to get the desired product from the reaction of it with butylene oxide.

Cram (2) prepared his phenylbutanols by a Darzens condensation of acetophenone with ethyl chloroacetate, followed by reaction of the resulting 2-phenylpropionaldehyde with a methyl Grignard reagent. This chemistry appeared to hold some promise for the cyclopropyl analog. Cyclopropyl methyl ketone was readily available. By using ethyl 2-chloropropionate which was also available one could directly obtain 3-cyclopropylbutanone-2, which could be easily reduced to the desired alcohol. By this method one would get a mixture of diastereomers, whereas by reaction of trans-2,3-epoxybutane with cyclopropyllithium -- or Grignard reagent -- one would expect to get only the erythro product. Several Darzens condensations were run with no success. It appeared that a 1,3-dicarbonyl compound was the predominant product. In retrospect, it is the opinion of the writer that success could likely be achieved by this route if effort were devoted to determination of the most suitable condensing agent.

At about this time a new method for the preparation of cyclopropyl compounds was reported by Simmons and Smith (33), namely, reaction of methylene iodide with an olefin in the presence of zinc-copper couple. The results of one experiment with a model compound were unsatisfactory and this

route was not pursued further. In light of research results published since that time there exists little doubt that 3-cyclopropyl-2-butanol can be made by the Simmons-Smith methylene addition. Obtainment of the necessary substrate could be the major task.

During this period some work was published by Sneen (34) in which he reported the effects of the nature of the substituent at the six position on the rate of solvolysis of cholesteryl tosylate. As a diversion from the main objective of this research, the preparation of 6-cyclopropylcholesterol was undertaken, with the intent of determining how the rate of solvolysis of its tosylate compares with that of the tosylates studied by Sneen. Several sequential preparative steps toward 6-cyclopropylcholesterol were carried out with good success. Ultimately, for the introduction of the cyclopropyl group the need for cyclopropyllithium -- or Grignard reagent -- arose again. At this time it was discovered that -- contrary to past reports (3,35) -- cyclopropyllithium could be made from the chloride in ether solvent. With this new capability attention was now returned to application of it to the preparation of 3-cyclopropyl-2-butanol. Very soon the successful preparation of cyclopropyl bromide -- which until now had been substantially unavailable -- by a modified Hunsdiecker reaction was reported (36,37,38). This synthesis was found to go very well and eliminated the somewhat tedious task of preparation of

cyclopropyl chloride and also removed any remaining difficulty from the preparation of the lithium derivative. It should be remembered that the Grignard reagent, even though it could be made, did not yield the desired product with butylene oxide. It was still expected that the lithium derivative would succeed in this respect.

Even though some difficulties had been overcome, it was soon learned that some serious ones still remained. The major product of the reaction of cyclopropyllithium with trans-2,3-epoxybutane turned out to be 3-buten-2-ol, an isomer of the epoxide. Nucleophilic elimination of hydrogen was predominating over substitution. The desired alcohol was obtained in 8 to 15 percent yields. There were enough other minor products, including dicyclopropyl and an unidentified carbonyl compound, to make it virtually impossible to purify the 3-cyclopropyl-2-butanol. The best material obtained by preparative glpc still showed considerable impurity by nmr. One might expect that purification would be achieved in the course of preparation and recrystallization of the tosylate. The latter was prepared with no more difficulty than a 30% loss of yield, which was significant in view of the scarcity of the material. Regardless of the number of recrystallizations, on formolysis of the tosylate the mixture always took on a deep blue color. This made it impossible to use an indicator in the titrations necessary for the rate studies. Preparations were made to

run the titrations potentiometrically and it appeared that this would circumvent the color problem, at the cost of some added complexity.

By this time nmr and glpc -- with techniques for fraction collection -- had become sufficiently available that there was reason to think that isolation and identification of solvolysis products would be feasible even with the very small quantities of material available. Considerable work was devoted towards this end and some success was realized.

A rather large amount of time had been spent on the project. Indications were that the solvolysis products of 3-cyclopropyl-2-butyl tosylate consisted of a rather complex mixture. The outlook was that the ratio of useful results to effort required would not improve. Also by now several other people (6a,7,8) had reported results of studies which were rather closely related to the objectives set out for this project. In August 1964 the decision was made to discontinue this research.

B. Preparation of Cyclopropyl Chloride and Cyclopropyl Bromide

The development of the state of the art during the period 1958-62 was such that, at the beginning, cyclopropyl chloride was the preferred intermediate for the preparation of cyclopropyllithium, while towards the end the odds shifted in favor of the bromide. Up to 1961 the bromide was available

only by the classical Hunsdiecker reaction (39) through decarboxylation of the silver salt of cyclopropanecarboxylic acid, and this was reported to be very unsatisfactory. As opposed to the bromide, the chloride could be made by direct chlorination of cyclopropane. In 1961 Cristol (36) published an improvement over the classical Hunsdiecker reaction in which red mercuric oxide and bromine are reacted with a carboxylic acid to yield the bromide having one less carbon atom. This method was optimized for cyclopropyl bromide by Meek and Osuga (37,38), and has been reported as satisfactory by several others (40). Reported yields are 40-50%. In the present work 60% yield was readily obtained. In view of the facts that the bromide reacts more smoothly with lithium than does the chloride and that the preparation of the chloride requires rather elaborate apparatus, there is little doubt that the bromide will be the choice for most, if not all, needs of the future. Another point of considerable importance in favor of the bromide is the fact that preparation of the chloride requires the recovery and re-use of a sizeable amount of cyclopropane which could entail a serious fire hazard. During the course of this writing Davis (51) reported a rather broad study of the Cristol modification of the Hunsdiecker reaction from the standpoint of synthetic use.

The yields of cyclopropyl chloride obtained by chlorination of cyclopropane in the early works of Roberts (29) and

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Slabey (35) were not reported. This is not too surprising in view of the fact that about 70-80% of the cyclopropane fed into the chlorination system comes through unreacted and must be recovered. Any lack of efficiency in the recovery would be reflected about three-fold as loss in yield. In the present work it was estimated that about 30-35% yield was obtained, this being the percentage of the cyclopropane not recovered which could be accounted for as cyclopropyl chloride.

In 1962, Gunning and co-workers (42) reported that the large excess of cyclopropane is not needed to prevent excessive polychlorination, and that equally good yields or better are obtained using a 1:1 mole ratio of chlorine and cyclopropane. A yield of 20% was claimed. They also reported that cyclopropyl bromide could be obtained in the same manner as the chloride by reacting a mixture of chlorine and bromine with cyclopropane. This was of particular interest to the writer because he had given consideration to such an experiment earlier, the thinking being that the avoidance of HBr would prevent destruction of the ring. This latter has no doubt been the obstacle to direct bromination in the past. Naturally as long as free chlorine is present there will be no HBr. In the above reported work only about 10% yields of bromide were obtained, but the investigation of the mixed halogenation was only preliminary.

There are a number of other possibilities for preparation of cyclopropyl chloride or bromide.

The bromide and the chloride have been prepared by Roberts (43) and Hart (44), respectively, by decomposition of the peroxide of cyclopropanecarboxylic acid in the presence of carbon tetrahalide. Yields of 40-70% were obtained. With the present ready availability of cyclopropanecarboxylic acid this route to the halides may well be preferred in some instances.

Cyclopropyl bromide was obtained in 62% yield by Kirmse (41) by reaction of 1,1,3-tribromopropane with methyllithium. He also obtained the chloride by reaction of methyllithium with 1,3-dibromo-1-chloropropane, yield not given. This paper was a short communication in 1963 and no further details have appeared.

Walling and Fredricks (45) studied the effect of temperature on the photochemical chlorination of cyclopropane in solution. They obtained a much higher yield of cyclopropyl chloride -- 48% vs 15% -- at 68^0 than at 0^0. They also found that t-butyl hypochlorite reacts with cyclopropane to give yields better than were obtained by direct chlorination, i.e. 85% of the products was cyclopropyl chloride. Since t-butyl hypochlorite can be prepared very readily -- but note the explosion hazard (47) -- if this procedure can be scaled up to preparative dimension it could provide a simple method for synthesis of cyclopropyl chloride. This immediately suggests the preparation of the bromide by use of NBS (N-bromosuccinimide) or t-butyl hypobromite. The use of NBS for preparation of cyclopropyl bromide has

not been reported. t-Butyl hypobromite preparation has not been reported to nearly the extent as the hypochlorite and is claimed to be more difficult to prepare (48). However, in a recent article (49) it is stated that it can be readily prepared by reaction of NaOBr with t-butyl alcohol in acetic acid.

Very recently Huyser (52) reported that trichloromethanesulfonyl bromide is a very effective and convenient free radical brominating agent.

Also by this time another modification of the Hunsdiecker reaction has made its appearance (50). On the basis of only a few data in one short paper, it appears worthy of further study. Cyclohexyl iodide was prepared in 91% yield by reaction of cyclohexanecarboxylic acid with lead tetraacetate and iodine.

Finally, Seyferth and associates (14) report good results with the synthesis of substituted cyclopropyl bromides. C_6H_5-Hg-CBr_3 is refluxed with an olefin to give a dibromocyclopropane. The latter is reduced to the monobromo compound by tri-n-butyltin hydride.

C. Attempted Preparation of 3-Cyclopropyl-2-butanol by Reaction of Cyclopropylmagnesium Chloride with trans-2,3-Epoxybutane

A total of eight attempts were made to prepare 3-cyclopropyl-2-butanol by the title route, with no success. The

preparation of the Grignard reagent is difficult due to the inert character of the cyclopropyl chloride, though some degree of success was achieved with this step. The reaction of the Grignard reagent with the epoxide is apparently plagued with side reactions to a considerably greater extent than is the case for the less sterically hindered epoxides.

At the time this work was done, 1957-58, the state of the knowledge was to the effect that the preparation of cyclopropylmagnesium chloride had not been realized (39). The Grignard reagent had been readily prepared from the bromide (39), but, as discussed earlier, at that time the bromide was quite difficult to obtain. Although preparation of cyclopropyllithium had been accomplished (3), varying degrees of difficulty were still being encountered with its preparation in this laboratory.

In the present research one attempt at the preparation of cyclopropyllithium had met with failure when the research of Ramsden and co-workers (30) came to our attention. They were able to prepare vinylmagnesium chloride in yields of over 80% by using tetrahydrofuran as a solvent, running the reaction at reflux temperature (65^0), and initiating the reaction with a bit of ethyl bromide. It seemed that this procedure would have a chance with cyclopropyl chloride.

One run was made according to Ramsden's procedure (30b), and although some reaction appeared to occur, much magnesium

was left at the end. When butylene oxide was added to the Grignard, again reaction appeared to take place, however, on work-up very poorly defined and unstable products were obtained. In the remaining trials a number of the reported techniques for preparation of "difficult" Grignards (53) were tried, e.g., grinding of the magnesium in a mortar before use, abrasion of it in a Waring Blendor, fresh machining of the magnesium followed by immediate immersion in THF before use, and use of a number of different organic halides as initiators. Simultaneously, R. Cipriani working in this laboratory was having some success in the preparation of cyclopropylmagnesium chloride by using about 20 mole percent of benzyl bromide as an entrainer. From the reaction of the Grignard with ethylene oxide he obtained 42% yield of cyclopropaneethanol based on the cyclopropyl chloride used (4,31).

A number of runs were made using Cipriani's method and it did appear that considerably improved formation of the Grignard reagent was achieved. Subsequent reaction with 2,3-epoxybutane, however, always led to complex mixtures which were unstable to distillation. Considerable carbonyl-containing product was formed as shown by infrared spectra. Possibly some of the epoxide was isomerized to methyl ethyl ketone which in turn reacted with the Grignard to form tertiary alcohol. The latter might be expected to undergo dehydration on heating.

A more thorough study of the literature disclosed that the results obtained should not have been entirely unexpected. Quoting from a paper by Norton and Hass (54) published in 1936, the reactions of epoxyalkanes with Grignard reagents may be summarized as follows.

> Epoxyethane and epoxypropane are known to react by simple splitting of the oxygen to carbon linkage; but the more highly substituted epoxyalkanes rearrange to produce alcohols which can be obtained from the corresponding aldehydes or ketones by use of the same alkylmagnesium halide.

It was demonstrated by these men that with dialkylmagnesium reagent the "normal" product was obtained with epoxides having from two to six carbon atoms. When they used alkylmagnesium halide "normal" products were obtained from ethylene and propylene oxides, and rearranged products from all those of higher molecular weight. All the yields were quite low -- 15 to 35% -- and no accounting was made of the fate of the remaining material. For the specific case of trans-2,3-epoxybutane plus diethylmagnesium Norton and Hass obtained 22% yield of 3-methyl-2-pentanol, a "normal" product.

Cottle and Powell (55) working with 2,3-epoxybutane and the ethyl- and methylmagnesium compounds obtained results which confirmed those of Norton and Hass (54). They also noted the formation of condensation products of 2-butanone.

Since the present work was done the chemistry of the reaction of epoxides with Grignard reagents has been reviewed (56). An older but useful review of this same topic is that of Tiffeneau (57).

Unrewarding as this entire Grignard chemistry might seem with respect to the present goal, one should not lose sight of the possibility that dicyclopropylmagnesium reacting with butylene oxide may constitute a feasible method of synthesis of 3-cyclopropyl-2-butanol. Since the present Grignard attempts were made, cyclopropyl bromide has become available as described earlier. Roberts (39) found the reaction of the bromide with magnesium to be satisfactory.

While this was being written Johnson and Herr (144) reported some research findings which support those cited above. They got about 85% yields of 2-pentanol by reaction of 1,2-butylene oxide with dimethylmagnesium, $CH_3Li(LiBr)$, or with $(CH_3)_2CuLi$. Using methylmagnesium bromide they got only 4% while with the chloride the yield was 45%. With both of the Grignards large amounts of halohydrins were formed.

D. Preparation of 3-Cyclopropyl-2-butanol by Reaction of Cyclopropyllithium with trans-2,3-Epoxybutane

Fourteen experiments towards preparation of 3-cyclopropyl-2-butanol from cyclopropyllithium and trans-2,3-epoxybutane were carried out. In ten of these cyclopropyl chloride was used as a starting material, while the bromide was used for the other four. (As noted elsewhere during the early part of this work cyclopropyl bromide was not available.) Many difficulties were encountered. These were overcome to varying degrees with the net result that

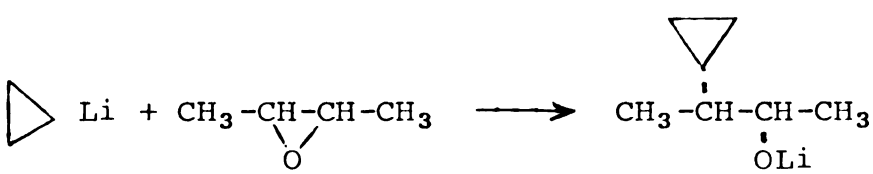
eventually a technique was developed such that about 20% yield -- before purification -- of the desired product could be obtained. Unfortunately, it remained very difficult to purify and at best some uncertainty regarding its purity existed.

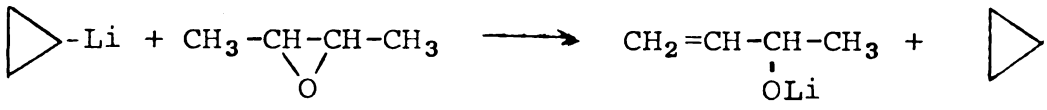
It was found that cyclopropyllithium could be prepared from the chloride in ether medium with considerably better success than in pentane, e.g., 53% yield of tricyclopropylcarbinol was readily obtained by reaction of cyclopropyllithium so prepared, with dicyclopropyl ketone. In pentane it was very difficult to get the lithium to react even when trace amounts of various reactive "starters" were added. In ether no additives were needed. The published information regarding this matter (3,35) was to the effect that the preparation of cyclopropyllithium in ether is unsatisfactory while in pentane about 70% yields can be obtained. In the present work it was found that a very high speed stirrer is of distinct advantage in preparation of the lithium sand. This was recommended by Hart and Sandri (3). In the interval between the present work and the time of this writing two papers (4,58) have appeared which report satisfactory preparation of cyclopropyllithium by reaction of lithium sand with cyclopropyl chloride in ether.

Having achieved success in the preparation of cyclopropyllithium it soon became apparent that the next step -- reaction of it with butylene oxide -- is far from being

as facile as the same reaction with ethylene oxide. Hart and Cipriani (4) obtained 66% yield of cyclopropaneethanol from the latter. In all probability the difference is due to (a) the lower reactivity of butylene oxide to nucleophiles and (b) the steric hindrance of the oxide ring by the methyl groups. It is known (59) that propylene oxide is substantially less reactive to nucleophiles than ethylene oxide and the difference is sufficiently great that it is unlikely to be due mainly to steric effects, although they may well be involved. In the present work considerable unreacted butylene oxide was recovered. When the ether was replaced with dioxane to permit higher reaction temperatures a complex mixture of products was obtained. A greatly prolonged reaction time also did not help. No doubt in both cases the cyclopropyllithium was lost to side reactions.

The only major by-product which could be isolated and identified was 3-buten-2-ol which was obtained in about 40% yield. It is no doubt formed as the result of an E2 reaction competing with the desired S_N2 reaction. Both the steric effects and the statistical bias of six available hydrogen atoms would favor the E2 over the S_N2 reaction. The reactions are:





Some dicyclopropyl was formed. In one run its yield was estimated at about 10%. This material has been reported by Slabey to be one of the products obtained from the reaction of cyclopropyl chloride with lithium (35). More recently the preparation of dicyclopropyl by other methods along with property information has been reported (101,103, 104).

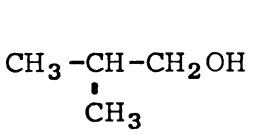
In all of the experiments the total material recovery was very low. It seems now that this was most likely due to the loss of unreacted butylene oxide during ether removal prior to fractional distillation of the product. In later runs when gas-liquid partition chromatography (glpc) was being used to greater benefit, it was found that as much as 45% of the butylene oxide was coming through unreacted. Halide ion conversions were quite consistently of the order of 90% after the best procedure for preparation of the cyclopropyllithium was worked out.

Even with the interferences thus far described one might reasonably expect to obtain the required quantity of the desired product by this route. However, the difficulties did not end here. It was always difficult to perform a well-behaved fractional distillation of the products. Some decomposition always occurred which gave rise to foaming and residues. A quick flash distillation at the start

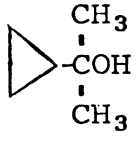
helped somewhat, but did not eliminate the problem. Some analytical research with a number of different glpc substrates showed indeed that the material was not pure.

In one experiment a substantial amount of 2,3-butylene chlorohydrin was found in the product. The crude material in ether solution had been washed with dilute HCl to remove the last of the alkali. Obviously some unreacted butylene oxide had reacted with the HCl. Most likely some 2,3-butylene glycol was also formed. Thereafter HCl was avoided.

Several of the more abundant impurities in the crude product were trapped from the effluent of a glpc column and identified by infrared and nuclear magnetic resonance spectroscopy (61). These were the following:



I



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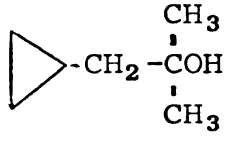
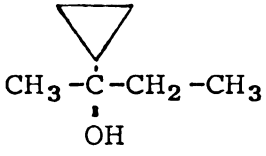
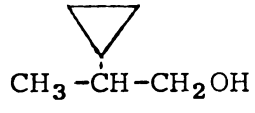


III



IV



V

By estimating on the basis of glpc peak area, the total amount of the compounds I to V formed was of the order of 1/3 of that of 3-cyclopropyl-2-butanol which was produced. Above structures I and II were identified as pure materials

representing two glpc peaks. The remaining three were suggested as components of a single peak.

Compound IV could be formed by reaction of cyclopropyllithium with methyl ethyl ketone, which might have been formed by isomerization of the oxide. One of the difficulties all the way through was that carbonyl compound showed up in practically everything and was difficult to completely eliminate. The other four structures can only be rationalized by assuming that the starting butylene oxide contained isobutylene oxide and propylene oxide as impurities. The former of these was ultimately found to be present in the 2,3-oxide in amounts no greater than 2%. It was quite difficult to resolve by glpc from the 2,3-oxide. No propylene oxide was ever found in the butylene oxide and it was shown that 1/4% could be readily detected.

Evidence was now at hand for the following side reactions: isomerization to olefinic alcohol, isomerization to ketone or aldehyde, reduction of ketone, aldehyde, or oxide to saturated alcohol. With carbonyl compounds present it is not hard to imagine that some aldol type condensation and dehydration might occur. This latter, along with the tertiary alcohols, could rationalize the instability to distillation as evidenced by a wet distillate.

In spite of the success achieved in preparation of cyclopropyllithium from cyclopropyl chloride, significantly better yeilds of 3-cyclopropyl-2-butanol were obtained when the bromide was used. The best yield obtained from the

chloride was 12%, while from cyclopropyllithium prepared from cyclopropyl bromide about a 20% yield was realized, as shown by experiments 3 and 4 in the Experimental section. In experiment 3 the ether solution of the reaction product was washed with dilute HCl which caused butylene chlorohydrin formation from the unreacted butylene oxide. This by-product was very difficult to remove. A plain water wash to remove alkali was used in experiment 4, which is representative of the best procedure achieved for the preparation of 3-cyclopropyl-2-butanol.

In the light of some research results reported in recent literature the present experience with the behavior of cyclopropyllithium towards butylene oxide does not appear inconsistent. Lithium bromide has been found to catalyze the rearrangement of epoxides to carbonyl compounds (134) in benzene solution. Lithium diethylamide was reacted with 2-epoxypentane to give a high yield of 1-penten-3-ol plus some 3-pentanone (135) and a like reaction with 4-epoxyoctane has been reported (136). Crandall and co-workers have studied the reaction of lithium diethylamide with a number of more or less hindered epoxides (137) and report ketones, olefins, and both saturated and olefinic alcohols among the products. 1,2-Epoxybutane and 1,2-epoxycyclopentane gave 37% and 41% yields of corresponding butyl-substituted olefin when treated with n-butyl- and t-butyllithium respectively. Yields of about 30% of 3-alkylbutyrolactones were obtained by reaction of alkyllithiums with allyl alcohol (138).

To date the preparation of 3-cyclopropyl-2-butanol has not been reported in the literature. Two syntheses of rather closely related compounds have been reported, which offer promise of utility for the synthesis of 3-cyclopropyl-2-butanol. Brown and Kim (130) obtained 3-phenyl-2-butanol by reaction of a phenyl Grignard reagent with 2-butanone, dehydration of the resulting tertiary alcohol to the olefin, followed by hydroboration-oxidation of the olefin. Yields were not given. Hanack and Ensslin (6a) obtained a 96% yield of 2-cyclopropylpropene by reaction of cyclopropyl methyl ketone with methyltriphenylphosphonium bromide and potassium t-butoxide in dimethylsulfoxide. By hydroboration-oxidation of the olefin the primary alcohol was obtained in a yield of about 80%.

At just about the time this was ready to go to press Rhodes (147) reported the acetolysis of erythro- and threo-3-cyclopropyl-2-butyl tosylates as noted under Review of the Literature C. The report is in the form of an abstract of a paper to be presented at a meeting and no preparatory information is given.

E. Preparation of Tosylates

To gain experience, tosylate preparation from several readily available alcohols -- 2-octanol, 2,4-dimethyl-3-pentanol, and 2-butanol -- was undertaken according to the procedure of Cram (18). Before the work with these had progressed very far, work with 3-cyclopropyl-2-butanol was

also begun and was showing indications of success. The work with the first two above mentioned alcohols was dropped. The preparation of 2-butyl tosylate was continued for two reasons. Firstly, it was planned to compare the solvolysis rate of its tosylate with that of 3-cyclopropyl-2-butanol, and, secondly, others (63,66) had not been able to obtain this ester in crystalline form and there existed the temptation to try where others have failed. Purification of methyl and n-butyl tosylates by distillation is reported (64,66) as being feasible. Purification of 2-butyl tosylate by distillation at 3 microns Hg (bp 59-61°) was reported by Roberts (63).

For the present work the preparative procedures used were those of Tipson (67) and Cram (18). (Both of these men carried out the reaction in pyridine medium at low temperature.) For the most part this area of the work proceeded quite satisfactorily. Yields of 60-80% were obtained. Regardless of the number of crystallizations, the melting point of the 3-cyclopropyl-2-butyl tosylate was never as sharp as would be desirable to establish confidence of purity. This, along with the fact that during the crystallizations there often was difficulty in getting the material completely into solution.

Attempted purification of the 2-butyl tosylate both by crystallization and by distillation was unsuccessful and it was used in the crude form. Stoichiometric solvolysis data indicated that it was reasonably pure.

At about the time when most of the work reported in this thesis had been completed, a publication appeared (68) in which it is stated that the tosylation rates are substantially different for primary, secondary, and tertiary alcohols, with the last mentioned being the slowest. It was further claimed that within each class the rates were very nearly the same. Many primary alcohols were completely reacted in one hour. The secondary alcohols, isopropanol and 2-butanol, required 3 hours for 83% reaction. However, 2-octanol was 94.5% reacted in one hour. Tertiary alcohols did not react under the conditions used, which were as follows: the alcohol was mixed with about twice the theoretically required amount of a 5% solution of p-toluenesulfonyl chloride in pyridine. After a chosen length of time the mixture was hydrolyzed with aqueous pyridine and titrated with standard base to determine the extent of reaction.

It appeared from this publication that one might determine the rate of tosylation for any alcohol of interest and thereby become better able to prepare a desired tosylate ester in good yields. A rate determination could also suggest something about the structure of an unknown alcohol, for example, the by-products which were obtained in the present work from the reaction of cyclopropyllithium with trans-2,3-epoxybutane.

A few tosylation rate experiments were run using 2-propanol and 2-ethyl-1-hexanol and figures of about the same

order as reported in the above cited publication, were obtained. The data for 2-propanol are shown in Figure 1.

Very recently a new method for preparation of tosylates was reported. The alcohol is reacted with p-toluenesulfenyl chloride and the resulting sulfinate is oxidized with m-chloroperbenzoic acid to the desired sulfonate ester (139). This method is claimed to be especially suitable for the preparation of p-toluenesulfonates of labile alcohols in that dehydration, rearrangement, etc. are avoided.

F. Formolysis of 3-Cyclopropyl-2-butyl Tosylate

The tosylate concentration chosen for the rate of formolysis studies was 0.08 molar to match that used by Winstein (69a), who found the rate of formolysis of 2-butyl brosylate at 25.0^0 to be $1.4\text{-}1.5 \times 10^{-4}$ per second. On the basis of past work by a number of people, Cram (18) divided by three to convert the rate for the brosylate to that for the tosylate, which yields a "literature" value for the rate of formolysis of 2-butyl tosylate at 25.0^0 of $0.47\text{-}0.50 \times 10^{-4}$ per second. In the present work a first experiment at 27^0 gave a value of 0.75×10^{-4}

When rate studies were undertaken with the cyclopropyl compound the reaction mixture took on a deep purple color which made it impossible to carry out the normal indicator titrations which are needed to determine the extent of reaction at chosen time intervals. Attention was turned to the use of a pH meter and some exploratory experiments were

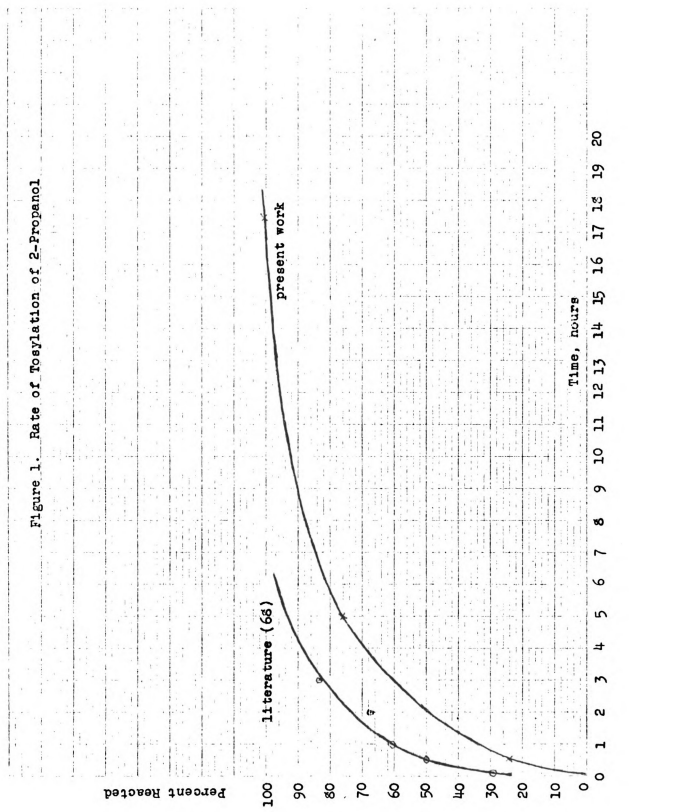


Figure 1. Rate of Tosylation of 2-Propanol
Percent Reacted
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Time, hours
literature (68)
present work

run to optimize the conditions for potentiometric titration. When standard perchloric acid was titrated against standard sodium acetate, all in acetic acid, a very good endpoint was observed. When the perchloric acid was replaced with p-toluenesulfonic acid the endpoint was somewhat less sharp, and when formic acid was added to the mixture it was still poorer, perhaps just barely acceptable (see Figure 2). At this point it was decided to investigate the nature of the solvolysis products. At about this time an item in the literature (70) came to our attention, in which it is stated that propionic acid is superior to acetic as a solvent for this type of titration. This information was listed for reference in case the rate studies were resumed.

The results of the examination of the solvolysis products are described in detail in the Experimental, Part H. The products were sufficiently complex that only a start towards isolation and identification was made.

The initial work was done on the solvolysis products as obtained. Subsequently some solvolysis product was reduced with lithium aluminum hydride and the reduction products were subjected to examination. Most of the information was obtained by a study of the reduction products. It appeared that about 10% of the formolysis product was olefinic hydrocarbon and that the major portion was a formate ester. Investigation of the reduction product showed some 8 to 12 components to be present. No 3-cyclopropyl-2-butanol

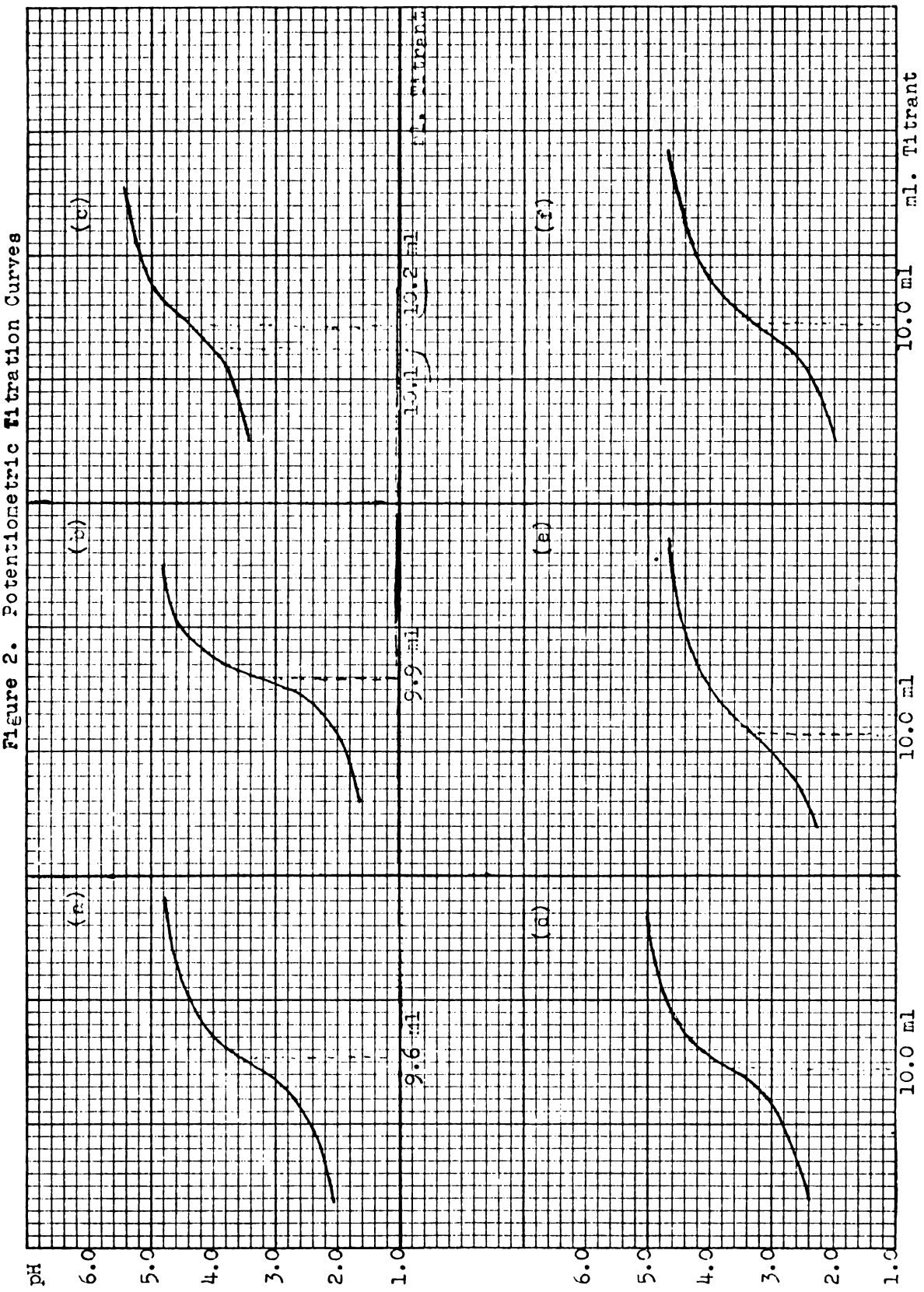


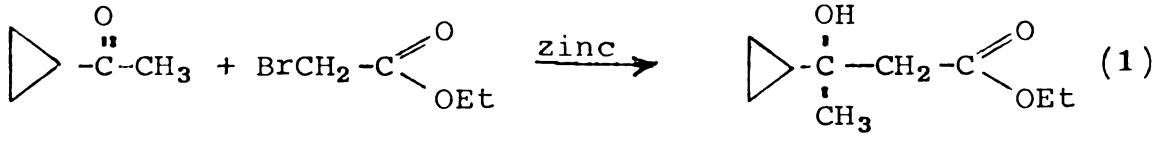
Figure 2. Potentiometric Titration Curves

could be detected. There may have been some 2-cyclopropyl-2-butanol. Only a few of the glpc peaks were large enough for trapping with existing apparatus and for these the ir spectra (111) did not correspond to any of the standards available. Dimethylcyclopentanol and 2-(2-hydroxyethyl)-tetrahydrofuran were suggested.

The above described results were obtained by micro techniques involving gas liquid partition chromatography and infrared spectroscopy. Preparative scale glpc columns were not yet readily available, but fractions were collected from analytical columns using repeated injection. A convenient micro ir cell to fit a Perkin-Elmer Infra-Cord became available about this time and this was of considerable help. Even though these tools increased capabilities considerably, when it was found that the number of products was so very large -- each time glpc temperature was increased more peaks showed up -- and that likely some of the components were due to impurities in the starting material, it was decided that this course should not be pursued. Nmr spectroscopy would be required for the materials for which the ir spectrum does not match that of any of the standards, and not enough material could be trapped in most cases for nmr examination.

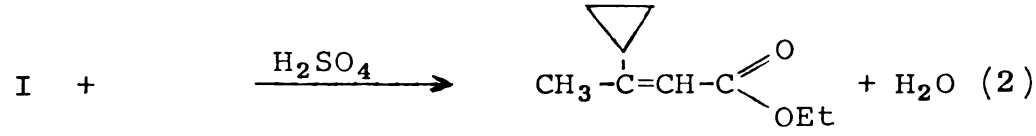
G. Attempted Preparation of 3-Cyclopropyl-2-butanol by a Multi-step Route Beginning with a Reformatsky Condensation of Ethyl 2-Bromoacetate and Cyclopropyl Methyl Ketone

At this time a few unsuccessful tries had been made at preparation of cyclopropyllithium and cyclopropylmagnesium chloride. The following sequence of reactions was devised as an alternative procedure for the synthesis of 3-cyclopropyl-2-butanol. Although the number of steps required is large, most of them represent well established reactions of quite general applicability. Also for a fair number of them the yields can be expected to be nearly quantitative.



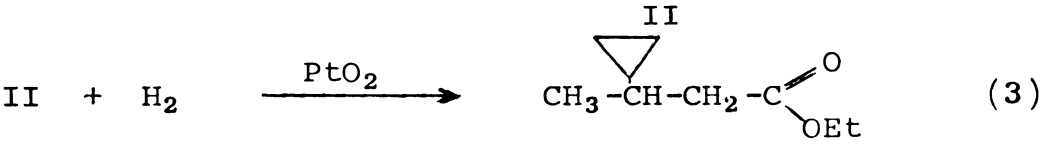
(1)

I



(2)

II

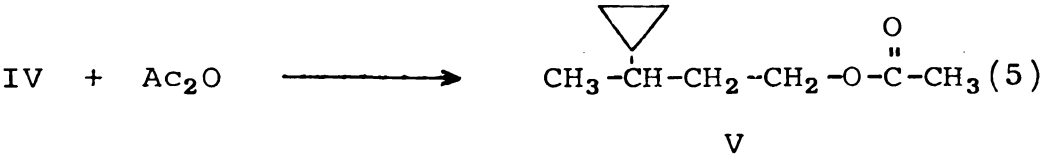


(3)

III

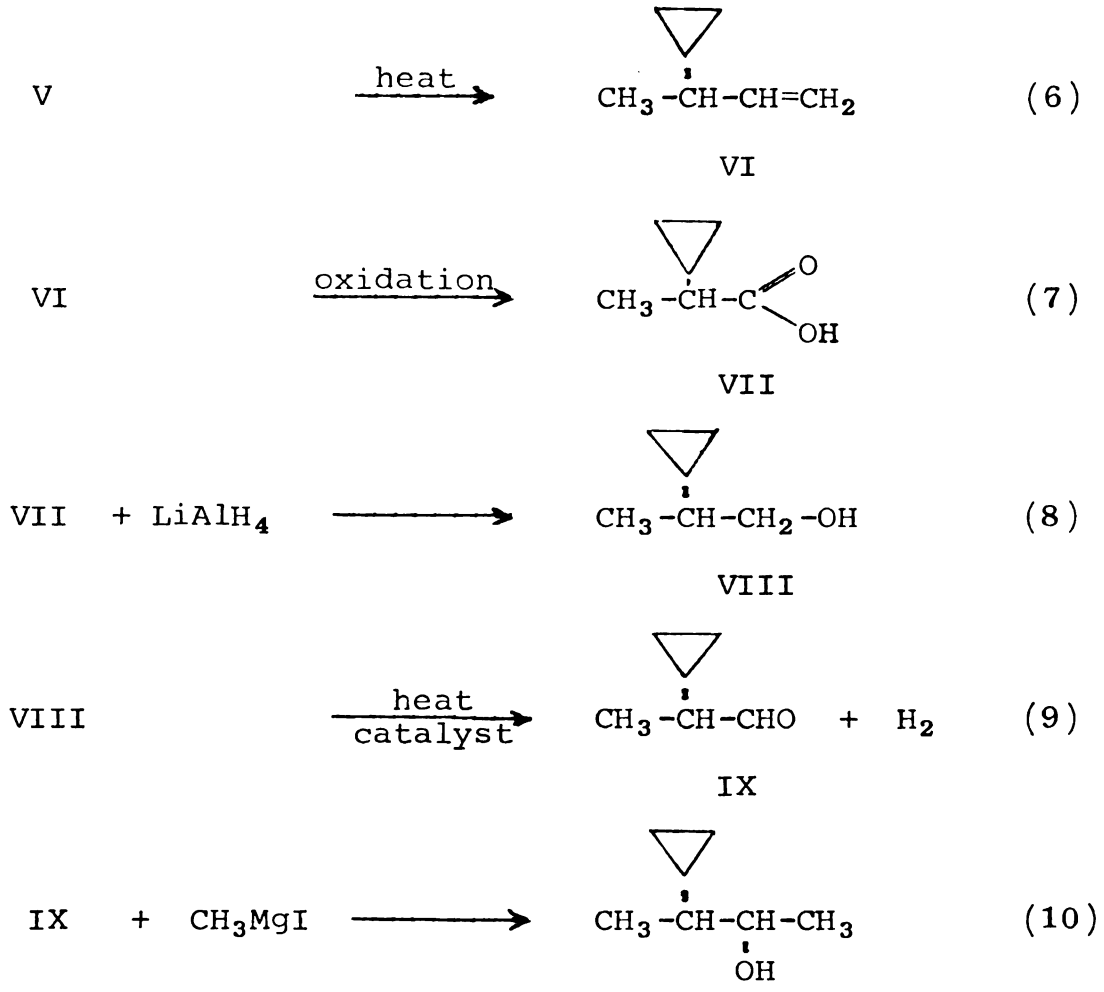
(4)

IV



(5)

V



3-cyclopropyl-2-butanol

In this laboratory a number of these reactions had been run using closely related compounds (32,44). Reaction of dicyclopropyl ketone with ethyl bromoacetate gave 58% yield of the expected hydroxy ester. The latter was dehydrated to olefinic ester in 87% yield by addition of a few drops of sulfuric acid followed by vacuum distillation. The unsaturated ester was reduced with lithium aluminum hydride. The resulting 3,3-dicyclopropylallyl alcohol could not be distilled due to excessive polymerization, but based on the weight of crude product it was estimated to have been

obtained in about 86% yield. The crude alcohol was hydrogenated using PtO_2 to 3,3-dicyclopropylpropanol in essentially quantitative yield.

For the present work methyl cyclopropyl ketone was reacted with ethyl bromoacetate and zinc dust (32,72). The reaction appeared to go very well. Purification of the hydroxyester was not attempted. According to the weight of the crude product a yield of about 75% was obtained.

After some exploratory attempts with iodine (73), sulfuric acid (32), and phosphorous oxychloride (74), dehydration of the hydroxyester was accomplished with either of the latter two reagents. The best yield of olefinic ester II obtained was 47.5% based on cyclopropyl methyl ketone. Rather sizeable distillation residues were produced. Possibly the unsaturated ester was polymerizing, or the cyclopropyl ring may have undergone some cleavage followed by polymerization of allylic material produced in this manner.

Hydrogenation of the double bond of II was found to be somewhat erratic. A first sample took the hydrogen very rapidly and the absorption ceased rather sharply when the calculated pressure drop had occurred. In the next run the material would not absorb hydrogen nearly so well. More catalyst (PtO_2) was added, the pressure was increased, and eventually a change to Raney nickel was made. Ultimately only a trace of unsaturation remained. A third run was made with PtO_2 and required considerable time at 60 lbs per sq in pressure. The saturated ester III had an ir spectrum

consistent with its structure. It showed some drift in refractive index on successive distillation fractions and was somewhat high in hydrogen content.

Calcd. for $C_9H_{16}O_2$: C, 69.2; H, 10.3.

Found: C, 69.8; H, 11.5 (100).

We might insert here that at the time this was done glpc and nmr were not yet available for routine use.

Reduction of saturated ester III to the alcohol IV with $LiAlH_4$ proceeded quite well. On two runs 61% and 72.5% yields were obtained. A small amount of a carbonyl compound (two ir peaks) remained. The refractive index of the alcohol showed a drift on successive distillation fractions. It is most likely that troubles which arose in the previous steps were still present.

At this time R. Cipriani (4), working in this group on a related project, was having some success at preparation of cyclopropylmagnesium chloride. The present line of work was discontinued in favor of renewed attempts at preparation of 3-cyclopropyl-2-butanol from trans-2,3-epoxybutane and the cyclopropyl Grignard reagent.

Within the scope of the work done there is no reason to believe that 3-cyclopropyl-2-butanol cannot be prepared feasibly by this series of reactions. One must expect to get a mixture of threo and erythro isomers which would pose an additional separation problem. In view of the large number of steps required the overall yield would naturally be low,

e.g., if yield of individual steps were to average 80%, the overall yield for the ten steps would be only 10.8%.

To the best of the writer's knowledge the compounds prepared are all new, although insufficiently purified and characterized. Those physical properties which were obtained are listed below. The ir spectra of these compounds are included in Experimental, I.

Ethyl 3-cyclopropyl-3-hydroxybutyrate, not purified

Ethyl 3-cyclopropylcrotonate, bp 100.5°(20mm), n^{25}_{D} 1.4780

Ethyl 3-cyclopropylbutyrate, bp 78°(20mm) n^{25}_{D} 1.4200

3-Cyclopropyl-1-butanol, bp 166°(atm.) n^{25}_{D} 1.4350

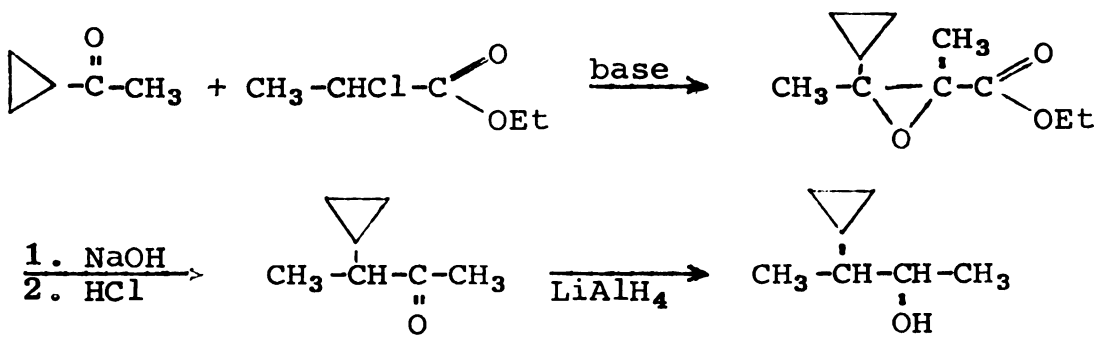
H. Attempted Preparation of 3-Cyclopropyl-2-butanone by Darzens Condensation of Ethyl 2-Chloropropionate with Cyclopropyl Methyl Ketone

At this time in the course of the research the preparation of 3-cyclopropyl-2-butanol had been attempted by three different chemical routes, namely, (a) the reaction of cyclopropyllithium with trans-2,3-epoxybutane, (b) the reaction of cyclopropylmagnesium chloride with the same and, (c) a sequence of ten reactions starting with a Reformatsky condensation on methyl cyclopropyl ketone. During this time a watch was maintained for other possible methods of preparing the desired compound. Cram prepared 3-phenyl-2-butanol by a reaction sequence which started with a Darzens condensation of ethyl chloroacetate with acetophenone (2). The

glycidic ester was hydrolyzed and decarboxylated to yield 2-phenylpropionaldehyde, which was then reacted with methyl Grignard reagent to provide the 3-phenyl-2-butanol. A mixture of <u>erythro</u> and <u>threo</u> racemates was obtained.

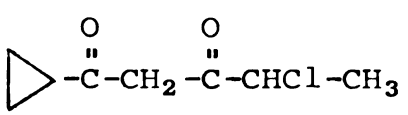
The existing reviews covering the Darzens condensation (75,76,77, 143) and those original works which seemed most pertinent were studied. And of course the current literature was continuously noted for anything of interest to the entire research project. At that time (1958) no record was found in the literature of any Darzens condensation involving a cyclopropyl ketone. As far as this writer is aware, there is still none. It does appear that the reaction goes best with aromatic carbonyl compounds, <u>e.g.</u>, benzaldehyde and acetophenone. However, one can easily find a half dozen examples of successful reactions with acetone and butanone, <u>i.e.</u>, yields from 45% to 60% (75).

Ethyl 2-chloropropionate was available (5). Use of it rather than the chloroacetate would yield the ketone which on reduction with $LiAlH_4$ would provide the desired 3-cyclopropyl-2-butanol and save going through the Grignard reaction as did Cram.

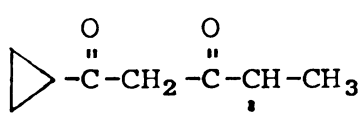


Two runs were made using the procedure (sodium methoxide) of Newman and Magerlein (75) for the reaction of cyclohexanone with methyl 2-chloropropionate (85% yield). The main product, which was obtained in about 60% yield, was not a glycidic ester, but a 1,3-dicarbonyl compound as evidenced by a very broad and intense infrared carbonyl stretch absorption at 1600 cm^{-1} and a sharp one at 1710 cm^{-1} (78). Characteristic of glycidic esters are a doublet carbonyl stretch absorption at 1700 to 1800 cm^{-1} and peaks at 877 and 893 cm^{-1} (78,79). These features were not present in the ir spectrum of the product at hand. The spectrum did show evidence of methoxy and of chlorine. Also indicative of chlorine content was a density of 1.106 at 22^0, and indeed, on analysis the product was found to contain 11.1% Cl.

The evidence is very strong that a reverse condensation occurred, i.e., the ketone anion, formed by removal of a methyl proton by the methoxide ion, attacked the carbonyl carbon atom of the ester to yield 1-cyclopropyl-4-chloro-1,3-pentanedione (I). It appears that there was considerable displacement of chlorine by methoxyl to give 1-cyclopropyl-4-methoxy-1,3-pentanedione (II). A calculation on the basis of the chlorine content would indicate 55% and 45% of I and II respectively.



I



II

No mention of either of these compounds could be found in the chemical literature, including Beilstein and Chemical Abstracts. The parent compound, 1-cyclopropyl-1,3-pentanedione has been reported by Cannon and Whidden (140) who prepared it by condensation of propionic anhydride with cyclopropyl methyl ketone using BF_3 as catalyst. The next lower homolog was prepared by condensation of acetic anhydride with the same ketone by both acidic (BF_3) and basic ($NaNH_2$) catalysis. C. and W.'s methods are illustrative of general preparative procedures for 1,3-diketones. Catalysis by alkali alkoxides is also used (141).

Morris and Young (79) reported physical constants of a large number of glycidic esters. For a ten carbon atom aliphatic ester they reported: $\underline{n}^{20}\underline{D}$ 1.4289, $\underline{d}^{20}_4$ 0.9597, bp 76° (3mm). For the material here prepared the corresponding data were: $\underline{n}^{20}\underline{D}$ 1.5118, $\underline{d}^{22}$ 1.106, bp 99° (7mm).

The use of 60% excess of ethyl 2-chloropropionate made no difference in the product except that it now contained some of this ester unchanged.

A condensation was carried out using 2-heptanone and ethyl 2-chloropropionate. A considerable amount of 1,3-dicarbonyl compound was again obtained. However, the ir spectrum did show some evidence of glycidic ester.

No further work was done on this procedure for preparation of 3-cyclopropyl-2-butanol.

It is interesting to speculate as to why the reverse condensation occurred in this case, or conversely, why it

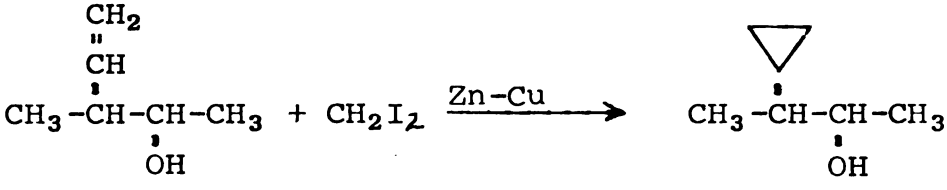
does not occur more frequently in other cases. It has been mentioned very little in the literature. Newman and Magerlein (75) point out that over the years very little attention has been given the by-products of the Darzens condensation, but that in a few cases chlorine-containing by-products have been reported. Some time after this portion of the present work was discontinued an example of an inverse Darzens condensation was reported by Barnes and co-workers (80). Reaction of 1-indanone with ethyl chloroacetate and sodium ethoxide resulted in a compound having the chloroacetyl group at the two position of the indanone nucleus. They cite an earlier paper by Bone and Cort (81) which reported a normal Darzens product from these two reactants when potassium tert-butoxide was used as the condensing agent. Johnson (82) and Morris (83) indicate a preference for potassium tert-butoxide. If this work should be resumed at some time this latter base should certainly be given first choice.

Another variant of the Darzens reaction which looks of some interest at its limited state of investigation is the use of 2-chloronitriles in lieu of chloroesters. Stork and co-workers (84) prepared a large number of glycidonitriles by reacting 2-chloronitriles with carbonyl compounds in the presence of potassium tert-butoxide. Yields were as good or better than reported in the literature for the same products from the chloroesters. The expected Darzens product from methyl isopropyl ketone and 2-chloropropionitrile was obtained in 67% yield.

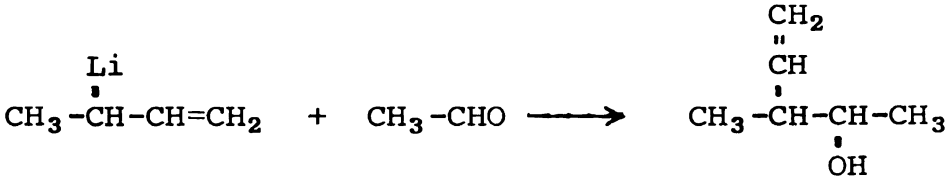
I. Attempted Preparation of Cyclopropylmethyl Acetate

At this time several of the possible routes toward preparation of 3-cyclopropyl-2-butanol had resulted in failure. Simmons and Smith (33) reported a new method for synthesis of cyclopropyl compounds, namely, reaction of methylene iodide with an olefin in the presence of zinc-copper couple.

Some literature study was undertaken to determine how an olefinic substrate might be prepared, which, when converted to the corresponding cyclopropyl derivative by methylene addition across the double bond would yield 3-cyclopropyl-2-butanol. The substrate required would be 3-vinyl-2-butanol or possibly a functional derivative thereof. For example, if for some reason it were more advantageous to perform the reaction on a non-hydroxylic compound one might choose a ketone or ester having the same carbon skeleton. The following reaction illustrates the formation of the cyclopropyl ring:



The most obvious and direct path to the vinylbutanol which came to mind was



The vinylbutanol would need to be esterified which might entail some risk of rearrangement or polymerization. At that point in time the available information was to the effect that the Simmons-Smith methylene addition reaction would not work in media which contained active hydrogen.

It seemed appropriate to attempt this new reaction on something which was readily available before spending the time needed to prepare 3-vinyl-2-butanol. One run was made with allyl acetate. When the product was distilled about half of it ended up as still residue, some allyl acetate was recovered, and the remainder of the distillate appeared to be a complex mixture. No further experimental work on this preparative method was done. It is perhaps in order to note here that the procedure had been reported only as a preliminary communication to the editor and only a minimum of information was available.

Since this work was done Simmons and Smith have reported their findings in more complete form (85). It was revealed now that best results are obtained when about five mole percent -- based on olefin -- of elemental iodine is used along with the methyl iodide. Even so yields obtained from olefinic esters were 9% and 31%. From reaction on olefinic hydrocarbons yields were 27% to 70%. Koch (86) reported successful use of this reaction with a large number of olefinic hydrocarbons but did not say anything about yields. In 1961 Winstein (87) reported the preparation in 75% yield of 3-bicyclo [3.1.0] hexanol from Δ^3-cyclopentenol

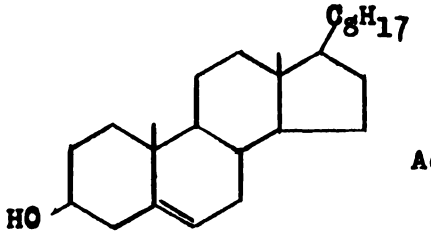
by the Simmons-Smith methylene addition, the first reported case of addition to a compound containing active hydrogen. An improved modification for the preparation of zinc-copper couple was reported by Shank and Shechter (94), and more recently a brief communication (88) reports the use of zinc alkyl in lieu of zinc-copper couple as an improvement.

J. Preparation of Cholesterol Derivatives

Sneen (34) reported rates of solvolysis in 90% aqueous dioxane at 50^0 for the tosylates of cholestanol, cholesterol, and several derivatives of the latter. He found relative rates as follows:

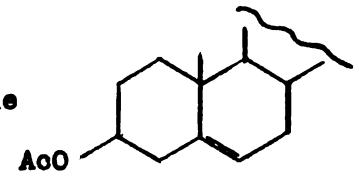
Tosylate Ester	Relative Rate
Cholestanyl	1
6-Phenylcholesteryl	37.6
Cholesteryl	118
6-Methylcholesteryl	8840

Since we were already engaged in the field of solvolysis of cyclopropyl derivatives it appeared of interest to prepare some 6-cyclopropylcholesteryl tosylate and see where its rate of solvolysis falls in the above pattern. Work was undertaken following the same preparative route as that used by Sneen (34). It is shown below. (The final product shown is saponified to the alcohol and then converted to the tosylate by traditional methods.)



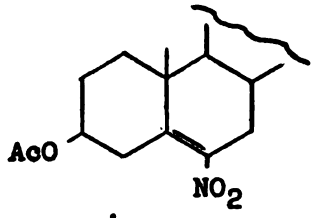
Cholesterol

Acetic Anhydride



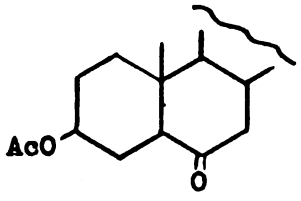
Cholesteryl Acetate

HNO_3
$NaNO_2$



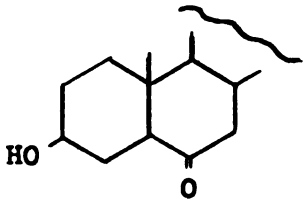
6-Nitrocholesteryl Acetate

Zn + Acetic Acid



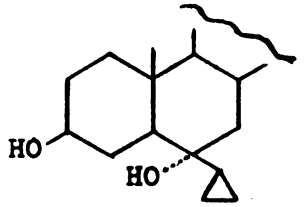
Cholestan-3-beta-ol-6-one Acetate

KOH in C_2H_5OH



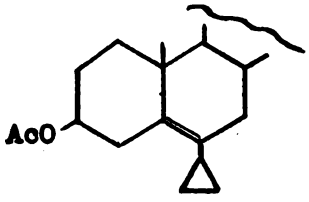
Cholestan-3-beta-ol-6-one

Cyclopropyllithium



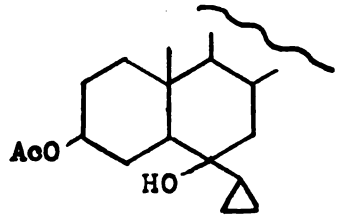
6-beta-Cyclopropylcholestan-3-beta-6-alpha-diol

Ac_2O



6-Cyclopropylcholesteryl Acetate

p-$CH_3C_6H_4O_2SOH$



6-beta-Cyclopropylcholestan-3-beta-6-alpha-diol Monoacetate

Cholesteryl acetate was prepared in 93% yield by acetylation (89) of cholesterol with acetic anhydride. The acetate was converted to the 6-nitro derivative by reaction (90) with concentrated nitric acid and sodium nitrite, following which the nitro compound was reduced with zinc dust and acetic acid to provide cholestan-3-beta-ol-6-one acetate in about 65% yield (90b).

Sneen used the acetate of the keto compound for most of the Grignard reactions. Theoretically the acetate requires three moles of Grignard reagent per mole and Sneen actually used six. For the present work it seemed best to first convert the acetate to the alcohol which should require only two moles of Grignard (or lithium compound) per mole, in view of the difficulty of getting the cyclopropyllithium.

Cholestan-3-beta-ol-6-one was prepared in about 75% yield by saponification of the acetate with ethanolic potassium hydroxide (91). All the intermediates up to this point were prepared and purified quite readily. In the case of this saponification product it was difficult to obtain a material having a sharp melting point. Values of 142^0 to 151^0 are reported in the literature (90b,91,92,93). The highest value was obtained by Fieser (93) on chromatographed material. To anyone working with these materials today thin layer chromatography would be of considerable help.

The ketone alcohol was reacted with cyclopropyllithium to give 6-beta-cyclopropylcholestan-3-beta-6-alpha-diol in

about 62% yield. On the basis of two experiments six moles of lithium compound per mole of ketone gave considerably better results than were obtained with 4 moles of lithium compound. This cholesterol derivative has not been previously reported in the literature. The purest sample prepared melted at 142.5-143.0°. Infrared absorption and elemental analysis were in agreement with the expected structure.

The 3-beta monoacetate of this diol was prepared in very nearly quantitative yield (34) by reaction with acetic anhydride in pyridine (mp 182°). This also is a new compound. Dehydration of this diol monoacetate to 6-cyclopropyl-cholesteryl acetate was accomplished by treatment with p-toluenesulfonic acid (34). Crystallization of the dehydrated product was very difficult and a satisfactory product could not be obtained. Some of the material was saponified with ethanolic KOH and crystallization of the alcohol was attempted. The results were no better.

At this point this project was tabled.

IV. EXPERIMENTAL PROCEDURES AND DATA

A. Preparation of Cyclopropyl Chloride

The procedure followed was the same as that used by Roberts (29) except that continuous recycle of the excess cyclopropane was not included. Instead the excess cyclopropane was recovered in each run and returned to the gas cylinder for use in later runs.

The continuous chlorination reactor was a 250 cm length of 7 mm i.d. Pyrex glass tubing in the shape of a planar grid. It was illuminated with two Ken-Rad RS 275 watt sun lamps placed at 1/4 to 1/2 inch from the reactor tubing.

The chlorine and cyclopropane were both Matheson Company products. The chlorine was passed into the reactor at a rate of 0.033 moles per minute -- a pressure differential of 70 mm on the flowmeter --, while the cyclopropane was fed at 0.100 moles per minute equivalent to a pressure differential of 110 mm on the flowmeter. A water bath at ambient temperature around the cyclopropane cylinder helped to keep the gas flow at a constant rate. The gases were mixed by means of a simple tee connecter at the entrance to the reactor tube. The lamps were turned on a few minutes before starting the gas flows. The cyclopropane was always started before the chlorine, and at the finish of a run,

shut off after the chlorine, in order to prevent carbonization by the presence of an excess of chlorine gas in the reactor.

The effluent gas from the reactor was passed in series through a water scrubbing tower, a 10% aqueous sodium hydroxide scrubbing tower, and through a calcium chloride tube into a one-liter distillation flask (receiver 1). Due to the rather high moisture content of the product gas at this point considerable trouble was encountered with plugging of the calcium chloride tube. This was corrected by use of an extra large tube -- 38 mm diam x 250 mm length --, a very coarse particle size of calcium chloride, and by placing the tube in a horizontal position. Assurance that the product stream was well dried eliminated serious freeze-up troubles in the downstream section of the train. The effluent liquors from both scrubbing towers were accompanied by some insoluble higher chlorinated cyclopropanes, which were separated and saved.

Receiver 1 was surrounded by a dry ice-isopropanol bath at -78^{0}. The reactor product coming from the calcium chloride tube entered this receiver through a tube which extended about two inches beyond the wall of the flask in a downward direction. The flask was fitted with a two feet long by 3/8 inch diameter vacuum-jacketed fractionating column (packed with glass helices) and a distillation head designed for dry ice mixtures. Receiver 2, another one-liter distillation flask, was connected to receive forward

product from the distillation column, and downstream from it another cold trap was connected.

The chlorinator was operated until the first receiving flask was almost full. It was then shut down and the receiver inlet tube was replaced by a thermometer. The cold bath was transferred to receiver 2 and a mantle was placed under receiver 1. While maintaining some reflux to the column the unreacted cyclopropane was distilled over to receiver 2. The distillation was stopped when the frost had disappeared from the distilling flask and it began to feel just warm to the hand.

The recovered cyclopropane from receiver 2 was transferred back to the cylinder for re-use. It is very important to be sure that one does not overfill a cylinder with liquid. Liquid expansion can result in extremely high pressure build-up and possible rupture of a cylinder. It would no doubt be best to avoid returning anything to a cylinder by use of a recycle system such as that of Roberts (29) or by some other means which assures maximum safety.

In the last two chlorinations which were run, receiver 1 was held at -30^{0} during the chlorination thus permitting the unreacted cyclopropane to distill continuously into receiver 2. In this manner about twice the amount of cyclopropyl chloride could be made in one continuous run of about one day's duration.

The crude product which remained in receiver 1 after distillation of the cyclopropane was dried with calcium

chloride and distilled through a 22 inch helices-packed column. About 50 ml of CCl_4 was used as a chaser to minimize hold-up loss. A fraction of good quality cyclopropyl chloride (bp 42-43°) was readily obtained. In one instance a 15 inch long Vigreux column was used. Now the overhead product had a bp 41-46°, showing that a better column is needed. The distillations were always started very slowly in order to remove the remaining cyclopropane without too much loss of product.

The data for the five chlorinations are as follows:

Chlorination		Cyclopropane, g			Product			
					Crude		Distilled	
No.	Time hrs	In	Out	Used	Grams	% Yield	Grams	% Yield
1	3.25	675	390	285	182	26.0	212	28.5
2	3.30	688	565	123	184	82.0		
3	3.40	700			197		129	
4	6.50	1240	910	330	390	63.0	239	38.0
5	6.50			547	503	50.0	326	33.0

The amounts of distillation residue in the same order were 15.0, 52.5, 104.0, and 144.0 g.

Physical constants for cyclopropyl chloride as reported in the literature (35) are: bp 43.43° (760 mm), $\underline{n}^{25}\underline{D}$ 1.4079 and $\underline{d}^{25}$ 0.9899. Found for the above prepared material:

Run No.	1 & 2	3	4	5
$\underline{n}^{25}\underline{D}$	1.4078	1.4082	1.4086	
bp (atm.)	42.8°	42.8°	41 - 46°	42 - 43°

The material of run 4 was purified by fractional distillation through the Vigreux column as mentioned above. An ir spectrum (IR-53) of the product of run 4 was in agreement with that reported by Roberts (39), except for a very small peak at 1132 cm^{-1}.* There was no indication of any unsaturation. The product from run 5 was examined by glpc (7 ft 25% Oronite NI-W on Chromosorb W, 40°) and showed less than 0.1% impurities (GLC-140).

B. Preparation of Cyclopropanecarboxylic Acid (113)

A 3-liter three-necked flask was fitted with three water-cooled reflux condensers. Neither agitator nor thermometer was used. With 233 g (5.82 mol) of powdered sodium hydroxide already in the flask, 115 g (1.55 mol) of 4-bromobutyronitrile were added. The mixture was smoothed out by shaking and placed on the steam bath. After 18 min had elapsed vigorous reaction began. Heating was continued for one hr longer. Five hundred milliliters of water were added in small portions with shaking to provide mixing. The flask and contents were now heated 2.5 hr on the steam bath. At this point another lot which had been prepared in the same manner was combined with it.**

*Spectra and glpc charts identified by the more specific terminology, e.g., IR-84, GLC-3, etc. are on file at Michigan State University and are not included in this thesis. All those included are identified as Figure 26, for example.

**It would seem appropriate to the writer to do some purification at this point. The desired product is in aqueous solution as the sodium salt and non-acidic impurities could be readily removed by steam distillation, active carbon treatment, or solvent washing. However, the procedure as given in the cited literature reference was maintained.

The sodium salt solution was acidified to Congo paper with 40% sulfuric acid. Before layer separation the mass was well stirred for one hr to eliminate the possibility of leaving some sodium salt in the oil layer. The layers were separated and the water layer was extracted four times with 100 ml of ether each and the ether solutions were added to the product layer. Volhard analysis of the aqueous layer showed 2.99 moles of bromide ion (97% of theory). The product layer was washed with six small portions of salt water (neutral to Congo paper), dried with Drierite, and distilled free of ether.

By a Karl-Fischer titration the product was found to still contain 9.4% water. This was removed by azeotropic distillation with 300 ml of benzene. The last of the benzene distilled over dry and the boiling point rose sharply to 87^0 (20 mm). The product was collected in three fractions from a 22" long helices-packed column. The observed data for the fractions was as follows:

Fraction No.	Volume, ml	Neutral Equivalent	n^{25}_D	fp^0
1	50	87.2	1.4336	17.7
2	100	86.6	1.4337	18.1
3	50	86.4	1.4337	18.0

The calculated neutral equivalent is 86.1. The boiling point was $88\text{-}9^0$ (20 mm) throughout except for the very first distillate. The distillation residue weighed 9.3 g, and the combined weight of the three product fractions was 214 g,

or 80.4% yield. An ir spectrum of fraction 2 (IR-177) agreed with that published (114). Jeffrey and Vogel (115) report a freezing point of 17.0-17.5°. The density of the three fractions combined was found to be 1.070 at 25°, [lit. $\underline{d}_{24}^{24}$ 1.0847 (116)]. Refractive indices reported in the literature are 1.4355 at 27° (116) and 1.4353 at 25° (114) for the sodium D line. A sample of fraction 2 was examined by glpc (GLC-141a) on a 6' Oronite NI-O column and showed practically no impurities.

C. Preparation of Cyclopropyl Bromide

Four lots of cyclopropyl bromide were prepared, using 0.5, 0.5, 1.2, and 2.34 moles of cyclopropanecarboxylic acid, respectively. The first preparation was made according to the general procedure described by Cristol (36). As the figures show, the yield was quite low. A procedure specific for cyclopropyl bromide was then obtained from Meek (37,38) and it was used for the other three runs. For the first three runs the carboxylic acid was prepared as described in Section B above. For the fourth lot 200 g of the acid were purchased from Aldrich Chem. Co. Freezing points of the two 100 g bottles as purchased were 14.3° and 13.5°. Fractional distillation at 20 mm pressure through a 15" Vigreux column brought the freezing point to 18.0° which agreed with that of the prepared material and with the literature values (115). The bromotrichloromethane used was Dow Chemical Company material. It was fractionated through

a 40-plate Oldershaw column after which it showed no impurities by glpc. The 1,1,2,2-tetrachloroethane (TCE) was DuPont technical grade material. It was likewise fractionated and afterwards was very nearly glpc pure. It was considered important to remove from these solvents any impurities which might be difficult to remove from the cyclopropyl bromide later on. The red mercuric oxide was Mallinkrodt A.R. grade.

The reactions were carried out in a three-necked flask fitted with a stirrer, reflux condenser, dropping funnel, and thermometer. Shielding was used to protect the mixture from bright light. For the largest run a 3-liter flask was just about right. A substantial vacant space in the flask is desirable on account of the foaming due to CO_2 evolution. A bubbler containing tetrachloroethane connected to the vent made it easy to follow the reaction. The numerical values and other details as they pertain to individual runs are shown in the table below.

In runs 2, 3, and 4 the mercuric oxide and half of the solvent were charged to the reaction flask and the mixture of bromine, carboxylic acid and the other half of the solvent was added slowly. The carbon dioxide evolution was quite vigorous and stopped almost immediately after the addition was completed. The reaction flask was warmed slightly at the beginning and needed modest cooling afterwards to maintain the reaction temperature.

	1	2	3	4
Yield of Distilled Product, %	19.4	61.0	62.8	54.3
Solvent	$BrCCl_3$	TCE	TCE	TCE
Size of Run, Moles Br and Carboxylic Acid	0.5	0.5	1.2	2.34
HgO, Moles per Mole of Acid	0.76	0.56	0.56	0.56
Solvent, ml in at Start	*	125	300	600
Solvent, ml in with Br and Acid	*	125	300	600
Reaction Temperature	75-80°	40-50°	32-37°	25-40°
Time of Addition in Minutes	180	110	150	75
Time of Post-Reaction in Minutes	75	90	60	90

*In the first run the HgO, cyclopropanecarboxylic acid, and 200 ml solvent were charged to the flask at the start, and the bromine then added gradually. There was some bromine left at the end, and 16 g of sodium bisulfite in 50 ml of water were added to destroy it.

After the reaction was completed the mixture was cooled to about 10° and filtered using only the minimum of vacuum needed to avoid loss of cyclopropyl bromide by volatilization. The mercuric bromide filter cake was washed with some of the same solvent and discarded. The filtered solution was dried with calcium chloride or sodium sulfate. The product was separated from the large volume of solvent by a rough fractional distillation to get a more concentrated solution, followed by a finish fractionation to get pure cyclopropyl

bromide. The distillation fractions were tested for quality by glpc (GLC-141b) using a 6' Oronite NI-O column. Pure material boiling at 68-9^0 at atmospheric pressure (38) was readily obtained.

A portion of the distillation residue from run 3 was washed with base to see if it contained any unreacted cyclopropanecarboxylic acid. None was found.

Mass, infrared, and nmr spectra of the pure product were obtained (95) and found consistent for cyclopropyl bromide. The ir spectrum is in agreement with that reported in the literature (39,40b). The spectra are shown in Figures 3, 4, and 5.

D. Attempted Preparation of 3-Cyclopropyl-2-butanol by Reaction of Cyclopropylmagnesium Chloride with trans-2,3-Epoxybutane

Experiment 1, Ethyl Bromide as Initiator:- The tetrahydrofuran was distilled over $LiAlH_4$ before use. The magnesium was Merck Reagent and was stored in a desiccator before use. The reaction was run in a 500-ml three-necked flask fitted with stirrer, thermometer, and a reflux condenser which was vented through a drying tube. The flask was flushed with nitrogen and a nitrogen atmosphere was maintained while running the reaction. The cyclopropyl chloride (30.9 g, 0.40 mol) was dissolved in 72 g of tetrahydrofuran and five ml of this solution were added to 8.0 g (0.33 mol) of magnesium already in the flask. After heating to reflux

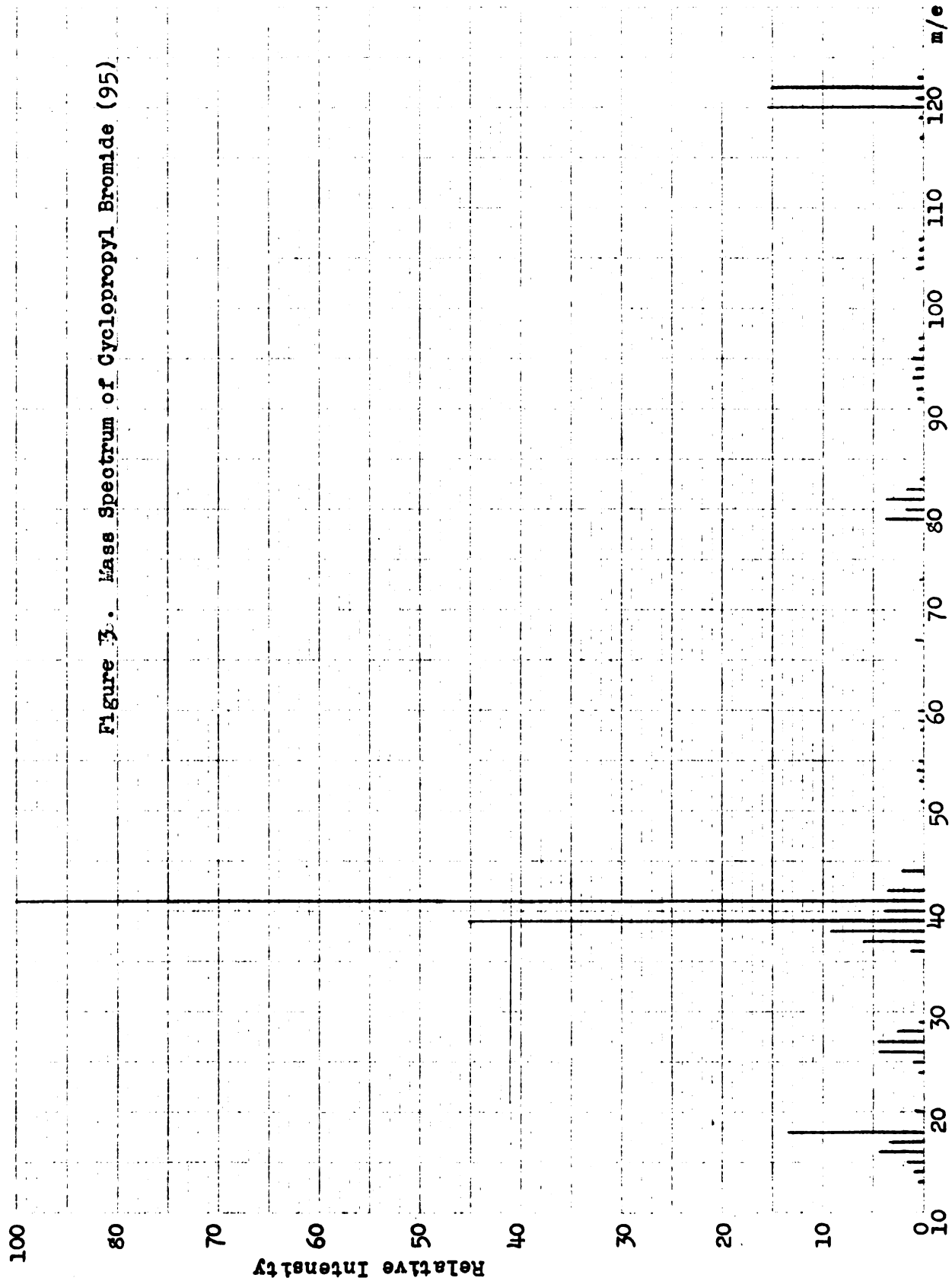


Figure 3. Mass Spectrum of Cyclopropyl Bromide (95)

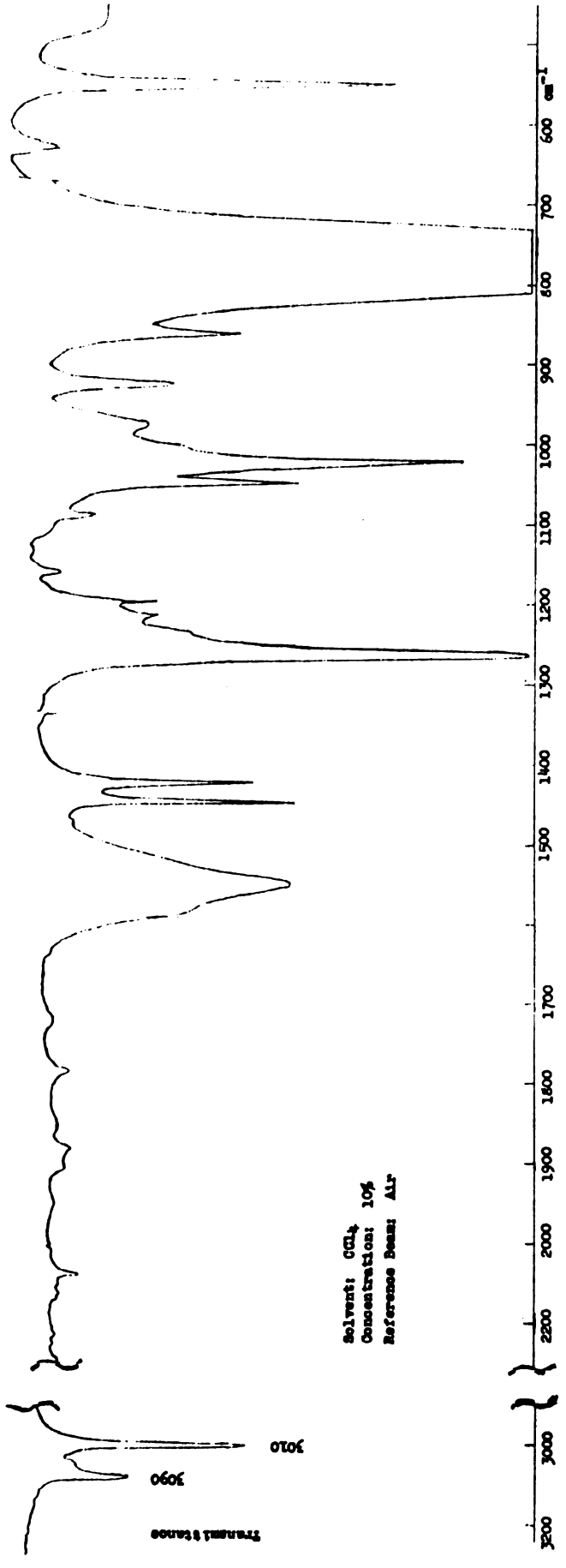


Figure 4: Infra-red Spectrum of Cyclopropyl Bromide (95)

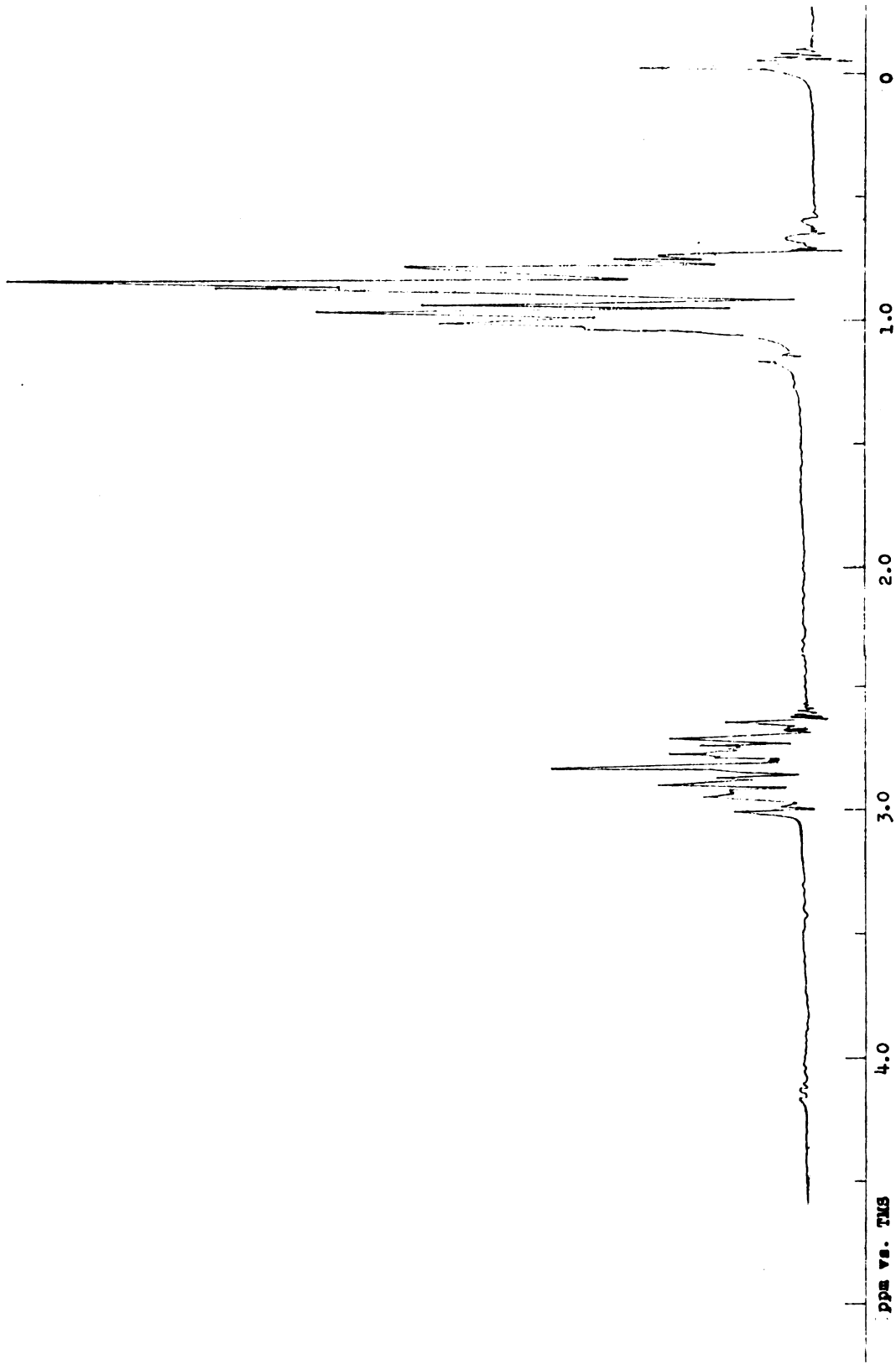


Figure 5. Nmr Spectrum of Cyclopropyl Bromide (95) at 60 MHz
(neat with TMS added)

temperature produced no signs of reaction one ml of ethyl bromide was added. There was still no reaction apparent, and addition of a crystal of iodine brought on only a very slight indication of reaction. All of the remaining cyclopropyl chloride solution was now added and the mixture was heated at reflux temperature for a period of ten hours. There were no other visible signs of reaction except that at the end of the heating period the magnesium was much more finely divided than at the beginning. At this point a few ml of solution were removed from the flask and treated with phenyl isocyanate in tetrahydrofuran in an attempt to detect the expected Grignard compound as cyclopropanecarboxanilide. The solid recovered melted at 240° which is about right for diphenylurea. Cyclopropanecarboxanilide is reported to melt at 110° (39).

trans-2,3-Epoxybutane (24.0 g, 0.33 mol) was added slowly to the reaction flask at room temperature. Sufficient heat was evolved that moderate cooling was required. The mixture was held an additional 0.5 hr at reflux. The contents of the flask were then poured onto ice and treated with 30 g of ammonium chloride. The resulting mixture was very messy due to the presence of magnesium metal and tars. The solids were separated by filtration, and the solids and the water layer were both extracted with benzene. The solvent portions were combined and distilled at atmospheric pressure. The distillate (7.1 g) boiled at 125-200°. An infrared spectrum (IR-1) showed the presence of hydroxyl,

carbonyl, and unsaturation (3450, 1710, and 1627 cm^{-1}). On redistillation the major part of the product (4.2 g) boiled at 148-9°. The ir spectrum (IR-1a) was now considerably cleaner but showed the same functionality.

Experiment 2, Magnesium Mechanically Abraided, Ethyl Bromide as Initiator:- The apparatus and general procedure were the same as for experiment 1 except that an inert atmosphere was not used. The drying tube at the vent was retained. The magnesium (12.0 g, 0.50 mol) was abraided in a mortar immediately before use. It was placed into the reaction flask along with 135 ml of tetrahydrofuran, 46.4 g (0.61 mol) of cyclopropyl chloride, and 0.50g(0.046 mol) of ethyl bromide. After 5 days at reflux some magnesium metal still remained. A small portion of butylene oxide was added at room temperature. No noticeable reaction occurred. The mixture was heated to reflux temperature and the remainder of the oxide (total added, 36.0 g, 0.50 mol) was added. Refluxing was continued for one hour. There were no visible signs of reaction. Thirty grams of ammonium chloride in 200 ml of water were added. Considerable heat was evolved. The resulting mixture was very messy and even addition of HCl did not completely clear it up. By extraction with benzene only 1.9 g of material were recovered.

Experiment 3, Magnesium Freshly Machined; Ethyl Bromide, Magnesium Iodide, and Benzyl Chloride as Initiators:- A block of Grignard quality magnesium (Commercial grade,

Peg-lock) was obtained from the Dow Chemical Company. It was reduced to the conventional size shavings on a milling machine (lowest rotational speed, 3rd feed speed, used homemade cutter, 0.030 inch cut) and immediately immersed in tetrahydrofuran, and kept there until use a few days later. A separate test showed that 21.0 g of the magnesium wet with solvent was equivalent to 8.0 g of dry metal. The cyclopropyl chloride (30.9 g, 0.40 mol) was dissolved in 120 ml tetrahydrofuran and a small portion of this solution was added to the magnesium already in the reaction flask. At 40^0 there was no sign of reaction, and addition of 3 drops of ethyl bromide had no effect. At the reflux temperature (64^0) there was still no sign of reaction. Two grams of magnesium plus one gram of iodine were heated together in a test tube until a gray powder was formed. Addition of a bit of this to the reaction mixture had no effect. The remainder of the cyclopropyl chloride solution plus 0.25 ml of benzyl chloride was now added and the entire charge was heated at reflux temperature for four days. At this point there were no signs that any reaction had occurred and the lot was discarded.

Experiment 4, Methyl Iodide and Ethyl Bromide as Initiators:- The apparatus and general procedure were the same as used previously. An inert atmosphere was not used. A dry ice-cooled condenser was used above the water-cooled one, and it in turn was vented through a drying tube as

before. Fifteen grams of Merck magnesium were placed in the flask and a solution of 38.3 g (0.50 mol) of cyclopropyl chloride, 14.2 g (0.10 mol) of methyl iodide, and 120 ml of tetrahydrofuran was added over a 45-minute period at 55-60°. The heat of reaction was just about enough to maintain the temperature. Heating at reflux was continued for five hours during which time 150 ml of additional solvent and 0.5 ml of ethyl bromide were added. At the end of the period some metallic magnesium and considerable white solid were present. The epoxybutane (43.2 g, 0.60 mol) was added at 55-60°. The white solid disappeared. The mixture was heated at this temperature for 45 minutes, then poured into 300 ml of ice water which contained 34 g (0.35 mol) of sulfuric acid. Nine grams of unreacted magnesium were filtered off. The lot was discarded.

Experiment 5, Ethyl Bromide as Entrainer, No Agitation:- The apparatus and general procedure were the same as for the previous experiment. The reaction flask was flamed and flushed with dry nitrogen before use and a nitrogen atmosphere was maintained during the reaction by use of a large plastic bag. Fifteen grams (0.62 mol) of Merck magnesium along with a small portion of the cyclopropyl chloride solution (38.3 g, 0.50 mol cyclopropyl chloride; 10.9 g, 0.10 mol ethyl bromide, 150 ml tetrahydrofuran) were charged to the reaction flask. Without stirring heat was applied to raise the temperature slowly to about 60° at which point

the heat of reaction appeared to be able to hold the temperature. Still without stirring the remainder of the solution was added over a 0.5 hr period. It was hoped that reactive sites might function better if they were not disturbed. Over a 6 hr period, during which a total of nine more drops of ethyl bromide were added, the amount of magnesium present appeared to have diminished considerably. The butylene oxide (43.2 g, 0.60 mol in 50 ml tetrahydrofuran) was added at 30^0 in 20 minutes. Very little, if any, heat was evolved. After stirring overnight at room temperature a small amount of magnesium was still present. After standing for one week it was poured into 150 ml of ice water which contained 0.37 mol of sulfuric acid. Three grams of unreacted magnesium were filtered off. The solvent layer was separated and the aqueous layer was extracted twice with 50 ml of solvent. The combined portions were dried with sodium sulfate and the solvent was removed through a 15" long Vigreux column. The tetrahydrofuran distillate was quite wet -- cloudy when mixed with benzene -- and some fresh solvent followed by some CCl_4 was added and distilled until the distillate came over dry. The product was distilled through a 22" column packed with glass helices at 50 mm Hg pressure.

Cut No.	Bp^0	IR No.	wt., g
1	29-35 (mostly 33)	54	9.8
2	35-47		2.1
3	47-62 (mostly 52)		4.3
4	62-88 (leveled off a bit at 84)	55	8.2
Residue			9.1

All the fractions were wet and portions were dried before obtaining ir spectra. Cut 1 showed a little unsaturation (1627 cm^{-1}), no hydroxyl (3450 cm^{-1}), no carbonyl (1710 cm^{-1} region), and no cyclopropyl (3080 cm^{-1}). Cut 4 showed a small broad hydroxyl absorption, two strong carbonyl absorptions, and a strong band for unsaturation.

Experiment 6, Benzyl Chloride as Entrainer, Iodine as Initiator:- The apparatus, procedure and the charge size were the same as in the previous experiment except as otherwise specified. The magnesium was stored in a vacuum desiccator over sodium hydroxide for a week before use. The vacuum was released with dry nitrogen. The reaction flask was flamed and swept with dry nitrogen after the magnesium was charged in. In place of ethyl bromide 0.10 mol of benzyl chloride and one crystal of iodine were used. The mixture was stirred only occasionally. Thirty ml of halide solution were added at once, the temperature was increased to 61^0 (reaction set in) and the remainder was added over 25 minutes. Reaction was more vigorous than in experiment 5. The mixture was heated at reflux for over six hr with

occasional stirring and two drops of additional benzyl chloride were added every 0.5 hr. Some unreacted magnesium remained at the end. After the mixture was cooled to room temperature, the butylene oxide solution was added and the batch was stirred overnight then let stand for a week. It was poured into a mixture of ice-water and sulfuric acid as before. This time ether was used as an extraction solvent in the hope that it might be more readily dried than the tetrahydrofuran by itself. (Later it was found that sodium sulfate is a pretty poor desiccant, and that $MgSO_4$ or K_2CO_3 are much better.) The dried solution was distilled to 75^0 liquid temperature to remove most of the solvent. The pressure was reduced to 15 mm Hg and 53.4 g of product were distilled without use of a fractionating column. An ir spectrum at this point showed hydroxyl with considerable hydrogen bonding, a doublet carbonyl 1666 and 1695 cm^{-1}), unsaturation (1600 cm^{-1}), and just a shoulder at 3050 suggesting cyclopropyl. The distillation residue weighed 7.4 g. Fractional distillation (22" helices) at 50 mm Hg yielded the following:

Cut No.	Wt., g	Bp^0	IR No.
1	0.40	to 60^0	
2	14.5	60-81 (71^0)	57
3	6.9	81-87	58
Residue	18.6		59

The ir spectrum of cut 2 showed H-bonded and unbonded hydroxyl, cyclopropyl, some unsaturation at 1610 cm^{-1}, and

a medium intensity carbonyl band at 1693 cm^{-1}. This could be 3-cyclopropyl-2-butanol in impure state, and would amount to about 25% yield. Fraction 3 showed no hydroxyl, some carbonyl at 1695 cm^{-1}. Ultraviolet spectra were obtained of fractions 2, 3, and the distillation residue.

Fraction	UV No.	λ_{max}	ϵ
2	1	237 mμ	3,090
3	2	235 mμ	20,950
Residue	3		3,980

The uv peaks were very broad, and for the residue so flat that there was no discreet maximum.

A sample of cut 2 (0.3 ml in 10 ml CCl_4) was washed with 5% $KMnO_4$ to remove unsaturation. After washing with water and drying the ir spectrum showed no carbonyl nor unsaturation. Fraction 2 was now redistilled through (22" helices) at 50 mm Hg.

Cut No.	Wt., g	Bp°	$\underline{n}^{25}\underline{D}$	IR No.
1	0.8	51-69		
2	1.6	69-70	1.4378	61
3	2.5	70-71	1.4384	62
4	3.4	71	1.4388	63
5	1.5	71	1.4387	64
6	3.6		1.4382	65

Fraction 6 was obtained by lowering the distillation pressure as far as the pump would take it. Only a trace of residue remained. On elemental analysis (100) fraction 4

was found to contain 73.22% carbon and 12.04% hydrogen (calc. for $C_7H_{14}O$: C, 73.6; H, 12.33). The ir spectra of fractions 2 through 6 agreed fairly well with that of 3-cyclopropyl-2-butanol which was later obtained in larger quantity by the reaction of cyclopropyllithium with butylene oxide. Carbonyl and unsaturation were present only in fraction 6 and then only in small amounts. Fraction 4 showed an absorption which is characteristic of cyclopropyl (99) in the near ir (IR-65a) at 1.63 microns (6130 cm^{-1}). By glpc (dodecyl phthalate at 140°) analysis (GLC-142-5) fractions 2, 4, and 5 were each found to contain two major components and several minor ones. An iodoform test on fraction 4 for methyl carbinol was inconclusive. An attempt to prepare a 3,5-dinitrobenzoate from it was unsuccessful. No halogen was found in fraction 3 by a sodium fusion test. An ir spectrum run in CS_2 (IR-67) showed no benzene ring content in cut 3. A considerable effort was made to obtain some pure 3-cyclopropyl-2-butanol by preparative glpc. When a larger diameter column was used the separations obtained were unsatisfactory. From the analytical size glpc column only very small fractions could be collected and these were wet to the point of containing an acidic water layer. It appeared that considerable instability remained even after two fractional distillations.

Experiment 7, Magnesium Abraided, Benzyl Chloride and Bromobenzene:- The reaction apparatus was flamed and

flushed with dry nitrogen. The magnesium (13.0 g, 0.54 mol) was abraided with a Waring blender and charged to the flask. An atomosphere of nitrogen was maintained by the use of a large plastic bag. A bit of the cyclopropyl chloride solution was added. When there was no reaction a few drops of bromobenzene were added with still no effect. The remainder of the cyclopropyl chloride (total 38.3 g, 0.50 mol in 150 ml tetrahydrofuran) solution was then added along with two more drops of bromobenzene. The mixture was heated slowly to 52°. There were still no signs of reaction. Addition of more bromobenzene, addition of benzyl chloride, ethyl bromide, and replacement of the magnesium with fresh metal all had no effect. The material was discarded.

Experiment 8, Benzyl Chloride in 30 mol %:- This experiment was a duplicate of experiment 6 except that twice as much benzyl chloride was used. The cyclopropyl chloride (32.3 g, 0.41 mol) and benzyl chloride (25.2 g, 0.20 mol) in 150 ml of tetrahydrofuran were charged to the reaction flask which already contained 16.0 g (0.67 mol) of magnesium, over a 35-min period. Reaction was in evidence throughout. Heating was continued at reflux temperature for an additional 5.5 hr with the addition of 3 drops more of benzyl chloride per hour. After the mixture was cooled 44.5 g (0.61 mol) of trans-2,3-epoxybutane were added at 20° over a period of 20 min. Little if any heat was evolved. The mixture was stirred 1 hr at room temperature and let stand for one week.

It was diluted with ice-water and extracted with ether as before. After being dried with K_2CO_3 most of the solvent was distilled off. Because the solvent came over wet some CCl_4 was added to azeotrope out the last of the water. A point was readily reached at which the CCl_4 came over dry, but, before the rest of the CCl_4 could be removed it would turn wet again. Apparently when the still pot temperature exceeded a certain value decomposition caused water to form. The product was distilled through the 22" column at 50 mm Hg.

Cut No.	Wt., g	Bp°	IR No.
1	2.6	32-52 (34)	68
2	4.5	52-71 (70)	69
3	2.8	71-77	70
4	1.6	77-80	71
5	5.9	80-85	72
6	3.8	85-86	73
7	2.4	86 (50 mm) to 95 (20 mm)	74
8	3.9	95 (20 mm) to 125 (20 mm)	75

The residue weighed 29.2 g. The ir spectra showed that cuts 2 and 3 could contain a considerable amount of the desired product. In the higher fractions the carbonyl content went up and the hydroxyl content went down and ultimately reached zero with fraction five.

At a later date when some 3-cyclopropyl-2-butanol had been prepared by the cyclopropyllithium method and was quite well purified and characterized, some of this material -- a

mixture of cuts 3 through 8 -- was analyzed by glpc. A peak but not an outstanding one, for the desired alcohol was obtained. However, there were also many other peaks. Obviously a very complex and somewhat unstable mixture of products is obtained by reaction of the Grignard reagent with butylene oxide.

E. Preparation of 3-Cyclopropyl-2-butanol. Use of Cyclopropyllithium Prepared from Cyclopropyl Chloride

trans-2,3-Epoxybutane:- Fractional distillation (50 plate Oldershaw column) of a large quantity of mixed butylene oxides (5) yielded a portion boiling at 53.0-53.5° and having a refractive index of n^{25}_D 1.3708. By glpc analysis it was quite pure. The physical properties of the cis and trans-2,3-epoxybutanes have been reported by Lucas and Wilson (96). Their data are as follows:

	cis	trans
Bp (corrected)	59.7°	53.5°
d^{25}_4	0.8226	0.8010
n^{25}_D	1.3802	1.3705

From the work of Lucas and Wilson there appears to be no doubt as to the cis and trans assignments. During the course of the present work numerous glpc analyses were made of this purified oxide. Ultimately evidence was obtained indicating that a few percent of isobutylene oxide might have been present and that this material is difficult to

resolve from the trans-2,3- isomer by glpc. All of the material used was thoroughly dried over barium oxide or soda lime.

Experiment 1, Attempted Preparation of Cyclopropyllithium by Reported Procedure (3), in Hexane:- The reaction was carried out in a three-necked flask fitted with a thermometer, reflux condenser, connection for inert gas (argon), and a very high speed turbine type stirrer. In some of the later experiments some of the more common types of stirrers were used and found to be less satisfactory than the high speed stirrer. Mineral oil (100 ml, sodium dried) was charged to the flask with 4.6 g (0.67 mol) of lithium. Heat was applied without stirring until the lithium melted at about 190°. At this point the stirrer was turned on and the material was allowed to cool while stirring. In this manner a very fine lithium sand was produced. n-Hexane (Phillips Pet. Co., permanganate washed and redistilled) was added to reduce the viscosity of the mineral oil and mild pressure was applied to expel the liquid phase from the flask through a filter stick. After washing the lithium sand twice more with hexane, 125 ml of the same were added preparatory to the next step. (In later experiments removal of the mineral oil-ether mixture was effected by application of mild suction and drawing the liquid into a trap in the vacuum line. This worked very well and is the preferred technique.) Cyclopropyl chloride

(25.5 g, 0.33 mol) was added and the mixture was heated at reflux temperature of 59° for 2.5 hr. Because there were no signs of reaction a few drops of n-propyl bromide were added. During another hr of heating there were still no signs of reaction. A bit of externally prepared ethylmagnesium bromide was added with no better results. The run was discontinued.

Experiment 2, Preparation of Cyclopropyllithium in Ether and Use of it to Prepare Tricyclopropylcarbinol:- To the lithium sand (2.18 g, 0.315 mol) prepared as above, in 90 ml of ether (sodium dried) the cyclopropyl chloride (12.1 g, 0.157 mol) in 25 ml of ether was added in a one-hour period at 5-8°. Visible reaction occurred. The mixture was heated at about 31° for an additional 0.5 hr. An attempt to analyze the mixture for lithium alkyl content was unsuccessful, probably because much cyclopropyllithium was out of solution. By the method of Gilman (97) samples of the liquid phase were titrated for base both with and without pre-reaction with benzyl chloride. From the difference in the titrations it was calculated that 0.009 mol of cyclopropyllithium was present. Two samples of the slurry were analyzed for ionic chloride and 0.122 and 0.170 mol were found.

Although this lot of cyclopropyllithium was prepared for the purpose of reaction with cholestan-3-beta-ol-6-one (see Experimental, L), the turn of events -- use of ether

rather than hydrocarbon for the preparation of cyclopropyllithium -- being somewhat contrary to past experience, a change of plan was made and the lithium compound was reacted with dicyclopropyl ketone (0.16 mol, made previously in this laboratory) to obtain tricyclopropylcarbinol (3) in about 53% yield. About 33% of the ketone was recovered unchanged.

Experiment 3, Cyclopropyllithium Reacted with Ketocholesterol:- In this experiment the practice of drying the ether with calcium hydride was initiated. It was found that regardless of how much the ether had been dried over sodium, upon addition of calcium hydride gas evolution would occur. After a few hours gas evolution ceases and is not resumed on addition of more calcium hydride. For all subsequent use the ether was dried in this manner.

Lithium sand (1.1 g, 0.16 mol) was prepared as above and reacted with 6.1 g (0.08 mol) of cyclopropyl chloride in 25 ml of ether. The latter was added at 0-10° in 10 min. Considerable cooling was required to maintain the temperature and after stirring for 30 min no more lithium metal could be observed. This lot of cyclopropyllithium was reacted with cholestan-3-beta-ol-6-one as described under Experimental L.

Experiment 4, Substantially a Repeat of Experiment 3:- This was a 0.12 mol of cyclopropyl chloride run with the latter added over a period of 1.5 hr at 10°. An attempt

was made to analyze the lot by direct titration of the base present. A one ml sample taken from the supernatant liquid after the solid had been allowed to settle consumed 3.9 ml of 0.1 normal acid. This corresponds to 0.0292 mol base present vs 0.119 as theory. A one ml sample taken while the mixture was stirred was found to contain alkali corresponding to 0.0592 mol total. This lot of material was also used for reaction with ketocholesterol.

Experiment 5, Products of Reaction of Cyclopropyllithium with Butylene Oxide:- The reaction was carried out in a 500-ml three-necked flask equipped with a thermometer, reflux condenser, a very high speed stirrer of the turbine type impeller. Prior to use the apparatus was flamed and flushed with argon from a large plastic bag. An argon atmosphere was maintained up to the point of addition of the butylene oxide. A calcium chloride tube was inserted between the plastic bag and the reaction flask. The lithium sand (4.17 g, 0.60 mol) was prepared as before. The cyclopropyl chloride (23.0 g, 0.30 mol) was diluted with 50 ml of ether and added to the flask at about -10^{0} over a two-hour period. After the mixture was stirred an additional 15 min at the same temperature a sample of the suspension showed by titration that 0.26 mol of base was present.

The trans-2,3-epoxybutane (21.6 g, 0.30 mol) was added at -10 to -4^{0} in a period of 0.5 hr. There were no signs of reaction. The material was heated to reflux at 37^{0} and

held there for 20 min. After the mixture was cooled to room temperature sufficient water (150 ml) was added to dissolve the salt. The layers were separated and the aqueous layer was extracted with two 50-ml portions of ether. The organic layers were combined and washed once with saturated salt-water and dried with potassium carbonate. After removal of most of the ether the following distillation fractions -- atomospheric pressure, no fractionating column -- were obtained.

No.	Wt. g	Bp° (plateau)	Infrared*				
			No.	OH	Unsat.	C=O	Cyclo-propyl
1	0.5	46-50	124	N	W	W	N
2	0.8	50-70	125	?	W	W	W
3	2.7	70-102(85-90)	126	S	W	W	M
4	0.9	102-140	127	S	M	N	M
5	0.5	140-7 w. dec.	128	S	W	W	M

There was 0.6 g of distillation residue.

*S, strong; M, medium; W, weak; N, negative. All for same absorption bands noted in the previous section.

An attempt was made to fractionally distill the combination of cuts 3, 4, and 5 through a 6" long Vigreux column at atmospheric pressure, however, decomposition occurred to an extent to render it impractical. This material was saved and added to that from the following experiment at the designated point.

Experiment 6, Development of Product Work-up Method:-

The preparation of the lithium sand (7.6 g, 1.1 mol) and reaction of it with the cyclopropyl chloride (38.3 g, 0.50 mol) were similar to that of the previous run. Titration of a sample of the reaction mixture showed 0.283 mol of base. (The sampling technique remains unproven.) The oxide (28.8 g, 0.40 mol) was added in 20 min at 5^0, and the mixture was stirred an additional 2 hr while slowly warming to 35^0. Water was added and the layers were separated. At this point the water layer contained 0.461 mol of chloride ion by Volhard titration and 0.51 mol of base. After extraction of the water layer the combined ether layer was washed to neutral with three 15-ml portions of salt-water, dried with K_2CO_3 and distilled using a 15" long Vigreux column at atmospheric pressure.

Fraction No.	Wt., g	Bp^0	IR No.	Remarks
1	3.8	35-7	129	mostly ether
2	1.1	37-50		
3	3.5	50-54	130	mostly butylene oxide
			130b	butylene oxide standard

On further distillation the pot temperature got quite high and the vapor temperature became quite variable. The material from the previous run was added at this point, the pressure was reduced to 50 mm Hg and the distillation was continued.

Cut No.	Wt. g	Bp°	Infrared				
			No.	OH	Unsat.	C=O	Cyclo-Propyl
5	1.3	28-38					
6	3.1	38	131	S	M	W	M
7	1.0	38-61					
8	2.4	61-79	132	S	W	M	M

At this point decomposition was occurring. The distillation was stopped. One gram of residue remained.

Experiment 7, Development of Product Work-up Method:- The quantities of reagents and the procedures were the same for the reaction steps as in the previous experiment. A few small lumps of lithium remained after reaction with the cyclopropyl chloride. The butylene oxide was added in 15 min at 20° and followed by heating at reflux for 20 hr. After extraction and removal of most of the ether the crude product weighed 30.8 g vs 57 g calculated for 0.5 mol of 3-cyclopropyl-2-butanol. The water layer contained 0.51 mol chloride ion and 0.58 mol base. Fractional distillation of the crude product through a 15" long Vigreux column followed by examination of the cuts yielded the following data:

Cut No.	Wt, g	Bp^0 (plateau)	$\underline{n}^{25}\underline{D}$	IR No.
1	0.7	40-79 (atm)		
2	4.9	79-94 (92-4)(atm)		
3	4.8	92-95 (atm)	1.4118	133
4	5.0	40-50 (40)(50 mm)		134
5	1.3	50-82 (50 mm)		
6	4.8	82-83 (50 mm)	1.4387	135 (Figure 6)
7	2.0	? to 121 (15 mm)		
8	1.4	121-145 (15 mm)	3 g of residue left.	

By physical constants and ir cuts 3 and 4 look similar, but not identical to, allyl alcohol. Allyl alcohol bp, 97^0; $\underline{n}^{25}\underline{D}$, 1.4134. By glpc cut 3 was very nearly pure (polyethylene glycol column, 120^0). It was suspected to be 3-buten-2-ol. None of the material was available for comparison, however, the literature lists the phenylurethane derivative (98) as melting at 50-51^0. Phenylurethane prepared from cut 3 melted at 51.5-52.0^0. We call this material 3-buten-2-ol. If one makes the reasonable assumption that fractions 2, 3, and 4 are mostly this material then it appears that about 40% of the butylene oxide undergoes isomerization to this alcohol.

By glpc fraction 6 consisted of one major and several significant lesser components. In the near infrared spectrum this material showed absorptions at 1.64 and 2.24 microns which are characteristic of the cyclopropyl group (99). The regular ir spectrum was consistent with the structure of 3-cyclopropyl-2-butanol except for some carbonyl and

Figure 6. Infrared Spectrum of 3-Cyclopropyl-2-butanol

some carbon-carbon double bond absorption which could be attributed to impurities. From a quantitative standpoint the sum of fraction six plus half of 5 was equivalent to approximately 12% of the butylene oxide used.

Experiment 8, To Accumulate More Material:- The procedure and run size were the same as for the two previous experiments. The aqueous layer from the extraction contained 0.485 mol of chloride ion and 0.543 mol of base. A first distillation through the 15" Vigreux column yielded 15.0 g (0.208 mol, 52% yield) of 3-buten-2-ol (bp_{50}, 36-8°) and 6.6 g (0.058 mol, 14.5% yield) 3-cyclopropyl-2-butanol (bp_{50}, 62-95°, mostly 82°, ir spectrum IR-136 match cut 6 of experiment 7) along with very small mixed cuts and 5.0 g distillation residue.

The desired product from this experiment and experiment 7 was combined and fractionated through a 15" Vigreux column at atmospheric pressure. It was hoped that without the use of vacuum the fractional distillation might be done at more nearly constant conditions and better purification realized. However, the material foamed so badly that no advantage resulted.

Fraction No.	Wt, g	Bp^0	$\underline{n}^{25}\underline{D}$	IR No.
1	0.5	97-134	1.4366	
2	1.2	134-139	1.4354	138
3	1.3	149-152	1.4378	139
4	1.6	152-153		140
5	0.7	153	1.4388	141
Residue	0.7		1.4420	142

The ir spectra of fractions 2, 3, and 4 were very similar and consistent with spectra which have been accepted thus far as representing 3-cyclopropyl-2-butanol. Number 5 showed considerable carbonyl group absorption whereas the others showed only a trace. The isomer of the desired product, 2-cyclopropyl-2-butanol was available in this laboratory from earlier work, and its ir spectrum (IR-137) was clearly different from that of the above distillation fractions. Carbon and hydrogen analyses were obtained on cut 4.

Calcd for $C_7H_{14}O$: C, 73.6; H, 12.36.

Found: C, 73.6; H, 12.30.

Experiment 9, Accumulation of Material and Product Investigation:- The apparatus and procedure were essentially the same as for the several preceding runs. The cyclopropyl chloride (114.9 g, 1.5 mol) in 100 ml of ether was added to the lithium sand (21.5 g, 3.1 mol) in 100 ml of ether at -8^0 to +5^0 over a 2.75 hr period, followed by stirring at 0^0 for an additional 0.5 hr. The trans-2,3-epoxybutane (108 g, 1.5 mol) was added in 1.5 hr at 0-30^0.

Significant heat evolution took place, and gas evolution was also noted. Heating at reflux was continued for an additional 20 hr. A sample of the gas evolved was collected and was found to boil at about -10^0 -- probably cyclopropane plus ether.

Water (450 ml) was added cautiously until all the solids dissolved. The water layer contained 1.34 mol of chloride ion and 1.44 mol of base. The composite ether layer was washed with salt-water and dried with potassium carbonate. On distillation through the Vigreux column at 50 mm Hg about a 7% yield of 3-cyclopropyl-2-butanol was obtained. The 3-buten-2-ol comprised about 31% yield, and there were 19.6 g of distillation residue.

Fraction 5 of experiment 7, fractions 2,3, and 5 of experiment 8, and the good fraction of this run were combined and carefully fractionated.

No.	Wt,g	Bp^{o}_{50}	$\underline{n}^{25}\underline{D}$	GLC No.	Glpc Observations
1	1.20	50-80	1.4322	3	bad mixture
2	1.75	80-81	1.4375	4	two large peaks A:B=ca.1:2
3	1.90	81-82.5	1.4382	5	Ratio A to B is about 1:6
4	1.57	82.5	1.4386	6	Mostly B, trace of A
5	2.24	82.5-83	1.4390	7	B plus traces of others
6	1.73	83	1.4392	8	B plus traces of others
7	1.39	83	1.4398	9	B plus traces of others
8	1.20	83-90(83-5)	1.4410	10	B plus two small highers

Residue 1.35 g

An Oronite NI-0 (ethylene oxide adduct of an alkylphenol) 6 ft column at 160^0 was used for the glpc analysis.

Fractions 4, 5, and 6 were used as obtained for tosylate preparation. The remaining fractions, except the first, were combined and re-distilled. The best material obtained still showed a carbonyl infrared absorption (IR-154) and this persisted after a wash with bisulfite (IR-155). Three scattered impurity peaks showed on the glpc charts (GLC-11 thru 22). The material used for tosylate preparation contained not over perhaps two percent of impurities by glpc. All the material of this quality was combined and designated number 65X. By glpc at a later date (GLC-23 to 26) using a number of substrates (diglycerol, dioctyl sebacate, and Oronite NI-O) it was found to contain something like 2-5% of total impurity spread over several components.

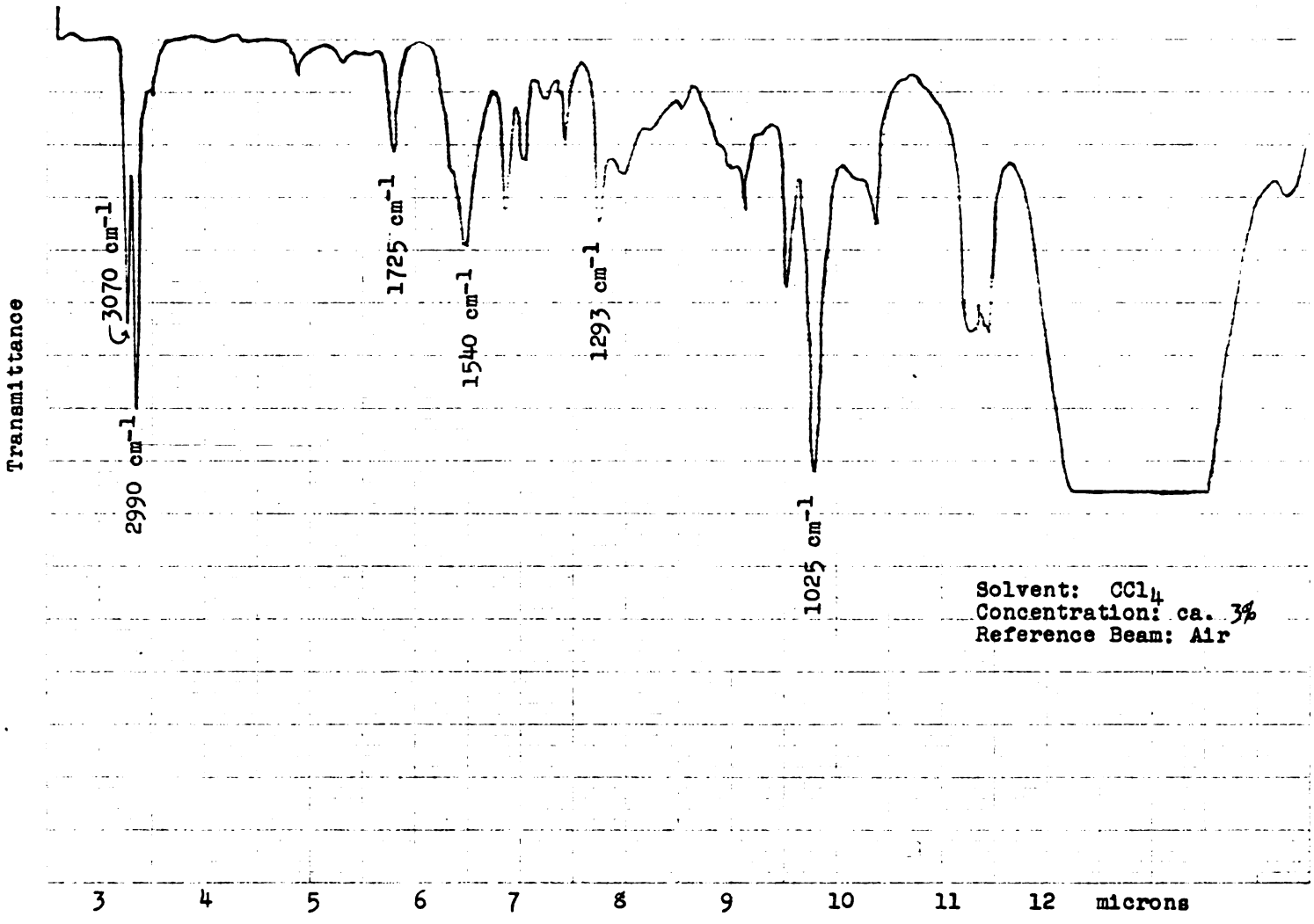
Experiment 10, A Preparation Oriented Toward Material Accounting and Identification of By-products:- The procedure was essentially the same as in the preceding runs. The batch size was 0.84 mol. The turbine type stirrer was not available so a crescent-shaped Teflon blade stirrer was used. The lithium sand was definitely inferior. Lithium was used in 10% excess. The butylene oxide was added at -30^0 this time and no heat evolution could be detected. The reaction mixture was then allowed to warm up to room temperature over a 9-hr period. Water was added carefully and the layers were separated. The ether layer was washed successively with water, dilute HCl, and salt-water. It was dried with K_2CO_3. The ether was distilled through a

22" helices column. By glpc the ether distillate was found to contain 8.4 ml of butylene oxide. The remaining crude product was analyzed by glpc (7' 25% Oronite NI-W at three different temperatures, GLC-27, 28, 29). Thirteen components were found and are listed below with L, S, and M standing for large, medium, and small.

Peak No.	Relative Size	Retention Time, min at Temperature Shown				Comments
		40°	100°	130°	160°	
1	L	2.7	1.3	0.8		ether
2	LL	7.0	2.2	1.5		butylene oxide
3	M	10.6	3.2	2.0		dicyclopropyl
4	LL		8.4	4.1		3-buten-2-ol
5	S			5.0		
6	S			7.2		
7	S			8.5	4.7	
8	M			10.0	5.9	
9	M				7.7	
10	M				8.8	
11	M				11.0	3-cyclopropyl-2-butanol
12	S				12.5	
13	L				17.0	

By matching of glpc retention times and by collection of peaks from the glpc column with accompanying infrared examination, the identification of components was accomplished to the extent shown in the table. No authentic dicyclopropyl was available, but the ir spectrum of peak 3 (Figure 7) agrees with that published by Slabey (35). The crude product was now fractionated to yield a number

Figure 7. Infrared Spectrum of Dicyclopropyl



of cuts as was done in the preceding experiments. The residue was a very viscous material weighing 3.72 g, which by ir contained much OH, little carbonyl, and no unsaturation (IR-175). It is likely a polybutylene glycol. The distillation cuts were analyzed by glpc and quantitative estimations of amounts were made by use of appropriate standards. It was estimated that of the butylene oxide used, two percent was converted to 3-cyclopropyl-2-butanol, 12% to 3-buten-2-ol, and about 47% remained unreacted. The amount of dicyclopropyl accounted for about 9% of the cyclopropyl chloride used. In a later run some butylene chlorohydrin was found. Since in this run HCl was used to wash the product solution it is very likely that one of the many glpc peaks was due to this chlorohydrin.

F. Preparation of 3-Cyclopropyl-2-butanol. Use of Cyclopropyllithium Prepared from Cyclopropyl Bromide

Experiment 1, Dioxane Instead of Ether as a Solvent:- Lithium (0.72 g, 0.104 mol) was converted to sand by melting under mineral oil and allowing to freeze while being stirred vigorously. Air was excluded by slowly dripping pentane into the flask. The mineral oil was replaced with 50 ml of dioxane (re-distilled center cut, less than 0.01% water, glpc pure except for the slightest traces). The cyclopropyl bromide (6.0 g, 0.05 mol) in 20 ml of dioxane was added in about 10 min at room temperature. No reaction occurred even after heating to 60°. The mixture was discarded.

The observation in previous experiments that not all the oxide was being reacted led to the idea of using dioxane. It was hoped that the butylene oxide might react better by working at a higher temperature. It comes as a surprise that cyclopropyl bromide will not react with lithium in dioxane. In the following experiment the plan was to prepare the cyclopropyllithium in ether, then replace the ether with dioxane for the reaction of butylene oxide with the lithium compound.

Experiment 2, Use of Ether and Dioxane in Succession as Solvents:- The lithium sand (1.52 g, 0.22 mol) was prepared in mineral oil under a helium blanket. The oil was displaced with ether and the cyclopropyl bromide (12.0 g, 0.10 mol) in 10 ml of ether was added at 20-25°. Reaction occurred readily. The trans-2,3-epoxybutane (7.2 g, 0.10 mol) in 10 ml ether was added at 21° in 3 min. No reaction was evident. Dry dioxane (100 ml) was started in and the temperature was gradually elevated to 72°, while ether was being distilled out. After the mixture stood for a week water was carefully added followed by sufficient dilute HCl to make it neutral. The dioxane could not be layered out by addition of salt, so the whole mass was extracted with ether. Analysis of the ether by glpc showed a yield of less than 2.5% of the desired product. The material was discarded.

Experiment 3, Return to Use of Ether Alone as a Solvent:- The cyclopropyl bromide (65.2 g, 0.539 mol) in 50 ml of ether was added to the lithium sand (8.23 g, 1.18 mol) in ether at about 0^0 in 45 min. After the mixture was stirred for 10 min 38.7 g (0.539 mol) of butylene oxide was added (5 min) at 10^0. The flask's contents were heated for 3 hr at the reflux temperature (39^0). After the mixture was cooled, water and just enough dilute HCl to make it neutral were added. The product was extracted with ether which in turn was washed with several small portions of salt-water and dried with sodium sulfate. Analysis of the ether solution by glpc indicated a yield of cyclopropylbutanol of about 20% (GLC-30 and -31).

The ether was distilled through a 6" helices column and collected as six 30-ml fractions. No butylene oxide was found in these by glpc. The next 25-ml fraction contained only a trace of oxide and was substantially all ether. The remainder of the crude product was fractionally distilled through a 15" Vigreux column at 50 mm Hg.

Cut No.	Wt, g	Bp^0	GLC No.
1	1.2	22-30	32
2	9.1	37-38	33 & 34
3	4.1	67-68	35 & 36
4	7.5	68-75	37
5	16.6	77-83	38
6	1.5	83	39
7	1.5	to 78^0 at 11 mm	40
Residue	4.3		41

Note: GLC-42 thru - 46 are standards.

Cuts 1 & 2 were mostly 3-buten-2-ol with small amounts of butylene oxide and dicyclopropyl identified by comparison of glpc retention times. Fraction 3 contained a little 3-buten-2-ol, a trace of an unknown B, a major component, C, a trace of 3-cyclopropyl-2-butanol, and a trace of an unknown E; with glpc retention times in the order named. Cut 4 was mostly C with small amounts of two higher peaks. Cut 5 contained a trace of each of B and C, while the major portion consisted of about equal parts of 3-cyclopropyl-2-butanol and E. Fraction 6 was mainly cyclopropylbutanol along with about 15% of E. Fraction 7 was found to consist mainly of cyclopropylbutanol along with a bit of E, while the residue showed just a trace of cyclopropylbutanol and nothing else. A composite sample of fractions 3 and 4 was examined by ir and found to be strong in hydroxyl, with no signs of carbon-carbon double bond, carbonyl or cyclopropyl groups. All of the fractions were recombined and an attempt was made to distill the lot at atmospheric pressure with the hope that improved separations might be realized. Upon heating the material turned very dark. Since carbonyl was shown to be present by ir it was considered that this might be the cause of the instability. By treatment with a bit of $LiAlH_4$ the carbonyl content was considerably reduced (IR-89b & -c), but not completely eliminated. No change in the glpc pattern was brought about by the $LiAlH_4$ treatment. The fractional distillation was now carried out at 100 mm and ten cuts were taken (GLC-47 thru -58). The separations

were not improved very much. C was obtained in quite pure state, and since it was a major by-product, attention was directed to its identification. It was noted that all the fractions which contained some of it developed color on standing. Chemical analysis (102) for the elements and for hydroxyl content strongly suggested butylene chlorohydrin. A micro boiling point was approximately the same as the handbook value of 137° for the 2,3 isomer. From the distillation data the atmospheric boiling point for C was estimated at 133°. Nmr and mass spectroscopy confirmed C to be 2,3-butylene chlorohydrin (61,95). Eventually a sample of authentic 2,3-butylene chlorohydrin was obtained, and its ir spectrum (IR-89d and IR-89e) was found to match that of C. It was a mistake to use HCl in work-up of the reaction product.

Experiment 4, A Larger Run Using Ether as Solvent for More Material to Use for Identification of By-products and to Obtain More 3-Cyclopropyl-2-butanol:- This run was made using 151.3 g (1.25 mol) of cyclopropyl bromide, 19.1 g (2.75 mol) of lithium, and 90.0 g (1.25 mol) of 2,3-epoxybutane. The cyclopropyllithium was prepared as in the preceding run. The butylene oxide in 100 ml of ether was added (7 min) at room temperature and the resulting mixture was heated at reflux (40°) for 3 hr. Water was added -- carefully at first -- to a total of 400 ml which was the amount required to dissolve the solids. The layers were separated

without any neutralization of the free base and the water layer was extracted with three 25-ml portions of ether. The total ether solution was washed with 10 ml of water then 8 times with 10 ml each time of saturated salt water and dried with K_2CO_3. By glpc the 410 ml of ether solution was estimated to contain 30 g (21% yield) 3-cyclopropyl-2-butanol. In the past even though the ether solution had been dried it was usually found that the material which distilled right after the ether came over wet. Therefore, this time extra effort was made to get the ether solution dry. After several treatments with anhydrous potassium carbonate a Karl-Fischer titration still showed 0.5% water. The ether was distilled off and by glpc was found to contain about 24 ml of 2,3-butylene oxide (fractions 1 thru 5). The remainder was distilled through a 22" long helices-packed column at 50 mm Hg. Ten ml of diethylene glycol monomethyl ether (bp 193 at atm., pure by glpc) were added as a chaser after cut 6 was taken.

Cut No.	Wt, g	Bp^0	Analysis (GLC-60 thru -72)
6	18.4	to 45^0 (mostly 39)	Mostly 3-buten-2-ol
7	2.6	45-72	Many peaks
8	7.4	72-79	Mostly B, 10% D*
9	7.2	79-83	25% B, 75% D
10	6.4	83-84	Trace B & C, mainly D
11	3.9	84-85	Mainly D, traces of C & E
12	2.6	85-91	Mainly D, traces of C & E
13	0.7	91-115	Traces of C & E, rest equal parts D and chaser

*D is 3-cyclopropyl-2-butanol.

Fraction 7 was estimated to contain about 18% 3-buten-2-ol, 53% of an unknown A1, and 29% of another unknown A2. Some A1 was trapped and shown by ir (IR-97a, IR-97b) to be isobutyl alcohol. The 53% concentration corresponds to a total of 1.3 g of this material. Likewise, some of A2 was trapped and by ir (Figure 8) and nmr (61) appeared to be 1,1-dimethylcyclopropylmethanol. Some of B was also trapped. Its infrared spectrum (Figures 9, 10) was very similar, but not identical, to that of 3-cyclopropyl-2-butanol. The nmr spectrum (61) could be rationalized by considering B as a mixture of cyclopropyl-t-butyl alcohol, 2-cyclopropyl-2-butanol, and 2-cyclopropyl-1-propanol.

If we calculate the yield of the most abundant components of the reaction mixture on the basis of butylene oxide we get; recovered butylene oxide 16%, 3-buten-2-ol 21%, isobutyl alcohol 1.4%, B approximately 4.5%, 3-cyclopropyl-2-butanol 13.5%; for a total of 56.4%. All other components which were distilled were present in amounts smaller than these.

Further Attempts at Purification of 3-Cyclopropyl-2-butanol:- Mixed fractions from the several preparations were combined and re-fractionated. The best cuts obtained were combined with the like already at hand and the entire lot was fractionated once more. The desired alcohol obtained in this manner was still not free of contaminants (GLC-73 thru -107). A number of glpc substrates were screened and it was found that a triethanolamine column would show

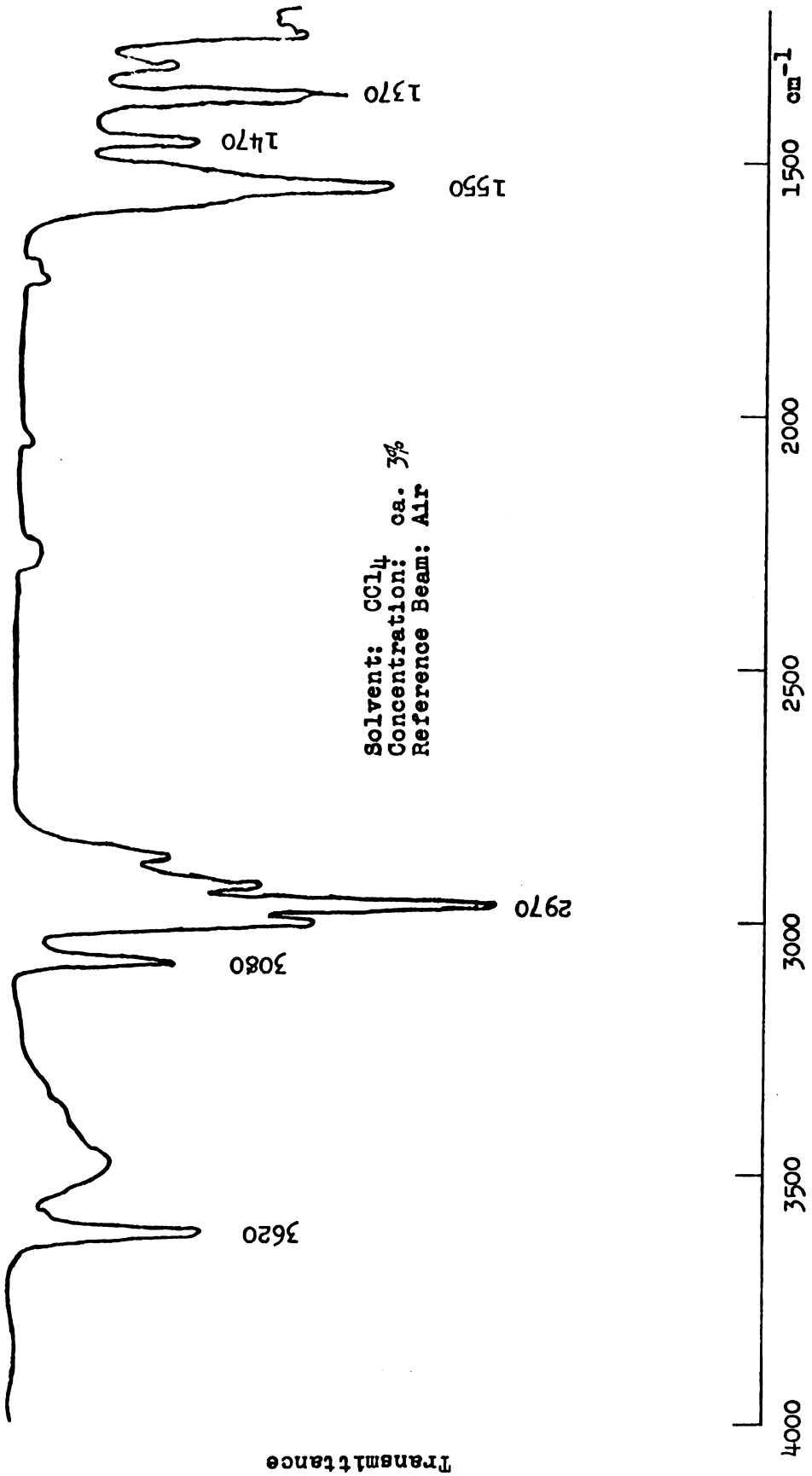


Figure 8. Infrared Spectrum of Glpc Fraction A-2 (Grating Machine)

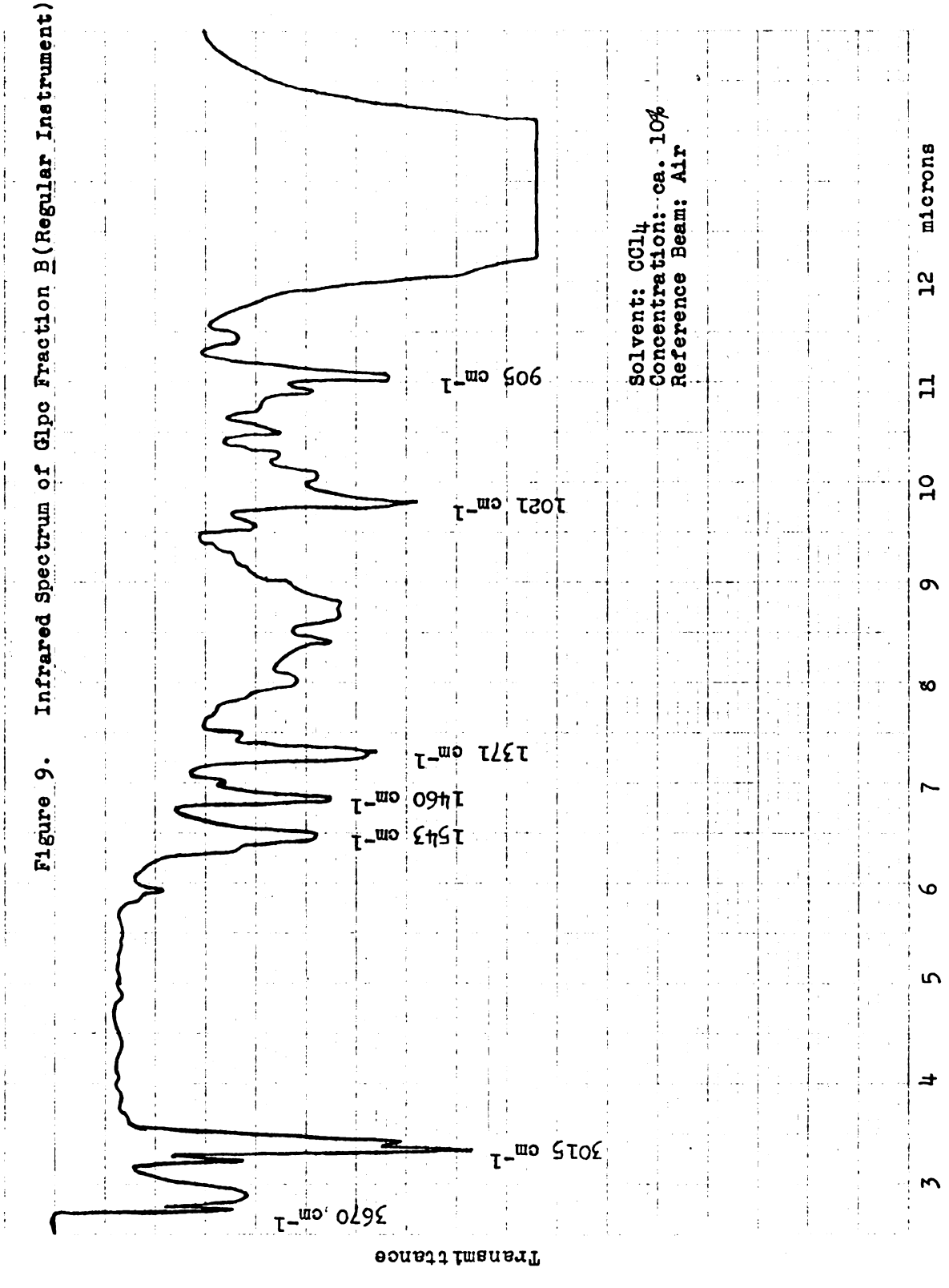
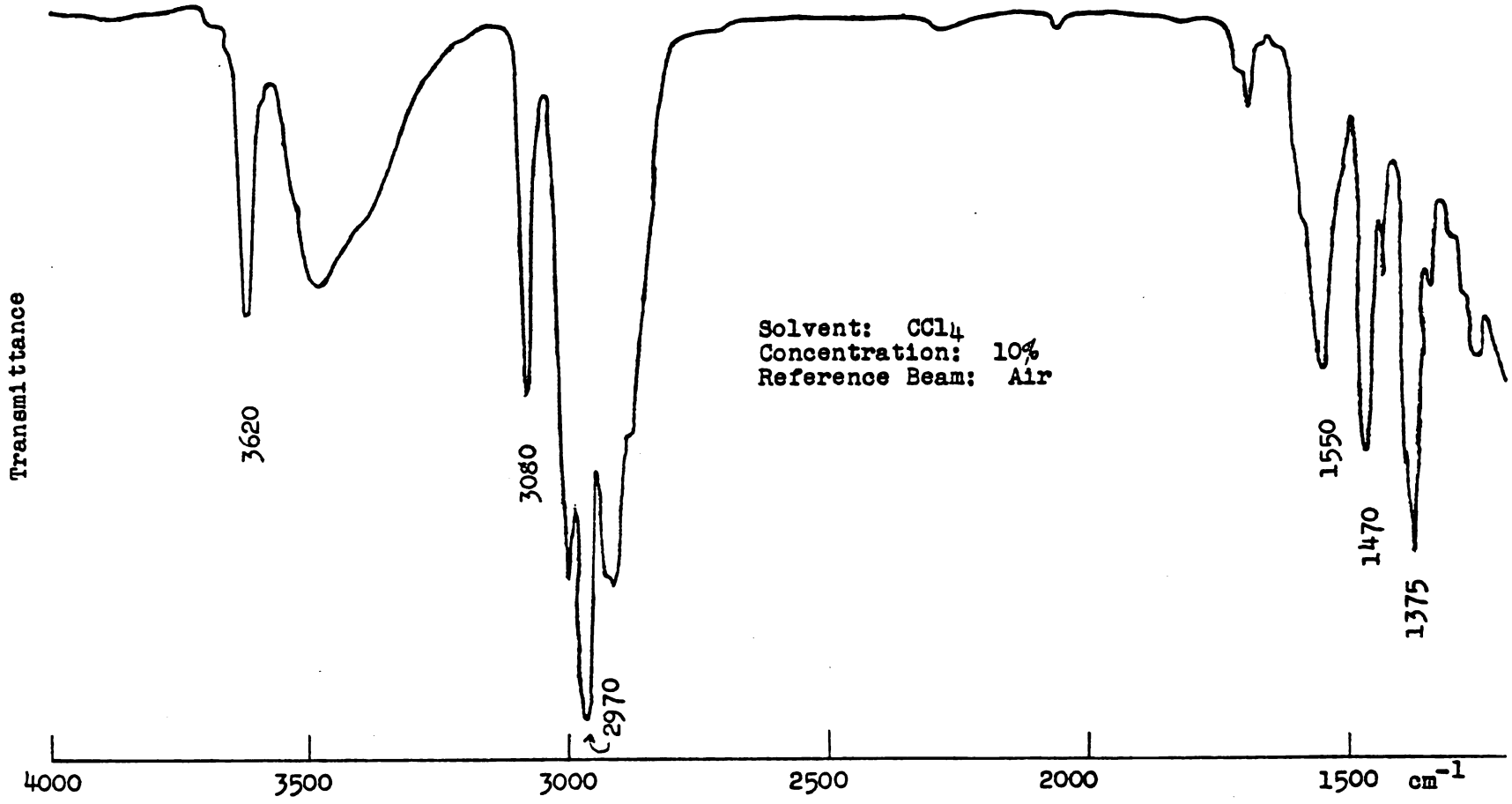


Figure 9. Infrared Spectrum of Glpc Fraction B (Regular Instrument)

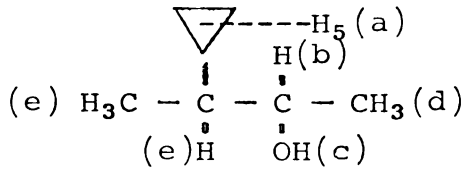
Figure 10. Infrared Spectrum of Glpc Fraction B (Grating Machine)



2-4% of impurity in material which an Oronite column had shown to contain only traces. Two grams of the purest material available were further purified by preparative glpc (120) using a column of N,N,N',N'-tetra(2-hydroxyethyl)ethylenediamine (GLC-98). Six significant impurity peaks showed up, which when taken as a group gave a mass spectrum suggestive of a mixture of hydrocarbons. The glpc purified material yielded mass (120) and ir (121) spectra which are consistent with the structure for 3-cyclopropyl-2-butanol (Figures 11-12). Analysis for the elements (102) gave 72.8% C, 12.05% H, and 15.7% O by difference. The calculated values for $C_7H_{14}O$ are 73.6, 12.4 and 14.0 respectively.

The hydrogen distribution as determined by nmr (Figure 13) is shown below (60),

Designation	Theory	Found
a	5	5.1
b	1	0.96
c	1	1.24
d	3	3.3
e	4	3.5



It was somewhat unexpected that the absorption band of the hydrogen on the tertiary carbon should fall in with that of the hydrogen of the adjacent methyl group. But, the major inconsistency of the nmr spectrum with the expected structure is the very high hydroxyl hydrogen content. It appears impossible to imagine an organic impurity which would

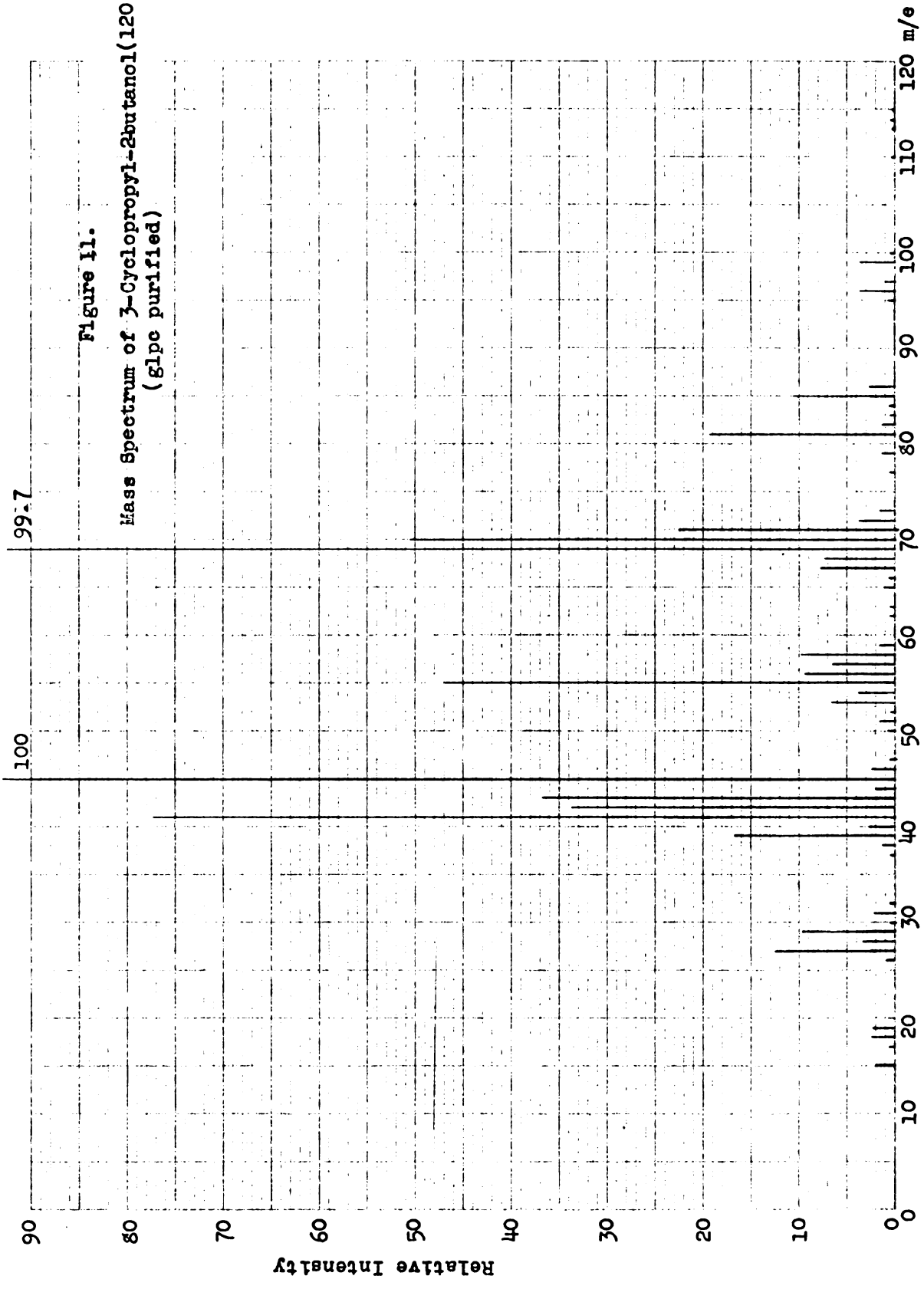


Figure 11.
Mass Spectrum of 3-Cyclopropyl-2butanol(120)
(glpc purified)
99.7
100
Relative Intensity
m/e
0
10
20
30
40
50
60
70
80
90
100
110
120

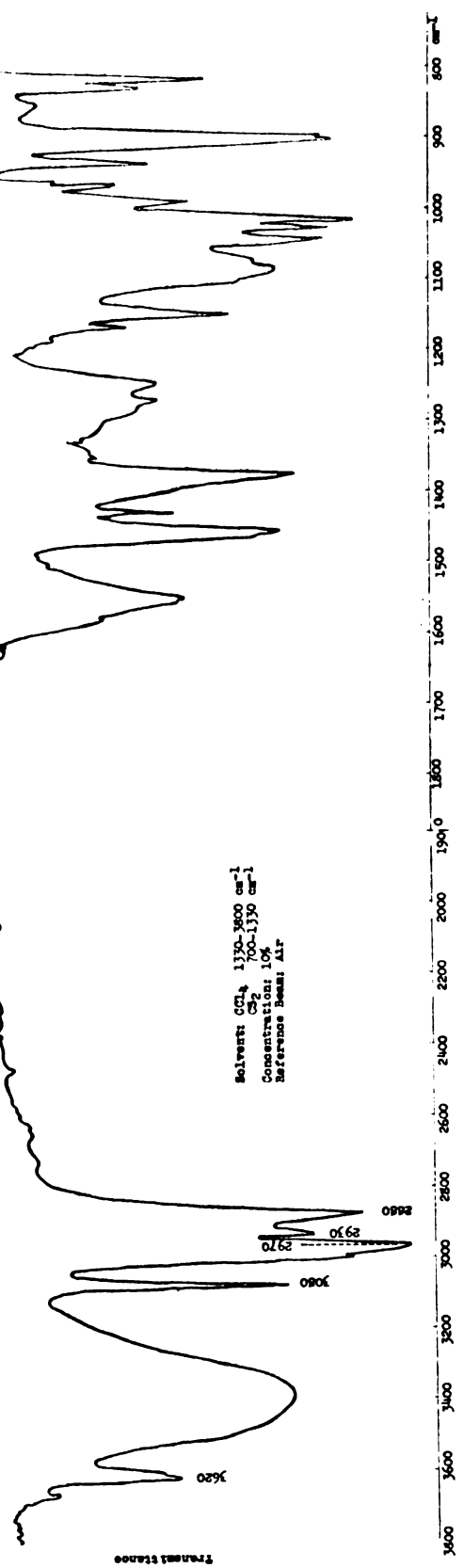
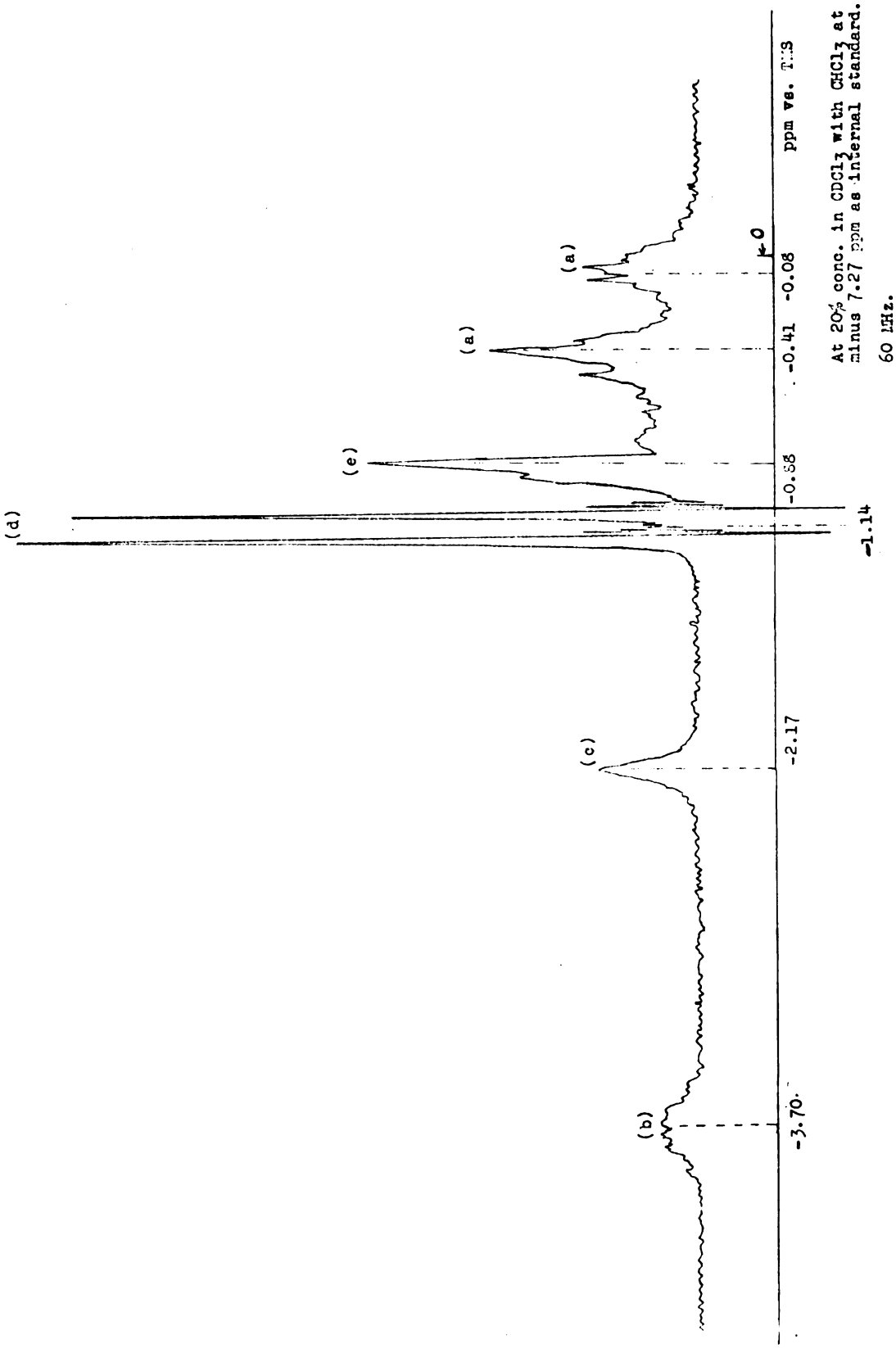


Figure 12. Infrared Spectrum of 3-Cyclopropyl-2-butanol(121)
(glpc purified)

Figure 13. Nmr Spectrum of 3-Cyclopropyl-2-butanol (60)
(glpc purified)



At 20% conc. in $CDCl_3$ with $CHCl_3$ at minus 7.27 ppm as internal standard.
60 MHz.

have this effect. The 1.24 figure could be approximated by a water content of about 7%, which also seems quite incredible, although some moisture could have been picked up. In retrospect, it would have been best to have dried the nmr solution before obtaining the spectrum.

A quite substantial number of glpc columns of different substrates were available and it was elected to screen a number of these with the hope of finding a substrate which would resolve the last remaining impurity from the 3-cyclopropyl-2-butanol. (GLC-108 thru -116). For this work the best fractionally distilled material was used. Of eight substrates tested only Lac (adipate of diethylene glycol crosslinked with pentaerythritol) showed any promise. It was used at 25% on phosphoric acid (2%) treated Chromosorb W, 80-100 mesh. Using a 6 ft long column at 130^0 a new impurity peak was found just ahead of and partly overlapping the main peak. It was estimated by area measurement to represent about 5% of impurity content. The quality of the resolution varied somewhat from sample to sample. A 12 ft column of the same substrate was prepared. Order of peak elution was now reversed and the resolution was very poor. Polyethylene glycol (mol wt 400, 25%, 10 ft long) performed very much like Oronite. Others tried and found unsatisfactory were; mannitol, phenyldiethanolamine succinate, polyethylene oxide diamine (Jefferson Chemical Co. L-1000), an adduct of glycerine and chloromethylated diphenyl oxide, and sorbitol.

G. Preparation of Tosylates

2-Butyl p-Toluenesulfonate:- Some Eastman Kodak practical grade 2-butanol was well dried over anhydrous potassium carbonate and fractionated through a 22" long Vigreux column. The end cuts were rejected and material boiling at 97.5-99.0° was retained for use. By glpc it showed no impurities. The pyridine was dried and distilled similarly. The p-toluenesulfonyl chloride was M. C. & B. practical grade and was used as obtained.

The butanol (3.181 g, 0.429 mol) and the sulfonyl chloride (9.82 g, 0.0514 mol) were added to 25 ml of ice-cold pyridine, well mixed, held in a cold chest at 4° for two days followed by an additional two days at room temperature (18). At this point the material was very light colored and a considerable quantity of pyridinium hydrochloride crystals was present. The mass was transferred to a flask containing 100 ml of 2N sulfuric acid and 50 ml of hexane which had been well cooled. After hydrolysis the lower aqueous layer was separated and washed successively with 25 ml of hexane, then ether (2X). The organic layers were combined and washed in succession with 2 ml of water (2X), 2 ml of salt water (2X), and dried with anhydrous sodium sulfate. The solvent was removed by application of reduced pressure and sufficient heat to maintain the temperature. The non-volatile product weighed 8.8 grams, which is a 90% yield if it is all the desired tosylate ester. No crystals

were formed even after one week at 4^0. By saponification and also by Volhard analysis the material was found to fit the composition of 8.1% p-toluenesulfonyl chloride and 91.0% 2-butyl tosylate.

The product was taken up in pentane (60 ml) and washed (3X) with 2-ml portions of 5% potassium carbonate solution, then with 1 ml of water (3X) and 1 ml of salt-water (2X). It was dried with anhydrous calcium sulfate and the solvent was removed under vacuum. At this point it was decided to repeat the experiment on a larger scale using the procedure of Tipson (67).

The 2-butanol (10.0 g, 0.135 mol) and 100 ml of pyridine were placed into a 500-ml flask which was provided with a stirrer and thermometer and sealed with a drying tube. The p-toluenesulfonyl chloride (28.3 g, 0.148 mol equals 10% excess over theory) was added over a 5-min period at 0^0, and stirred at this temperature for 2 hr. No heat evolution was apparent. Water (100 ml) was added -- very slowly at first -- while holding the temperature at $1\text{-}5^0$. The mixture was extracted (3X) with 100-ml portions of chloroform. The combined chloroform solution was washed with 2N sulfuric acid solution -- all kept cold -- to remove the pyridine, until the washes tested blue on congo red paper. Ten washes were made and a total of 520 ml of acid was used. After the product was washed with dilute potassium carbonate, dried with anhydrous sodium sulfate, and the chloroform was evaporated, 26.8 g of product were at hand, 87% yield based on the butanol used.

An attempt to distill a few grams of the crude product at 0.07 mm Hg resulted in decomposition (bath temperature 106°). However some of the material condensed on the upper part of the flask as a solid. A few crystals were removed with the object of getting an ir spectrum and possibly using them for seeding some of the crude to try and start it crystallizing. The ir spectrum (IR-145) showed absorptions at about 1190 and at 1370 cm^{-1}, which are reported (105) as characteristic of sulfonate esters. A spectrum of the crude material (IR-147) showed these same bands along with substantial differences. Attempts at crystallization of the crude product by seeding with this material met with no success. Saponification analysis of the crude came out at 106% pure indicating that it still contained sulfonyl chloride. This crude material was used as such for solvolysis rate studies.

3-Cyclopropyl-2-butyl p-Toluenesulfonate (18):- For the first preparation 0.445 g (0.0039 mol) of 3-cyclopropyl-2-butanol and 0.77 g (0.00403 mol, 3.0% excess) of p-toluenesulfonyl chloride were dissolved in 3 ml of pyridine while being kept well cooled. The mixture was held for 30 hr at room temperature then added to 20 ml of 2N sulfuric acid with good cooling (acid to Congo Red paper). It was extracted with pentane (2 x 5 ml) and ether (5 ml). The solvent layers were combined and washed with water (1 ml), dilute K_2CO_3 (1 ml) and again with water (3 x 1 ml). After

being dried with anhydrous sodium sulfate the solvent was removed and the product became crystalline. It was first washed with just a bit of pentane and then dissolved in a larger amount of pentane and recrystallized, mp 49.5-52.5°. After another recrystallization from 2 ml of pentane the melting point was 50.0-52.0° and the material weighed 0.422 g (0.00155 mol). It was now dissolved again in 2 ml of pentane, treated with activated charcoal and crystallized once more. The product now weighed 0.278 g and melted at 51.5-53.0°.

At this point the product was unintentionally left exposed to the atmosphere for two days. No change in appearance or weight occurred and it melted at 52.0-53.0°. (Note: the melting points were determined in capillaries in a liquid bath with a thermometer graduated in 0.2 degrees. No stem correction was applied, but the thermometer was immersed to the manufacturer's mark.) On recrystallization from 80% aqueous methanol it melted at 52.0-54.0°. An infrared spectrum (Figure 14) showed an absorption maximum at 3075 cm^{-1} (cyclopropyl C-H stretch) and rather broad peaks at 1190 and 1370. The latter two are in the ranges cited by Bellamy (105) as being characteristic of sulfonates.

Anal. Calcd for $C_{14}H_{20}O_3S$: C, 62.7; H, 7.51; S, 11.93.
Found: C, 62.8; H, 7.66; S, 11.96 (100).

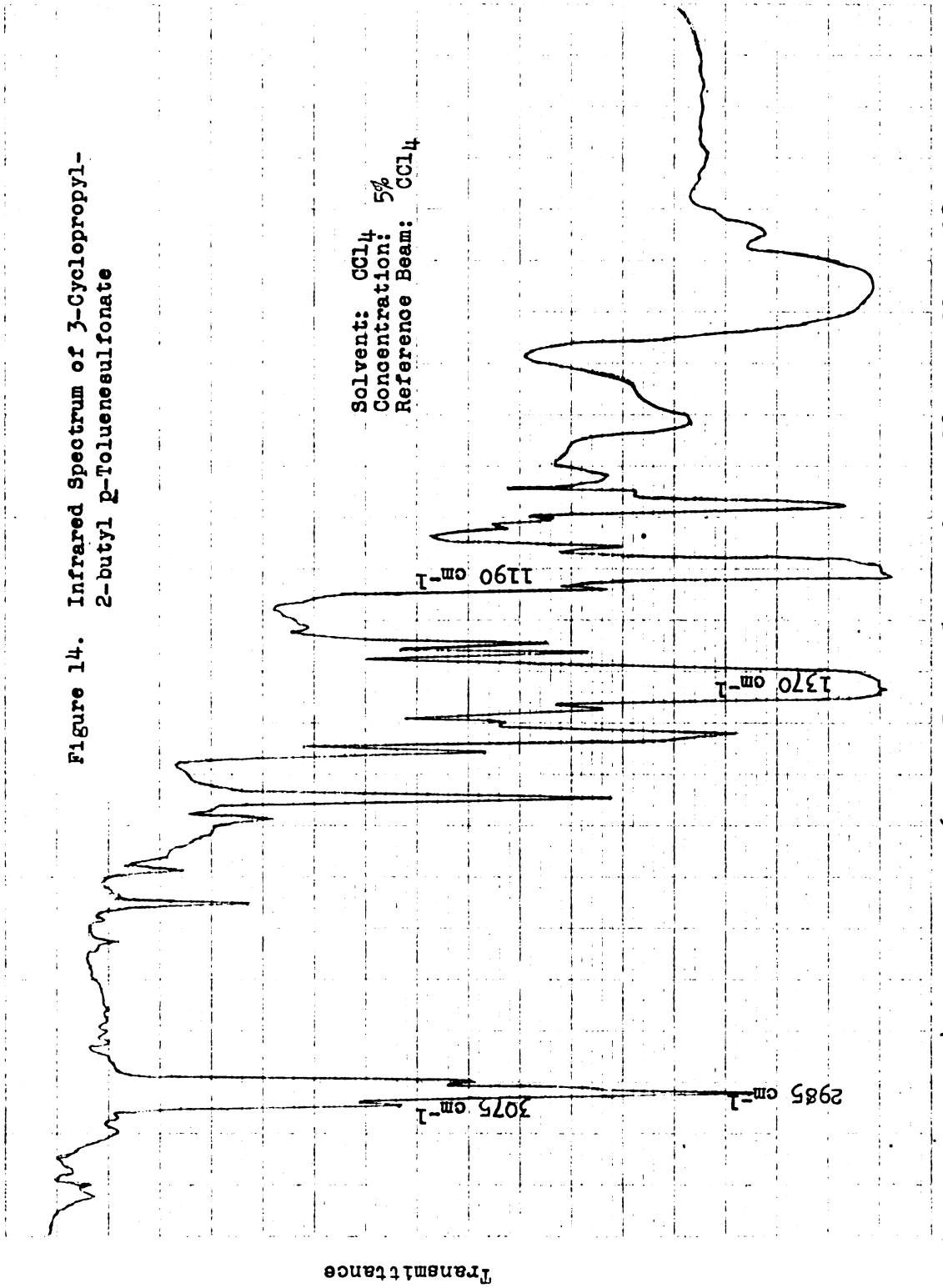


Figure 14. Infrared Spectrum of 3-Cyclopropyl-2-butyl p-Toluenesulfonate

With hope of getting material having a sharper melting point it seemed appropriate at this point to take a look at the quality of the p-toluenesulfonyl chloride. It was a very old appearing bottle and had no doubt been opened many times, although the chloride itself was not bad in appearance. It melted at 68.0-68.5° (Handbook of Chem. and Phys. gives 69.0°). A sample (3.1435 g) was saponified by prolonged stirring with 40.0 ml normal sodium hydroxide. According to the base consumed the purity of the chloride was calculated to be 100.1%. Chloride ion found in the solution corresponded to a purity of 99.6%. It appeared that the quality of the p-toluenesulfonyl chloride was satisfactory.

For a second and larger preparation of the sulfonate ester 3.51 g of 3-cyclopropyl-2-butanol (0.0307 mol) and 7.04 g (20% excess) of sulfonyl chloride were dissolved in 15 ml of cold pyridine. The mixture was held at 4° for two days and at room temperature for two additional days, by which time it had turned quite brown and contained much solid pyridine hydrochloride. Recovery of the crude product was accomplished in substantially the same manner as in the case of the previous run. The yellow crystalline crude product weighed 7.3 g, equals 88.5% yield. It was recrystallized twice from hexane and once from 80% aqueous methanol leaving 3.83 g with a mp of 51.5-54.0°. It continued to be consistently difficult to obtain a sharp melting product. Also in the case of the crystallization from hydrocarbon

solvent there appeared to be a second component present which was more difficult to get into solution than the bulk of the material.

A third lot of sulfonate was prepared using one gram (0.00877 mol) of alcohol with 20% excess of p-tosyl chloride in 5 ml pyridine, holding at ice-water temperature for 3 hr, then working up as before except that everything was kept cold right through the work-up procedure. Approximately 0.50 g of the tosylate (mp 51.5-53.9°, calcd 27% yield) was obtained.

A fourth lot (2.0 g alcohol) was prepared essentially as the third except that the mixture was held at 4° overnight. Results were about 57% yield and a melting point of 52.8-54.0°.

Throughout the four runs it was not possible to get material of sharp melting point. Also there appeared to be some insoluble oily impurity present. Attempts at recovery of second crops of crystals yielded only very small returns.

Tosylation Rate Study:- Two hundred grams of p-toluenesulfonyl chloride were purified by recrystallization from methylcyclohexane. A weighed sample was hydrolyzed with aqueous pyridine and analyzed for chloride ion and total acidity. The respective assays calculated from the analytical figures were 99.5% and 101.4%. The melting point of the recrystallized material was 67.4-69.0°. A standard solution of this tosyl chloride was prepared by dissolving

7.013 g (0.0369 mol) in 100 ml of dry center cut pyridine (0.02% water by Karl-Fischer titration). A weighed sample of i-propyl alcohol (0.210 g, 0.00350 mol) was mixed with enough of the standard solution (0.00925 mol) to give exactly 25 ml of reacting solution. Five-ml aliquots of the reacting solution were analyzed at several time intervals by hydrolysis followed by titration with base (phenolphthalein).

The results are shown in the following table.

Hours	Titer Decrease ml 0.1N NaOH	% Reaction
0.6	2.0	24
5.0	5.3	76
17.5	7.0	100
50	7.2	103

The base (0.1N NaOH) titer for zero time was determined using 5 ml of the tosyl chloride solution alone, and found to be 37.0 ml. It was calculated that at 100% reaction 0.000700 mol of acid should have disappeared, corresponding to reduction in titer of 7.0 ml NaOH. The second column in the table shows the NaOH titer decrease. The last column shows the same figure as a percent of 7.0, the 100% titer decrease. The data are plotted as Figure 1, page 51.

In a similar experiment with 2-ethylhexanol-1 33% reaction took place in the first five minutes and 105% in 11 hours.

2-Octanol (0.611 g, 0.00470 mol, E. K. Co. white label grade) was treated with the tosyl chloride solution and the following rate data were observed.

Hours	Titer Decrease ml 0.1N NaOH	% Reaction
0.25	2.2	23.4
1.0	3.8	40.4
15.5	8.0	85.0
30.0	7.5	80.0

It appears that some interfering process was taking place.

H. Formolysis of Tosylates

Purification of Formic Acid (69,106,107):- Phosphorus pentoxide (43.0 g, 0.30 mol) was added slowly with cooling to 156.6 g (4.7 mol) of 89.1% (by titration with base) B & A reagent grade formic acid and the mixture was allowed to stand overnight. The formic acid was now distilled away from the solid at 70 mm Hg through a 22" helices column. After a forerun of 8.8 g was discarded a main fraction of 94.3 g was collected. It boiled at 35.0-35.5^0 and was found to be 99.3% pure by titration with standard base.

Alternatively, some formic acid was purified by partial freezing. A portion (1131 g) of B & A CP grade material which assayed 98.0% was subjected to reduced pressure sufficient to boil it for a few minutes to remove any carbon monoxide decomposition product which might have been present. It was slowly cooled without being stirred until only a small portion of liquid phase remained. After this was

drained off the 1060 g of solid remaining were found to be 99.2% pure. An attempt was made to determine the water content by the Karl-Fischer method but there appeared to be some interfering reaction, perhaps reduction of the iodine by the formic acid.

The formic acids purified by both methods were used interchangeably in the formolysis work.

Preparation of Standard Solutions:- A concentrated (ca. 16%) solution of potassium carbonate in water was prepared and carefully analyzed by titration of a weighed sample; found, 2.365 meq per gram. A 1.829 g sample of this solution was diluted to 100 ml with anhydrous acetic acid to give a 0.0432N solution of potassium acetate, calculated. The acetic acid was CP Reagent grade and analyzed at 99.6% by titration; it was used as obtained.

Aqueous perchloric acid (70%) and acetic acid were used to prepare a 0.0500N solution of perchloric acid. Standardization was accomplished using the standard potassium acetate and bromphenol blue. It soon became apparent that there would be difficulty due to the low solubility of $KClO_4$ in the acetic acid, so a standard solution of sodium acetate at 0.0500N was prepared using the standard perchloric acid as a reference.

To get some feel for the reproducibility of analytical values, 1.007 g of p-toluenesulfonic acid was diluted to 100 ml with acetic acid and several aliquots were titrated

with the standard sodium acetate.

Acid, ml	Base Used, ml	Purity, %
5.00	5.10	96.5
9.00	5.18	96.5
9.00	9.00	94.7
9.00*	8.95	94.2

*Two ml of 100% formic acid were added to this aliquot.

Reproducibility was of the order of two percent. A blank was found to require about 0.05 ml of standard solution to show the color change of the indicator.

Rate Study:- Some preliminary experiments were without temperature control to develop confidence in analytical procedures and to determine whether approximate agreement with published reaction rate values could be obtained.

When 0.234 g (0.001025 mol) of 2-butyl tosylate was added to 11.7 ml formic acid and immediately titrated with standard sodium acetate, a titer of 0.05 ml was obtained, which corresponds to 0.23% formolysis at zero time. The endpoint was much harder to detect than was the case of the preceding titrations, due to the color of tosylate. (Note: As mentioned earlier, there was no purification of this tosylate.) To obtain a value for infinite time 0.2450 g (0.001073 mol) of the same tosylate was added to 12.2 ml of formic acid. (Note: The concentration of tosylate in formic acid was chosen at about 0.08 molar to correspond to

Winstein's work (69a,108).) After 137 hours at room temperature a determination of strong acid content showed 93.2% formolysis. Very likely this was about the purity of the starting tosylate. A number of determinations of the endpoint were made by titrating back and forth. Values obtained for net titers were 20.45, 19.55, 20.00 to give an average of 20.00 ml of 0.05N sodium acetate.

Exactly one gram of 2-butyl tosylate was now diluted to exactly 50 ml with formic acid. It was let stand at room temperature ($27.0^{0} \pm 0.2^{0}$) and at measured time intervals 5-ml aliquots were removed and titrated with 0.05N sodium acetate in acetic acid. The following formolysis rate data were obtained.

Elapsed Time Hrs:Min	Titer, ml	% Reacted
0:05	0.22	2.5
0:44	1.13	12.9
1:03	2.02	23.1
1:37	2.85	31.5
2:11	3.69	42.2
2:53	4.52	51.6
3:46	5.31	60.6
7:07	7.00	80.0

The titer values shown are averages of several numbers obtained by titrating back and forth to the endpoint. The color of the tosylate was definitely an interference. Some experimenting was done with the lighting arrangement and use of a fluorescent light was an improvement. Most of the titrations were done in 10 ml of acetic acid as diluent.

This appeared to be about the optimum dilution for observation of the indicator (bromphenol blue) color change. The percent reacted figures were obtained by multiplication of the ml titer by 11.41 which equals

$$\frac{0.0500N \times 228.2 \text{ mol wt} \times 100}{1000 \times 1.000 \text{ g tosylate}} .$$

First order rate constants were now calculated for the time intervals using the formula $k_1 = \frac{2.3 \times \log M_1/M_2}{t \text{ seconds}}$. The M's can be concentrations in any units and percent unreacted tosylate was chosen. M_1 was taken as 93.2 - 0.2 = 93.0. M_2 was arrived at by subtraction of the percent reacted from 93.2.

T, sec	M_2	Log M_2	Log M_1/M_2	k x 10^4
300	90.7	1.95761	0.01087	0.833
2640	80.3	1.90472	0.06376	0.555
3780	70.1	1.84512	0.12276	0.747
5820	61.7	1.79029	0.17819	0.705
7860	51.0	1.70757	0.26091	0.763
10380	41.6	1.61909	0.34939	0.773
13560	32.6	1.51322	0.45526	0.772
25620	13.2	1.12057	0.84791	0.760

The value reported in the literature (18,108) is 0.47-0.50 x 10^{-4} at 25^0 which is fair agreement at this point.

Approximately 7 ml of an 0.08 molar solution of 3-cyclopropyl-2-butyl tosylate in formic acid were placed in a constant temperature bath at $50^0 \pm 0.2^0$. At the end of 16 min one ml of this solution required about 2.3 ml of 0.05N base for neutralization. This is about 145% of theory

for complete formolysis. The solution had turned yellow and the endpoint was quite poor. After 13 more minutes the solvolysis solution had taken on a deep purple color, making further titrations impossible.

Attention was turned to the use of a pH meter as a means of endpoint detection. A MacBeth model 1051 pH meter with regular glass and calomel electrodes was at hand. Figure 2, page 53, shows the findings of some exploratory titrations using the pH meter. (The pH values plotted are just meter readings.) Figure 2a shows the quality of the break realized when 10 ml of the standard perchloric acid in acetic acid were titrated vs 0.050 N sodium acetate in acetic acid. By replacement of the aqueous KCl in the calomel electrode bridge with KCl in acetic acid a significantly better endpoint was obtained, as shown in Figure 2b. This same bridge was used in the remainder of the work. Plots 2c and 2d represent titrations of p-toluenesulfonic acid in acetic acid. Figure 2e shows the effect of addition of one ml of formic acid to the preceding case and Figure 2f that of one ml of formic acid plus one ml of acetic anhydride.

At this point the rate studies were tabled in favor of effort toward investigation of the products of formolysis.

Examination of Formolysis Products:- Some 3-cyclopropyl-2-butanol (0.461 g, 0.00172 mol) was added to 5 ml formic acid. After 5 minutes at room temperature no color had developed. After warming to 50^0 the material turned red in

a few minutes and after 2.5 hr at this temperature it had become deep purple. One half of the lot was added to ice-water and extracted with 2 ml of CCl_4. The extract was washed with potassium carbonate solution, with water, and dried. Its infrared spectrum (IR-148) showed a strong carbonyl absorption, medium carbon-carbon double bond, and weak hydroxyl, at 1726, 1652, and 3990 cm^{-1}. Cyclopropyl carbon-hydrogen stretch at 3040 cm^{-1} was not present.

The other half of the formolysis product was extracted with ether in a like manner. (In both cases the purple color disappeared during the extraction.) An attempt at distillation of the extracted material was unsuccessful.

To get more material for investigation one gram (0.00374 mol) of the tosylate was added to 25 ml of formic acid and allowed to stand for one week, by which time it was a deep purple color. The organic material was recovered by ether extraction as before. $LiAlH_4$ (0.00746 mol) was added to the dry ether solution with the intent of reducing esters and possibly carbonyl compounds to alcohols for easier identification. A limited amount of water was added and the ether solution was decanted from the solid inorganic hydroxides. After the solution was dried and the ether carefully evaporated, 0.322 g of product remained. If this were all 3-cyclopropyl-2-butanol it would constitute 75.8% recovery. By infrared (IR-153) it showed a strongly hydrogen-bonded hydroxyl absorption, a rather clean narrow carbon-hydrogen stretch at 2620 cm^{-1}, a small but significant

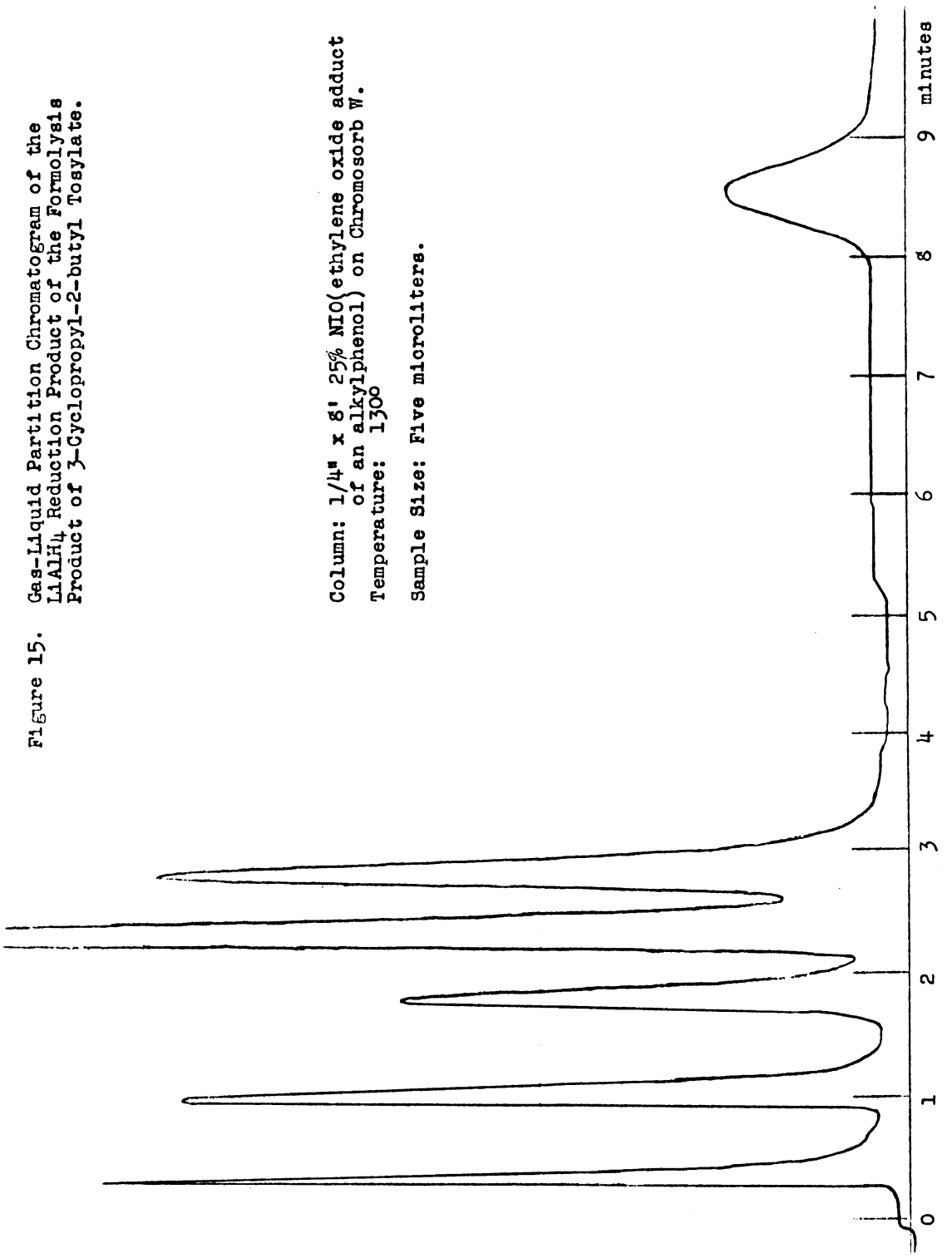
carbonyl at 1725, and no sign of unsaturation or cyclopropyl. By glpc (6' Oronite NIO at 130°) six significant components were observed (Figure 15).

Another 0.5 g of 3-cyclopropyl-2-butyl tosylate was formolyzed and recovered with ether as previously. Again the dry ether solution was reduced with $LiAlH_4$ (0.00792 mol). In order to separate the inorganic as a coarse solid (109), the following were added in order: 0.30 ml water, 0.22 ml 20% NaOH, 0.9 ml water. After being well shaken the inorganic material was a clean coarse solid which settled readily to leave a clear solution of the organic product. The solvent phase was decanted, dried further with sodium sulfate, and freed of most of the ether by careful distillation through a 15" Vigreux column. The ether was collected in four fractions which were run through a glpc column and shown to contain no significant amount of the product. (To be certain that no materials were being introduced with the ether some of the stock ether was distilled to about one tenth its original volume and the residue checked by glpc.) The residue from the above distillation was analyzed by glpc (6' Oronite NIO at 70° and at 130°). Observed were much ether, one major product peak plus a number of minor peaks.

Apparatus was now improvised for the collection of glpc fractions, and some of the major peak was isolated. It was estimated that about 0.266 g of this material were present

Figure 15. Gas-Liquid Partition Chromatogram of the $LiAlH_4$ Reduction Product of the Formolysis Product of 3-Cyclopropyl-2-butyl Tosylate.

Column: 1/4" x 8' 25% NIO(ethylene oxide adduct of an alkylphenol) on Chromosorb W.
Temperature: 130°
Sample Size: Five microliters.



in the lot. At the point when a few milligrams of this fraction were in hand it happened to be convenient to obtain a mass spectrum which identified the compound as ethyl alcohol (110). Ethyl alcohol was found to have the same glpc retention time as the component in question. Some additional glpc work was done to see if other glpc peaks would show up at higher retention times and/or higher temperatures. Nothing clear-cut resulted.

A 2.72 g (0.010 mol) portion of 3-cyclopropyl-2-butyl tosylate was now formolyzed at 0.20 molar concentration. When it was added to the formic acid at room temperature a light pink color developed at once. After 20 hr the solution had turned purple and an oily film had appeared at the surface of the solution (olefin ?). The mass was poured into ice-water and extracted with ether, and again the color changed from purple to a light yellow. An attempt to determine the amount of unsaturated material present by bromination yielded no useful information. An analytical hydrogenation apparatus was available and after an orientation trial with cyclohexene 5 ml of the total of 75 ml of the ether solution was hydrogenated and found to absorb 2.0 ml of hydrogen. Platinum oxide was used as a catalyst and isopropyl alcohol as a solvent. It was estimated that approximately 12% of the tosylate had been converted to olefin.

By use of infrared spectroscopy with ethyl formate as a standard it was estimated that the ether solution of the

formolysis product was 0.170 molar in formate ester (IR-161 to -164). By calculation this yielded the figure of 125% for the degree of ester formation. One can only say that most of the tosylate was converted to the formate ester, with something of the order of 10% going to olefin.

The remainder of the ether solution was treated with 1.2 g of $LiAlH_4$ for one hour at room temperature followed by one hour at reflux temperature. Addition of water and sodium hydroxide followed by separation of solid inorganic material was done as in the preceding lot. The ether solution was washed until free of alkali and dried over barium oxide. At this point the volume was 200 ml and by infrared no carbonyl was observable. The ether was removed through a 22" helices-packed column and collected in four equal portions which, by glpc (GLC-118 to -123), showed traces of methanol and ethanol and nothing else. The distillation residue comprised about 6 ml and by ir showed no carbonyl, but much hydroxyl.

A rather intense effort was made to isolate the reduced solvolysis products by preparative glpc and identify them. Analytical size glpc columns (6 ft length) of Oronite NI-W and dinonyl phthalate were used. A micro infrared cell (Limit Research Corporation, London; M-04N, 0.1 mm path length, 0.006 ml capacity) was obtained. The fraction collecting technique was strengthened. By running glpc chromatograms at various conditions eight rather well-defined peaks (GLC-124 through -139) were obtained, of which the

first two were ether and ethanol. It was estimated that peaks III through VIII represented about 0.5 g of material, which at a molecular weight of 100 would account for about one half of the starting tosylate. By running glpc at 200° it was found that there was present a considerable amount of less volatile material which yielded very broad and poorly-resolved peaks, which no doubt are an indication of what happened to the remainder of the tosylate. Peaks IV, V, and VI were successfully trapped and ir spectra thereof were obtained. In addition to the glpc trapping work a sample of the reduction mixture was also analyzed by a combination vapor phase chromatograph-mass spectrometer (110).

Peak III did not yield to trapping but by mass spectroscopy was indicated to be a C_7H_{12} hydrocarbon, probably cyclopropylbutene-2. By mass spec also traces of C_8H_{16} were found in the glpc region between peaks III and IV. For peak IV the glpc retention time was the same as for 2-cyclopropyl-2-butanol and the mass spectrum agreed with that of known material, however, the infrared spectrum (IR-166) of trapped IV was distinctly different than that of this tertiary alcohol, and in fact suggested (111) a structure resembling 2(2-hydroxyethyl)tetrahydrofuran. For peak V the evidence indicated a mixture of two completely hydrogen-bonded alcohols (IR-167) of mol wt 192. The ir spectrum (IR-168) of VI was consistent with a dimethyl-cyclopentanol structure (111). Peaks VII, VIII and those

higher must have been condensation products, but no information concerning the structure of these was obtained. By measurement of peak areas the amounts of the several materials contained in the 0.5 gram were estimated at; III, 0.014 g; IV, 0.086 g; V, 0.059 g; VI, 0.098 g; VII, 0.101 g; VIII, 0.101 g.

Further examination of the stock 3-cyclopropyl-2-butanol showed that it contained as an impurity the V doublet which was found in the reduced solvolysis products.

I. Attempted Preparation of 3-Cyclopropyl-2-butanol by a Multi-step Route Beginning with a Reformatsky Condensation of Ethyl Bromoacetate with Cyclopropyl Methyl Ketone

Ethyl 3-Cyclopropyl-3-hydroxybutyrate (32,72) and Ethyl 3-Cyclopropylcrotonate (72,73,74):- The cyclopropyl methyl ketone was Columbia Chemicals Co. material of bp 110-111°. The zinc dust was Merck Reagent. The ethyl bromoacetate was Eastman White label grade. All of these materials were used as received. The Reformatsky reaction was run in a three-necked flask fitted with stirrer, thermometer, dropping funnel, and reflux condenser vented thru a calcium chloride tube. The solvents were dried before use.

The ketone (42.0 g, 0.50 mol) and the ester (83.5 g, 0.50 mol) were dissolved in a mixture consisting of 100 ml of benzene and 100 ml of toluene. Twenty-five ml of this solution were added at once to 32.7 g (0.50 mol) of zinc dust already in the reaction flask. With a bit of initial

warming the reaction began readily and the remaining reaction mixture was dropped in at a rate such that the reaction continued vigorously. The solvent mixture served to control the temperature at about 90°. Addition of the reactants was complete in 20 min and the mixture was heated for one additional hour at 90°.

The mixture was now cooled to 18° and water plus 10% sulfuric acid were added until a clear aqueous layer was obtained. The water layer was separated and extracted once with benzene. The combined solvent layer was dried, filtered and distilled to 160° bath temperature at 100 mm Hg. At this point the vapor temperature was 55° and decreasing. Remaining in the distillation flask were 64.5 g of crude product, which, if it were all hydroxyester would be equivalent to a 75% yield. The product was transferred to a distilling flask with a short fractionating column, six drops of concentrated sulfuric acid were added, and the material was flash distilled at 100 mm Hg pressure. The wet distillate comprised 61.1 g, and there were 2.3 g of residue.

The distillate was dissolved in pentane and the solution dried with calcium chloride. An ir spectrum (IR-3) showed significant hydroxyl content at 3570 cm^{-1} and carbon-carbon double bond at 1640 cm^{-1}. After removal of the pentane and addition of 20 drops of sulfuric acid the material was heated at 135-40° for 2 hr, then flash distilled as before. The wet distillate weighed 49.1 g and there were

4.0 g of residue. The distilled material was dried as before and distilled through a 12" long Vigreux column at 30 mm Hg.

Cut No.	Wt, g	Bp^0	IR No.
1	1.4	40-100	
2	3.4	100-105	
3	4.8	105-110	IR-4
4	10.6	110-111	IR-5
5	13.7	111-114	IR-6
6	4.2	114-122	IR-7
7	3.9	122-132	
Residue	2.6	light-colored and salty-appearing	

The infrared spectra all showed hydroxyl and unsaturation and all were rather "messy" looking.

Some alumina was dried overnight at 200^0 and a 3/8" x 7.5" long column was prepared. One ml of cut 4 in 25 ml of dry pentane was passed through the column followed by pure pentane and the effluent was collected as five-ml fractions. About 60% of the material was found in eluent cuts 5, 6, and 7 and found to be unsaturated, and free of hydroxyl (IR-8, -10, and Figure 16). This procedure was now scaled up to a one-inch diameter by 14" long column, and distillation cuts 3 through 6 were dissolved in 300 ml of pentane and passed through. Eluent was collected as 50-ml fractions. Elution with pure pentane was continued until 13 fractions had been collected, followed by 300 ml of ether through fraction 19, finally with 300 ml of methanol to make a total of 25 fractions. The profile of material recovery was as follows:

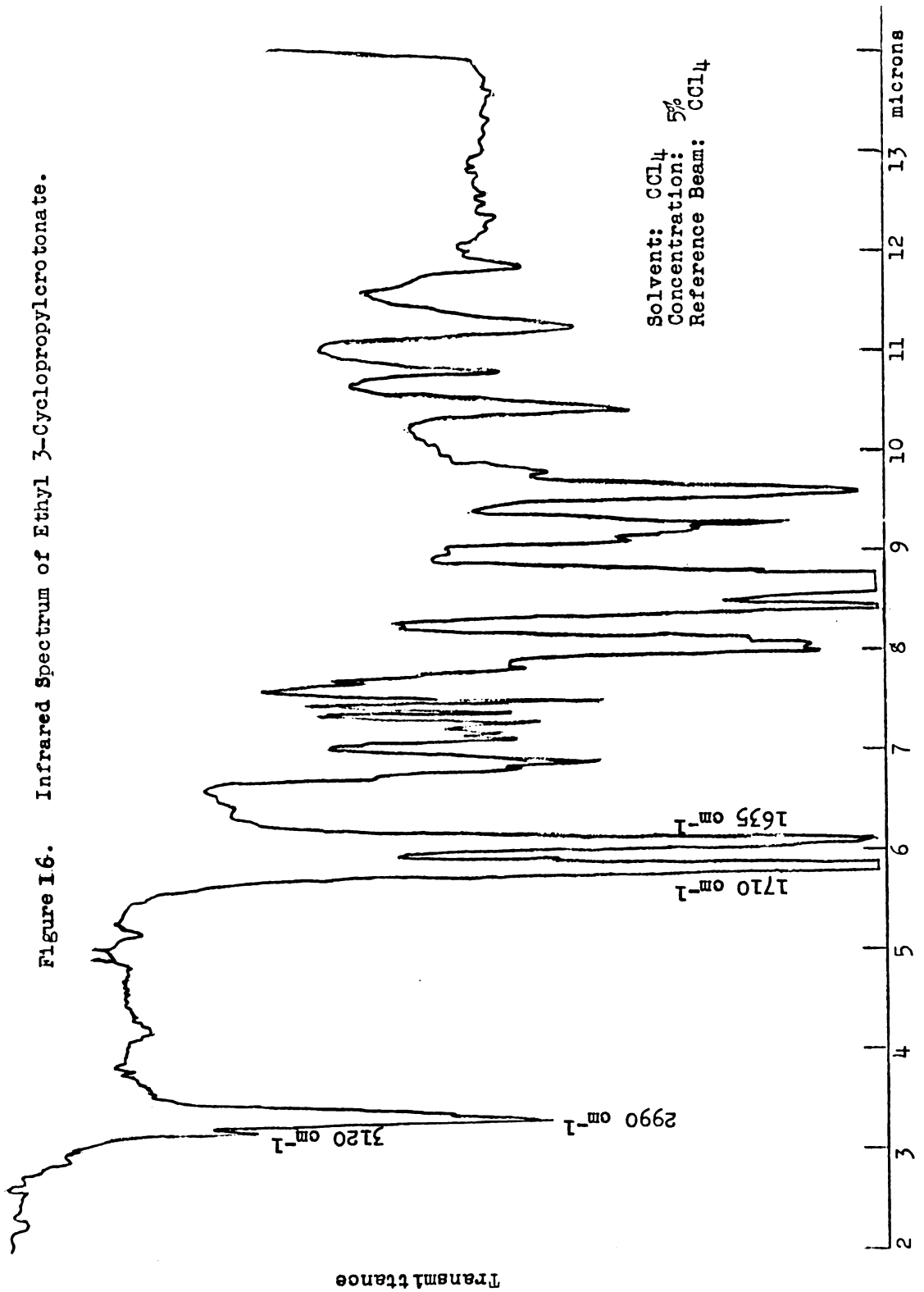


Figure 16. Infrared Spectrum of Ethyl 3-Cyclopropylcrotonate.

Fraction No.	1-4	5	6	7	8	9	10	11	12
Wt, grams	0	0.2	2.5	4.4	4.4	4.6	2.6	0.7	0.2
Fraction No.	13	14	15	16	17	18	19	20	21
Wt, grams	0.2	0.1	0.1	0.6	0.4	0.3	0.2	0.1	0.1
Fraction No.	22	23	24	25	Total Eluted			Total Charged	
Wt, grams	3.5	0.4	0.1	0.1	25.8			33.3	

By ir analysis fraction 6 (IR-11) was found to contain unsaturation and to be free of hydroxyl, fraction 9 (IR-12) contained both unsaturation and hydroxyl, while fraction 22 (Figure 17) contained hydroxyl but no double bond; showing that separation of the hydroxyester from the crotonate was not clean-cut.

All of the chromatography fractions together with the remaining distillation fractions were combined (34.0 g) and fractionally distilled through a 22" long helices-packed column at 22 mm Hg pressure.

Cut No.	Wt, grams	Bp^0	IR No.
1	3.3	75-79	IR-23
2	8.4	97-104	IR-24
3	5.8	103-104	IR-25
4	5.0	104-105	IR-26

Residue 2.1 g

By ir all of the fractions showed considerable hydroxyl content, except the first which showed only a trace. They all showed considerable unsaturation as well.

Dehydration of the tertiary alcohol ester by the method of Rinehart (74) was now attempted. The entire lot of

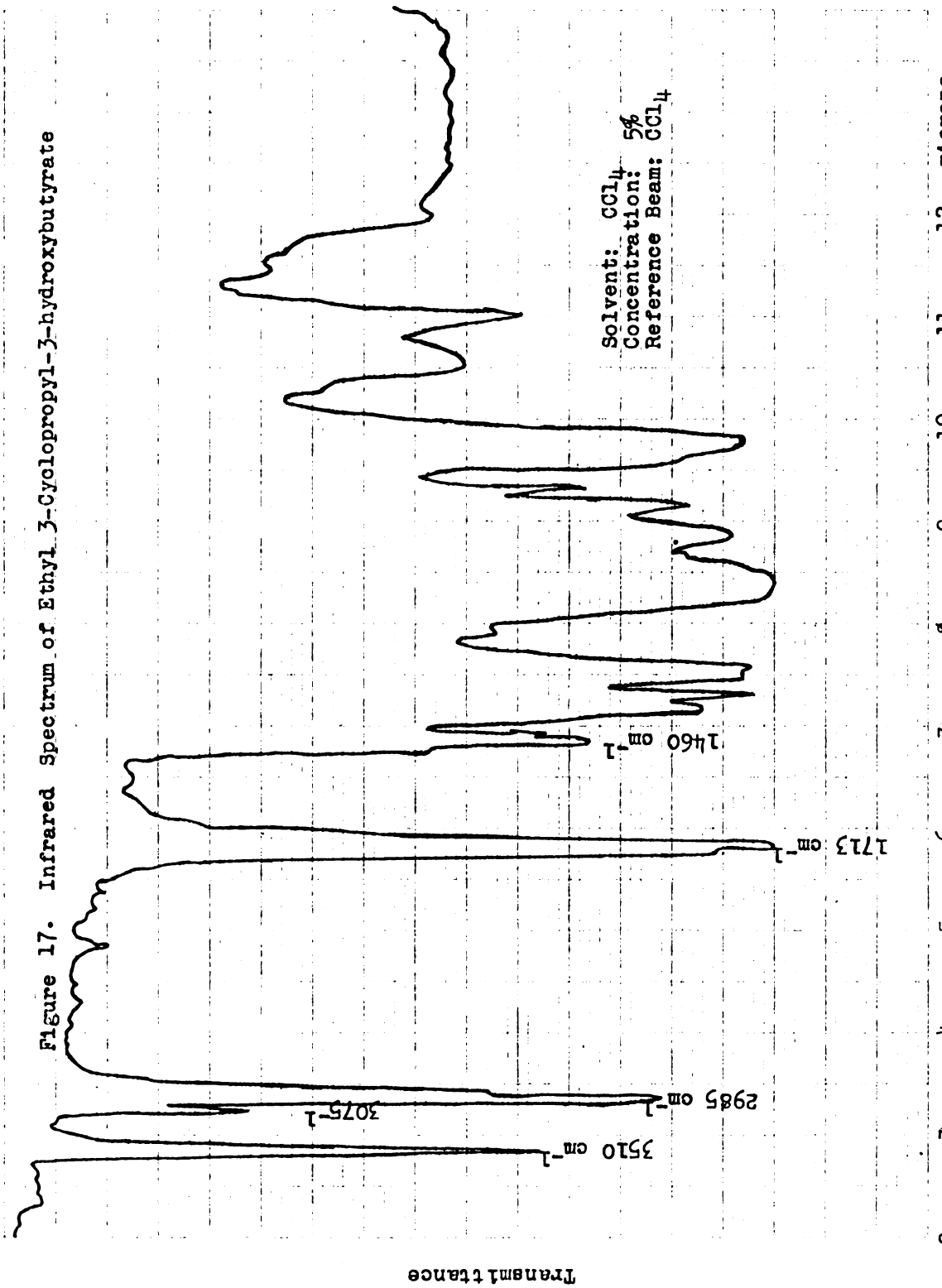


Figure 17. Infrared Spectrum of Ethyl 3-Cyclopropyl-3-hydroxybutyrate

distilled material was added to 100 ml of pyridine and cooled in ice-water while 22.6 g of phosphorus oxychloride were added. After standing one-half hour at room temperature the mixture had turned quite red and some crystalline material had formed. After standing three additional days it was poured into ice-water and extracted with hexane. The combined hexane extracts were washed with two 70-ml portions of 2N HCl, then twice with water, finally dried with sodium sulfate. An ir spectrum (IR-34) showed no hydroxyl content, and unsaturation was very prominent. After removal of the solvent the product was fractionated through an 8" long Vigreux column at 20 mm Hg pressure.

Cut No.	Wt, g	Bp^0	$\underline{n}^{25}\underline{D}$	IR No.
1	0.9	91-94	1.4566	IR-40
2	3.2	94-98	1.4606	IR-41
3	3.9	98-101	1.4730	IR-42
4	4.7	101-103	1.4782	IR-43
5	1.8	103-107	1.4775	IR-44

Infrared showed that all cuts were free of hydroxyl, and unsaturated.

Another lot of hydroxyester twice the size of the first one was now prepared. Instead of dehydration by sulfuric acid, 1.5 g of iodine were added (73) and allowed to react at 120-135^0 for four hours. Water appeared in the upper part of the apparatus. An attempt was made to azeotrope out the water with toluene, but only traces of water were obtained. Twenty drops of conc sulfuric acid were now added, and over a period of 1.5 hours eight ml of water

were removed by the distilling toluene (theory, 18 ml). After removing the toluene the product was flash distilled at 11 mm Hg, with the vapor temperature ranging from 75 to 120°. The distillate comprised 77.3 g and there were 25.0 g of residue. If the distillate had been all the olefinic ester it would have equaled 50% yield. It was fractionated through the 22" helices column at 20 mm Hg.

Cut No.	Wt, g	Bp°	$\underline{n}^{25}\underline{D}$	IR-No.
1	1.8	67-84	1.4550	
2	3.6	84-89	1.4500	
3	1.8	89-97	1.4634	
4	8.1	97-100	1.4768	IR-14
5	9.3	100	1.4777	IR-15
6	9.6	100.5	1.4780	IR-16
7	10.4	101	1.4786	IR-17
8	7.4	101-102	1.4793	IR-18
9	5.2	102-103	1.4801	IR-19
10	5.0	103	1.4812	IR-20
11	2.5	103-110	1.4850	
Residue	5.5			

All the ir spectra were free of hydroxyl absorption band and all showed cyclopropyl at 3080 cm^{-1} and strong carbon-carbon double bond absorptions at 3570 and 1640 cm^{-1}. Fraction 5 was chosen for elemental analysis. Calcd for $C_9H_{14}O_2$: C, 70.1; H, 9.15. Found: C, 70.09; H, 9.07. On titration with standard aqueous bromate-bromide solution a sample of fraction 6 consumed 104% of the stoichiometric amount of bromine. If one assumes 75% yield on the Reformatsky condensation, the sum of the fractions 4 through 10 is equivalent to a 47.5% yield on the dehydration.

Ethyl 3-Cyclopropylbutyrate (32):- The hydrogenations were carried out in a Parr "shaker bottle" apparatus. A first trial was made using cuts 4 and 5 of the second lot of olefinic ester (17.0 g, 0.11 mol) and 0.1 g of Baker's PtO_2 catalyst, all in 100 ml of ethanol. The H_2 pressure dropped from 43.0 to 32.8 pounds (8.0 lb equals 0.10 mol H_2) in 2.25 hr and then dropped no further. By ir analysis (IR-21) the unsaturation had disappeared. Fractions 6, 7, and 8 of the same lot (25.9 g, 0.161 mol) were now likewise hydrogenated using 150 ml of ethanol and 0.10 g of catalyst. Hydrogen absorption was much slower than in the previous run and the use of two additional portions of catalyst did not help much. After 8 hr an ir spectrum (IR-22) indicated the presence of much unsaturation and a bromate-bromide titration showed 0.086 mol of unsaturated material present. The platinum was removed by filtration and 10 g (wet) of Raney nickel which had been earlier prepared in this laboratory were added. Sixty pounds of hydrogen pressure was applied. Over an 18-hr period the pressure dropped by 3 lbs. Another 5 g of nickel and another 16 hr brought the material to the point where it showed no double bond by infrared (IR-27) and chemical analysis showed 0.7% of the material as being unsaturated. After filtration of the catalyst and removal of the solvent the product was distilled through a 12" long Vigreux column at 20 mm Hg.

Cut No.	Wt, g	Bp°	$\underline{n}^{25}\underline{D}$	IR No.
1	1.7	77-78	1.4192	IR-29
2	6.2	78	1.4193	IR-30
3	9.2	78	1.4194	Fig. 18
4	7.6	78	1.4200	IR-32
5	9.2	78-79	1.4213	IR-33
Residue	0.4			

The ir spectra showed no unsaturation except for the slightest trace in cut 5. Fraction 2 was analyzed for carbon and hydrogen: Calcd for $C_9H_{16}O_2$: C, 69.2; H, 10.3. Found: C, 69.8; H, 11.52.

All of the remaining ethyl 3-cyclopropylcrotonate -- distillation cuts 2 through 5 of the first preparation, and 9 and 10 of the second; total of 23.2 g, 0.150 mol -- was diluted with 200 ml of ethanol and hydrogenated using PtO_2 catalyst. Again, the hydrogen was absorbed rather sluggishly, but the reduction was accomplished (IR-51). The reduced product was distilled as before, yielding 20.5 g (89% yield) of ethyl 3-cyclopropylbutyrate boiling at 76.5-79.0° at 20 mm Hg. Infrared spectra (IR-52, -53, -54) showed no inconsistencies.

3-Cyclopropyl-1-butanol:- Lithium aluminum hydride (12.35 g, 0.325 mol) and 300 ml of ether were placed in a flask fitted with the usual accessories for the exclusion of moisture. The ethyl 3-cyclopropylbutyrate (33.9 g, 0.217 mol) in 100 ml of ether was added with stirring over a period of 75 min. The heat of reaction caused the ether to

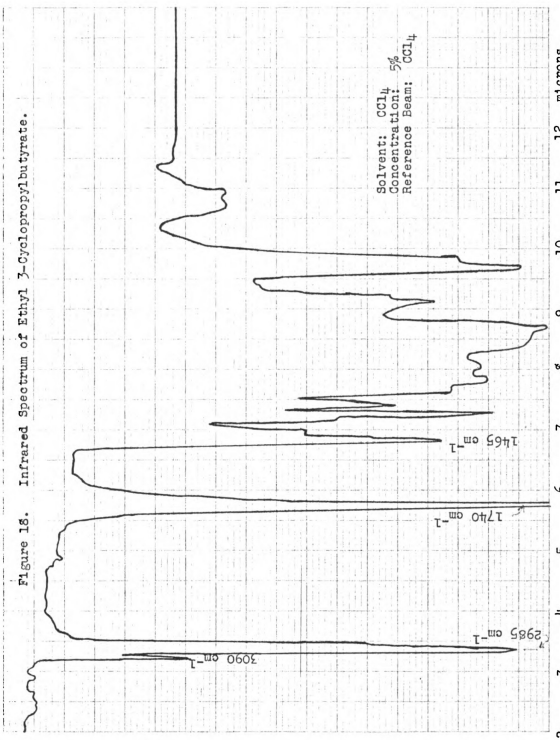


Figure 18. Infrared Spectrum of Ethyl 3-Cyclopropylbutyrate.

boil, and heating was continued for 30 min after the addition was completed. About 0.43 mol of ethyl acetate was added to consume any remaining $LiAlH_4$. Water (200 ml) and concd sulfuric acid (50 g) were added in sufficient quantity to bring about a clear aqueous layer. The ether layer was separated, the aqueous layer was extracted with ether (3X) and the combined ether layers were washed and dried. The ether and part of the ethanol had been removed by distillation when it was observed that the product was still wet. It was taken up in benzene, redried with sodium sulfate, filtered, benzene removed, and the product distilled at atmospheric pressure, using a 12" Vigreux column.

Cut No.	Wt, g	Bp^0	$\underline{n}^{25}\underline{D}$	IR No.
1	0.5	146-166	1.4220	
2	2.0	166	1.4322	IR-35
3	7.3	165-170	1.4342	IR-36
4	3.3	170	1.4350	IR-37
5	6.7	166-169	1.4356	IR-38
6	1.9	ca. 169	1.4363	IR-39
Residue	1.0			

The vapor temperature was quite variable indicating possible decomposition. Strong hydroxyl absorptions (strongly hydrogen bonded) were present in all of the ir spectra, and each also showed a carbonyl doublet at 1710 and 1740 cm^{-1}. The material was combined and redistilled using a 22" helices-packed column.

Cut No.	Wt, g	Bp^0	$\underline{n}^{25}\underline{D}$	IR No.
1	2.2	163-166	1.4278	IR-45
2	5.1	166	1.4318	Fig. 19
3	5.1	166	1.4350	IR-47
4	2.6	166	1.4366	IR-48
Residue	2.5		1.4368	IR-49

The infrared spectra showed that now the carbonyl impurities were concentrated in the first fraction 1710 cm^{-1}) and in the residue (1740 cm^{-1}), with only the slightest traces being evident in the cuts 2, 3, and 4. The cyclopropyl carbon-hydrogen stretch at 3080 cm^{-1} was present in all the fractions. Fraction 2 was submitted for elemental analysis. Calcd for $C_7H_{14}O$: C, 73.7; H, 12.4. Found: C, 73.1; H, 12.8.

One more ester reduction was carried out (0.128 mol) as before. This time rather than removing the inorganic material with acid and water, which is quite cumbersome, the technique of Amundsen and Nelson (109) was used. (This technique was also used in the present work in reduction of formolysis products. See Section IV, H.) After the $LiAlH_4$ reduction was completed, 7 ml of water, 14 ml of 10% NaOH, and 21 ml of water were added in order with stirring after each addition. There resulted one liquid phase containing the inorganic material as a white coarse solid. The liquid was separated by decantation and the solid was washed several times with ether and discarded. The combined ether solutions were devolatilized and the product was

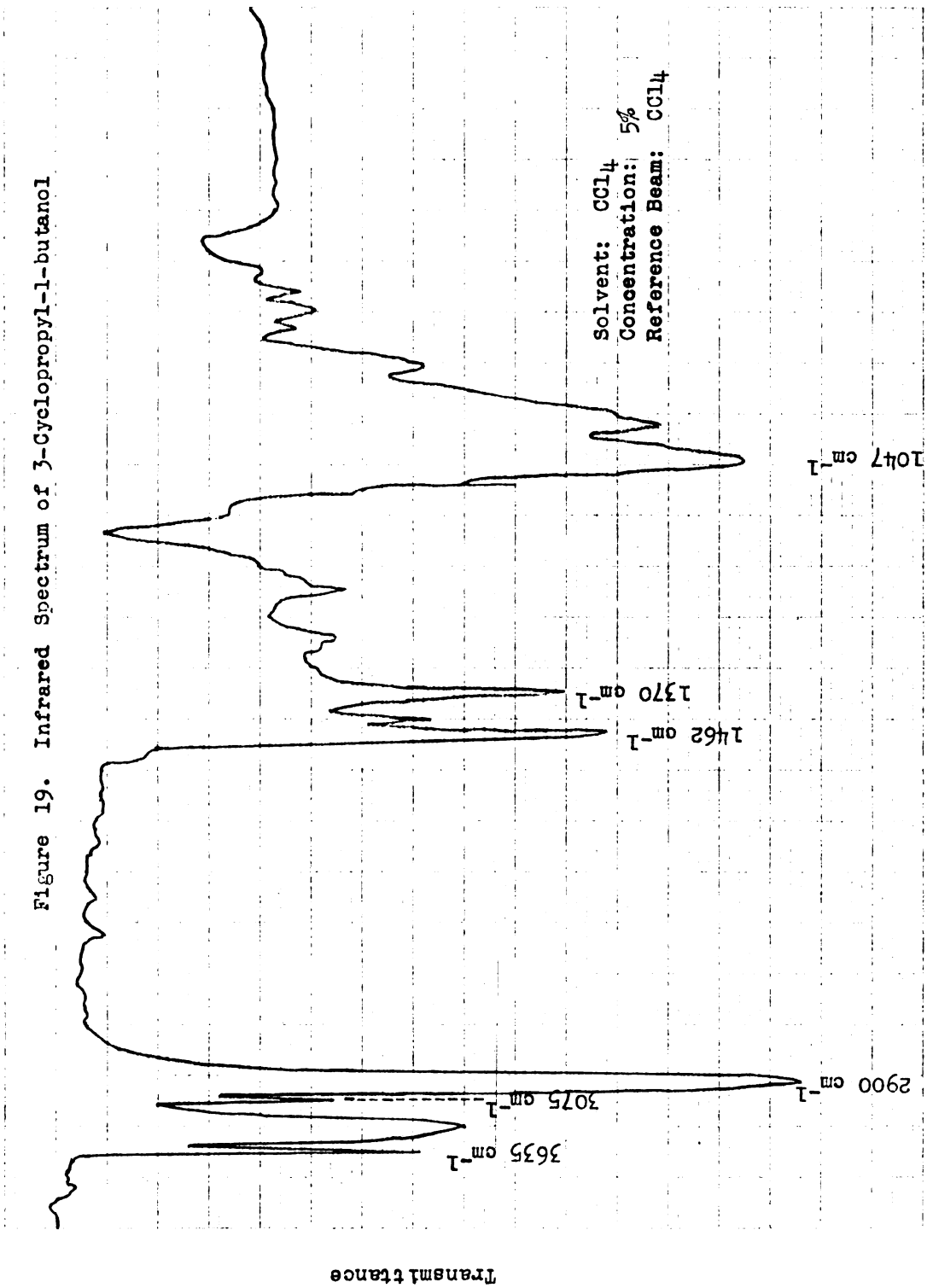


Figure 19. Infrared Spectrum of 3-Cyclopropyl-1-butanol

fractionated by means of a 15" long Vigreux column at 20 mm Hg. After a 0.5 g forecut, a main fraction of 10.6 g (0.0925 mol, 72.5% yield) of 3-cyclopropyl-1-butanol was obtained. Distillation residue, 0.7 g.

J. Attempted Preparation of 3-Cyclopropyl-2-butanone by Darzens Condensation of Ethyl 2-Chloropropionate with Cyclopropyl Methyl Ketone

The cyclopropyl methyl ketone was Aldrich Chem. Co. material and was used as obtained. The ethyl 2-chloropropionate was Dow Chemical Co. developmental product and was fractionated to yield material boiling within a two-degree range. The sodium methoxide was Matheson Co. material. The 2-heptanone (Eastman Kodak Co., technical grade) was fractionated before use to provide material boiling within a two-degree interval. The preparative procedure used was chosen from Newman and Magerlein (75).

The reaction was carried out in a one-liter three-necked flask provided with a stirrer, and a reflux condenser which was connected through a large calcium chloride tube to a large plastic bag filled with nitrogen. To the other neck of the reaction flask was connected a 125-ml Erlenmeyer flask by means of large diameter rubber tubing, for addition of the sodium methoxide. An ice-bath was used for cooling as needed.

The reaction flask was flamed while being flushed with dry nitrogen to remove air and moisture. Cyclopropyl methyl

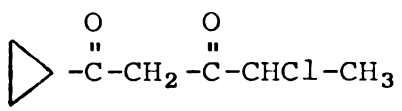
ketone (25.2 g, 0.30 mol) and ethyl 2-chloropropionate (41.0 g, 0.30 mol) plus 200 ml of dry ether were all added to the reaction flask and cooled to 0^0. Addition of sodium methoxide at this temperature caused no heat evolution. The temperature was permitted to rise to 10^0, at which point some heat evolution took place. The sodium methoxide was added over a period of one hour. The contents of the flask were stirred another 0.5 hr at $8-10^0$, warmed to 24^0 and stirred an additional 2.5 hr. During this latter period there were no further signs of reaction except that the color increased in intensity. The mixture was heated at reflux (36^0) another 0.5 hr, cooled to 5^0 and poured into a mixture of ice plus 30 ml of concd HCl (acid to Congo Red paper). The ether layer was separated, washed with water (3 x 50 ml), once with 50 ml of $NaHCO_3$ (aqueous layer colored), and once with 50 ml of saturated salt-water. The aqueous washes when combined, acidified and ether extracted, yielded 4.5 g of material, which was not saved.

The product ether layer was dried over sodium sulfate, and after removal of the ether was fractionated through a 15" Vigreux column.

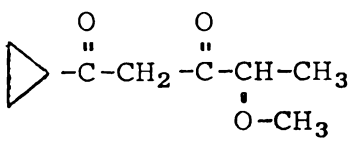
Cut No.	Wt, g	Bp^0 (mm Hg)	$\underline{n}^{20}\underline{D}$	IR No.
1	6.3	21-46 (17)	1.4152	
2	2.8	95-98 (7)	1.4983	
3	5.8	99 (7)	1.5063	
4	8.8	99 (7)	1.5118	IR-83
5	10.1	99-100 (7)	1.5142	
6	2.9	100-105 (7)	1.5150	

The residue weighed 3.7 g and the cold trap contained 1.0 g of material. Fraction 4 was chosen for further examination. Found: density, 1.106 at 22°; chlorine content by KOH hydrolysis followed by Volhard titration, 11.15%; carbon, 60.47%; H, 7.07%; equivalent weight, 141, obtained by KOH saponification and correction for chlorine content.

In the "Discussion" section H it is suggested that the product obtained was actually a mixture of A and B as shown below,

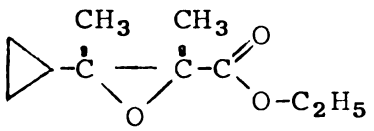


A



B

whereas the product C was expected.



C

The calculated compositions for these structures and the analytical data of cut 4 are tabulated.

	A	B	C	cut 4
Empirical Formula	$C_8H_{11}O_2Cl$	$C_9H_{14}O_3$	$C_{10}H_{16}O_3$	
Carbon, %	55.12	63.52	65.20	60.4
Hydrogen, %	5.83	12.08	8.76	7.07
Oxygen, %	18.35	28.20	26.05	21.35(by diff.)
Chlorine, %	20.30	0	0	11.15
Mol Wt	174.5	170.0	184.0	141.0

By computation based on the chlorine content the composition

of fraction 4 is found as 55% A and 45% B. By interpolation on carbon content the respective figures obtained are 64% and 36%.

With the hope of separating the two components which appeared to have been present, fractions 2 through 6 were combined and re-fractionated using a 22" long helices column at 6 mm Hg. Density was run on the cuts because the chlorine compound would be expected to be significantly more dense than the methoxy compound.

Fraction No.	Wt, g	Bp^0	$\underline{n}^{25}\underline{D}$	$\underline{d}^{24}$
1	3.2	93-94	1.4981	1.089
2	3.5	95	1.5120	1.107
3	3.8	95	1.5158	1.112
4	3.4	95	1.5193	1.112
5	2.7	95	1.5160	1.102
6	2.0	95	1.5115	1.102

There were 2 g of distillation residue. The cold trap contained 5 g which suggests that some decomposition occurred and that the distillation should perhaps have been done at a still lower pressure. It does appear that the boiling points for the two materials are too nearly alike to obtain separation by distillation.

A second preparation was carried out using 0.30 mol of ketone and 0.50 mole each of the ester and sodium methoxide. The latter material was added to the mixture at -5^0 over a 2-hr period. The mixture was stirred and allowed to warm up very gradually, to 2^0 in 2 hr, to 10^0 in 1 hr more, and finally to 20^0 over 20 additional hr. The mixture was then

refluxed at 35° for 0.5 hr. It was cooled and worked up as before except that sulfuric instead of hydrochloric acid was used for acidification. This was to permit determination of chloride ion in the water layer as an additional diagnostic item. The $NaHCO_3$ wash again was yellow. The chloride ion found in the composite aqueous phase was 0.275 mol. The organic layer, after being dried and stripped of ether, was rapidly flash distilled; vapor temperature, 25° (5 mm) to 150° (3 mm). One gram was found in the cold trap and there were 2.7 g of distillation residue. The flash-distilled product (52.0 g) was now fractionally distilled at 5 mm using a 15" Vigreux column.

Cut No.	Wt, g	Bp°	$\underline{n}^{25}\underline{D}$	IR No.
1	9.1	25-30		IR-85
2	8.2	30-50(most at 30-33)		IR-87
3	3.1	50-94(most at 93-94)		
4	7.8	94-95	1.5017	IR-88
5	9.7	95-96	1.5057	
6	5.8	96-98		
7	3.0	98-100		IR-90

The residue weighed 2.2 g and the cold trap contained 4.0 g of material. The ir spectra for fractions 1 and 2 looked very much like that of ethyl 2-chloropropionate (IR-86). The ir spectra of cuts 4 and 7, and also that of cut 4 of the preceding lot were quite similar and suggested a 1,3-dicarbonyl compound (78).

A practice preparation was now undertaken using 2-heptanone (20.0 g, 0.176 mol), 37.4 g (0.272 mol) of

ethyl 2-chloropropionate, and 15.0 g (0.277 mol) sodium methoxide. The procedure was essentially the same as previously. The methoxide was added over 2 hr at -5°. The mixture was allowed to warm to 10° in 16 hr and to 25° in 6 more hr. It was poured onto ice and made neutral with acetic acid. The layers were separated and the water layer, after being washed once with ether, was found to contain 0.126 mol of chloride ion. The ether solution was washed with water (3X), twice with saturated sodium bicarbonate solution, twice with saturated salt-water, and dried with anhydrous potassium carbonate. While the ether was being removed a white precipitate appeared, which was filtered off and discarded. After the remaining ether was removed the product was flash distilled at 5 mm Hg to yield 33.3 g of material. At the end of the flash distillation when the liquid temperature was 143° it appeared that some decomposition was taking place. There were 1.9 g of residue. The 33.3 g were now fractionated through a 15" Vigreux column at 5 mm Hg.

Cut No.	Wt, g	Bp°	$\underline{n}^{25}\underline{D}$	$\underline{d}^{25}$	IR No.
1	6.2	27-31	1.4104	1.052	IR-91
2	2.3	31-50*			
3	0.7	50-100			
4	11.3	100-107	1.4564	0.995	IR-92
5	6.1	107-110	1.4596	1.025	
6	3.8	110-112	1.4618	1.025	IR-93
Residue	2.1				

*Fraction 2 boiled almost entirely at 31°.

The infrared spectrum of cut 1 matched that of ethyl 2-chloropropionate quite well. The refractive index and the density of this ester were not determined, but the handbook gives 1.4185 and 1.087 respectively, with the temperature not specified. Fraction 6 by ir appeared to be mostly a 1,3-dicarbonyl compound (78) plus indications of a bit of aliphatic hydroxyl function and possibly some of the expected glycidic ester. Fraction 4 contained less of the carbonyl compound, and an ester having rotational isomers, probably the expected glycidic ester (78).

K. Attempted Preparation of Cyclopropylmethyl Acetate (33)

The allyl acetate and methylene iodide were Eastman white label grade. The zinc dust was Merck Reagent grade and the cupric oxide was Mallinkrodt AR grade. All were used as obtained.

The zinc-copper couple was prepared (112) by the reaction of 24.0 g (0.365 mol) of zinc dust with 3 g (0.046 mol) of cupric oxide in a 300-ml flask. The flask was fitted with a hydrogen inlet tube which extended about 2/3 of the depth and an outlet tube which extended inwards only through the stopper. Hydrogen gas dried by passage through sulfuric acid was passed through the flask for about 10 min to flush out all the air, after which time heat from a gas flame was applied while it was shaken for a 20-min period. The metal powder mixture did not change in appearance. However, there was evidence of reduction

having occurred in that the hydrogen outlet became wet for a period and then dried again, suggesting that the copper oxide reduction went to completion.

After the flask had cooled the hydrogen flow was discontinued, dry ether was added to the zinc-copper couple at once, and the flask was stoppered and kept until needed for the Simmons-Smith reaction (33).

For the methylene addition a one-liter three-necked flask fitted with a stirrer and a reflux condenser was used. A large plastic bag full of dry nitrogen was used to maintain the reaction free of air and moisture. After the flask was flamed, while being flushed with nitrogen, the allyl acetate (50.0 g, 0.50 mol), methylene iodide (67.0 g, 0.25 mol), and the zinc-copper couple in ether as made previously, were all charged to the flask along with 200 ml of additional ether. The mixture was refluxed for 48 hr, while an atmosphere of nitrogen was maintained over it. The contents of the flask were now filtered, the clear ether solution was washed with 10% acetic acid (2 x 25 ml), water (5 x 10 ml) and dried with sodium sulfate. After removal of the ether the product was fractionally distilled through a 22" helices column at atmospheric pressure.

Cut No.	Wt, g	Bp^0	IR No.	Remarks
1	1.5	50-69	IR-94	
2	2.2	69-77	IR-95	
3		77-104		Two layers
4		104		Decomposition

At this point some xylene was added to serve as a chaser, and the distillation was continued until the vapor temperature reached 135°, at which point it was fuming copiously. Much tarry material was left in the distilling flask. The ir spectra of fractions 1 and 2 showed a strong absorption band for ester carbonyl at 2110 cm^{-1} and the absorptions of the carbon-carbon double bond at 3120 and 1650 cm^{-1} were absent.

All of the distillation fractions were combined, the water was separated, the organic layer was washed acid-free with potassium carbonate solution, washed with saturated salt-water and dried with sodium sulfate. It was distilled again through the same column with xylene present as the chaser.

Cut No.	Wt, g	Bp°	IR No.
1	0.7	60-75	
2	3.5	75-96	
3	4.5	96	
4	3.5	96-99	IR-101
5	3.5	99-100	IR-96
6	3.2	100-105	IR-97
7	1.5	105-120	IR-98
8	4.6	115-127	IR-99

Present in all fractions was a bit of color due to iodine, which was removed by addition of a bit of mercury. After standing for one week fraction 2 had turned black. Infrared spectra of cuts 4 and 5 resembled that of allyl acetate (IR-102), and this resemblance decreased with increasing cut number. In fraction 8 very little unsaturation

was indicated. As fraction number increased the carbonyl content also decreased. During the distillation the temperature was quite unsteady, indicating decomposition. With the xylene present it was not possible to determine the amount of distillation residue.

No further work was done with this material.

L. Preparation of Cholesterol Derivatives

Cholesteryl Acetate (89):- Ten grams of USP cholesterol (0.0259 mol) and 16.3 g (0.159 mol) of acetic anhydride were refluxed together for 1 hr. After the mixture was cooled, the solid acetate was filtered off and washed with cold methanol. The white solid weighed 10.0 g, melted at 30-70° (literature value, 114-115°), and had a strong acetic acid odor. By digestion for 0.5 hr with absolute ethanol and drying the mp was brought to 113-114°. The weight was now 10.0 g, or a 90.0% yield.

Another lot of the acetate was prepared using 89.0 g (0.231 mol) of cholesterol and 145 g (1.43 mol) of acetic anhydride. The mixture was simmered for 1.5 hr, cooled a bit, treated with 60 ml of methanol, and further cooled to crystallize the acetate. After filtration, washing, and drying it was still somewhat sticky so it was digested with 400 ml of absolute ethanol, cooled, filtered and dried to yield 88.9 g (90.0% yield) of cholesteryl acetate having a mp of 113-114°. A mixed mp with cholesterol was 91-120°. The filtrate was concentrated and a second crop of 4.0 g of

product melting at 109-112° was obtained. An ir spectrum (IR-105) of the first crop product was obtained.

6-Nitrocholesteryl Acetate (90):- Ten grams (0.0233 mol) of cholesteryl acetate were added to 200 ml of concd nitric acid, and to this was added in small portions, 6.3 g (0.091 mol) of sodium nitrite over a 35-min period. Copious evolution of brown fumes occurred and very little if any heat was evolved. After the mixture was stirred an additional 15 min, 600 ml of water was added. The product now took the form of one solid lump, allowing the aqueous phase to be easily decanted. After another wash with hot water the solid product was sufficiently brittle to be easily broken up. It was dissolved in 300 ml of methanol (dissolved very slowly), a small amount of insoluble material was separated, and the solution was cooled to 8° to crystallize the product which was filtered off and washed with a bit more of methanol. Six and one-half grams of product melting at 97-102° were obtained. The literature (90) value is 101-102°. Recrystallized once more from methanol, it melted at 96-99°. Ethanol was then tried as a purification solvent and material melting at 104-105° was obtained, and another recrystallization did not increase the melting point any further. At this point 5.5 g of 6-nitrocholesteryl acetate were in hand which corresponded to a yield of 49.5%. A mixed mp with cholesteryl acetate was 81-88°.

A second run was made using 84.0 g (0.196 mol) of cholesteryl acetate. For this run the nitric acid ratio

was reduced to about one half of that for the previous lot and 800 ml were used. The sodium nitrite (53.3 g, 0.77 mol) was added in about 80 min. Heat evolution was clearly evident with the increased amount of reactants and cooling was required to maintain the mass near room temperature. After the mixture was stirred an additional 15 min, 2 liters of water were added, which caused the material to turn green. The product balled up as before and was washed with hot water until it was acid-free. The solid product was dissolved in 600 ml of absolute ethanol and treated with activated charcoal. By evaporation of alcohol the volume of the solution was reduced to 450 ml, and it was cooled to crystallize the product (41.0 g) which was somewhat sticky in appearance. It was recrystallized from 150 ml of ethanol to yield 35.2 g (37.8% yield) of 6-nitrocholesteryl acetate, mp 101.5-103.0^{0}.

All the filtrates were combined and concentrated to 200 ml, but no crystals could be obtained on cooling. A test showed the filtrates to be strongly acid to Congo Red paper. Water was added to precipitate the organic product which took the form of a very sticky brown semi-solid. It was washed with hot water to free it of acid, after which it was taken up in 300 ml of ether, washed with salt-water, dried with sodium sulfate, and freed of ether. An ir spectrum (IR-103) showed a strong hydroxyl absorption at 3300 cm^{-1} and a rather broad carbonyl band with several shoulders. The presence of the hydroxyl band suggested that some of the

acetyl group may have been split off. In an attempt to re-acetylate it, the material was dissolved in 150 ml of acetic anhydride and heated for 2 hr. After being diluted with much water, it was filtered and washed until free of acid. Successful crystallization was accomplished by use of 4:1 methanol-ethanol mixture, and 20.6 g of material melting at 101.0 to 103.0° were obtained. The hydroxyl absorption (IR-106) was now absent and the carbonyl absorption was considerably cleaner. The 20.6 g added to the 35.2 g first obtained now gives a total yield of 60.0%.

Cholestan-3-beta-ol-6-one Acetate (90b):- Three lots of this material were prepared. The 6-nitrocholesteryl acetate was dissolved in glacial acetic acid and water was added to this solution with good stirring. Considerable precipitation occurred during the water addition. Addition of the zinc dust was started at room temperature without cooling and the heat evolution brought the temperature substantially to the boiling point by the time the zinc addition had been completed. Heat was applied to continue the refluxing. After the reflux period the mixture was filtered while hot, and water was added to the clear solution to precipitate the product, which came out somewhat oily and ultimately solidified to lumps. These were broken up, water-washed until free of acid, and recrystallized from methanol. Attempts to recover a second crop of crystals were unsuccessful.

The particulars for the three lots of cholestan-3-beta-ol-6-one acetate which were prepared are as follows:

	Lot 1	Lot 2	Lot 3
6-Nitrocholesteryl Acetate, g (mol)	10.0(0.0211)	28.7(0.0606)	20.4(0.0432)
Acetic Acid, ml	200	570	410
Water, ml	20	57	41
Zinc, g (mol)	20.0(0.31)	57.0(0.875)	41.0(0.63)
Time of Zn Add.,hr	2.0	4.5	2.75
Additional Reflux Time, hr	2.5	0.25	1.0
Water Added After Filtration, ml	200	570	400
Product Yield, g,(%)	5.3(53.0)	17.0(63.0)	12.7(66.0)
Melting Point*	128°	126-128°	125-127°

*Literature value, 127-128° (90b).

An infrared spectrum (IR-107) of the lot 1 product was obtained.

Cholestan-3-beta-ol-6-one (91):- Of the above prepared acetate 16.9 g (0.038 mol) were dissolved in an ethanolic KOH solution (225 ml, 0.10 mol base) by warming. After 16 hr the quantity of base consumed had reached a constant value of 0.048 mol and the cholestan-3-beta-ol-6-one was precipitated by dilution with water, filtered, washed, and dried. The melting point was approximately 144°. The product was taken up in 150 ml of ethanol, a bit of solids was filtered off, and the product crystallized to yield 10.6 g

melting at 142-3°. An additional 2.8 g (mp, 141-2°) of material was obtained by dilution of the filtrate with one fourth its volume of water. After some exploratory crystallization tests the entire two crops of product were dissolved in 200 ml of methanol, a bit of insoluble material removed, concentrated to 125 ml and crystallized to yield 9.7 g of product melting at 141.5-142.5° (literature, 145-6° (92) for recrystallized and 150-1° (93) for chromatographed material). Its appearance, though improved, was still slightly pink. Additional drying raised the melting point to 146.5-147.0°. Infrared spectra before (IR-114) and after (IR-115) methanol crystallization were essentially alike.

A second lot of acetate (16.9 g, 0.038 mol) was saponified using the same procedure and giving a yield of 12.0 g (0.0298 mol, 78.3% yield) of 6-ketocholesterol melting at 143°. Considerable effort was spent trying to recover more product from the filtrate, but with no success.

6-beta-Cyclopropylcholestan-3-beta-6-alpha-diol:- Cyclopropyllithium (0.08 mol) was prepared in ether as described under Experiment 3, Section E, and to it were added 8 g (0.0198 mol) of cholestan-3-beta-ol-6-one in 200 ml of ether over a 25-min period at 0-5°. The mixture obtained was refluxed for 15 min, after which 50 ml of water were carefully added to it yielding two clear liquid layers. The ether layer was separated, washed several times with salt-water and evaporated. The crystals obtained were very

sticky and could not be recrystallized after being dissolved in methanol and cooled. Upon addition of water very sticky material was once more obtained. Sufficient water was now added to insolubilize all the organic material. After decantation of the water the product was dried and found to melt at 71-90°. (Note: This compound had not been previously reported in the literature.) There were 10.8 g. This was now dissolved in 75 ml of benzene, a bit of water was separated, the solution was dried with K_2CO_3, reduced to 25 ml, crystallized and filtered. Attempts to recrystallize the product from ethanol were unsuccessful.

The benzene filtrate was evaporated and ir spectra of both the crystals (IR-116) and the evaporation residue (IR-117) were obtained. There were significant carbonyl absorption bands in both spectra. Cyclopropyl absorptions at 856, 1008, and 3080 cm^{-1} were so slight that they had to be considered questionable. A shoulder at 3075 cm^{-1} was present in the spectrum of the impure fraction. Further attempts at purification using carbon tetrachloride and hexane gave no better results.

Another preparation was now undertaken using a higher ratio of lithium compound to ketone, namely, 0.0198 mol ketone and 0.119 mol of cyclopropyllithium, thus using a ratio of six to one in lieu of the previous four to one. The solution of ketone in ether was added to the cyclopropyllithium in ether in 1.25 hr at 0-5°, and refluxed an additional 0.5 hr. After addition of 50 ml of water the ether

layer was separated, washed, and dried as before. After removal of the ether 8.8 grams (0.0198 mol, as cyclopropylcholestandiol) solid melting at 85-130° remained. Again methanol and benzene proved unsatisfactory as crystallization solvents. The material would not dissolve in hexane, but by digestion with 10 ml of the same, 7.0 g of product of quite good appearance and melting at 115-136° were obtained. By infrared the carbonyl content was quite low now, but the cyclopropyl band at 3080 cm^{-1} was just barely apparent. The product was now dissolved in 350 ml of hexane, filtered to remove a bit of insoluble material, concentrated to 150 ml, and cooled to obtain 5.5 g of product melting at 141.5-142.5°. The melting point of a small sample recrystallized once more in the same way was increased to 142.5-143.0°. An ir spectrum of the 5.5 g showed no carbonyl, strong hydroxyl -- free and hydrogen-bonded -- and prominent cyclopropyl (at 3170 cm^{-1}) absorptions (IR-121). The 0.7 g recovered from the filtrate showed much carbonyl (IR-122), some hydroxyl and some cyclopropyl. The 5.5 g amounted to a 62.5% yield. A bit which was recrystallized from a 90:10 hexane-benzene mixture melted at 142-3° and was found to have the following carbon and hydrogen composition. Calcd for $C_{30}H_{52}O_2$: C, 81.0; H, 11.79. Found: C, 80.5; H, 11.40.

6-beta-Cyclopropylcholestan-3-beta-6-alpha-diol 3-Acetate:- The diol from above (4.9 g, 0.0110 mol) was acetylated (34) with 30 ml of acetic anhydride in 50 ml of pyridine, in an apparatus fitted with a drying tube. The

mixture was heated for 1.5 hr on the steam bath, poured into ice, filtered, washed, pasted up with a bit of $NaHCO_3$ solution, filtered and washed again to yield 5.6 g (0.0115 mol) of product melting at 179-180°. A bit recrystallized from ethanol melted at 181.5-182.5°.

6-Cyclopropylcholesteryl Acetate:- A solution of 5.3 g (0.011 mol) of the diol monoacetate in 300 ml of acetic acid was treated with 0.40 g of p-toluenesulfonic acid monohydrate, refluxed for 25 min, cooled, and then treated with 100 ml of water. After the mixture stood for a few days, an oily scum had formed on the surface, which was separated from the aqueous phase and washed free of acid. An ir spectrum (IR-123) showed a strong absorption for carbonyl, none for hydroxyl, and a medium one for carbon-carbon double bond. (Note: An extraction of the water layer yielded only 0.1 g of additional product.) The crude product was taken up in ether, the ether solution was dried with potassium carbonate, and the ether was evaporated again leaving an oil which could not be crystallized from methanol, ethanol, carbon tetrachloride, or hexane. Considerable effort was exerted towards crystallizing this product and also the alcohol obtained from it by saponification with alcoholic KOH, but the results were consistently negative.

V. LITERATURE CITED

V. LITERATURE CITED

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