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III. ISOLATION OF CHLORINE-CONTAINING COMPOUNDS FROM THE GORGONIAN, BRIAREUM ASBESTINUM PALLAS

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in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

BY

ROBERT WALLACE HYDE

Norman, Oklahoma

1966

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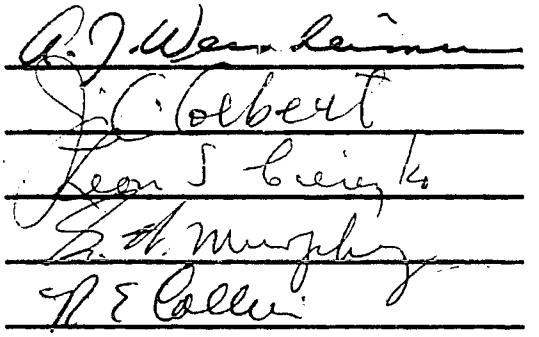
APPROVED BY



DISSERTATION COMMITTEE

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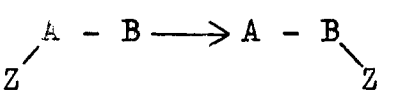
PART I

STEREOCHEMISTRY OF THE WITTIG REARRANGEMENT

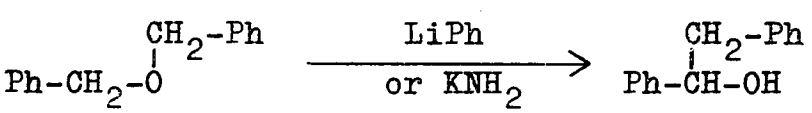
INTRODUCTION

The Wittig rearrangement belongs to a limited class of intramolecular rearrangements which has been designated as an electrophilic 1,2 rearrangement (1,18). The reactions are initiated when B becomes rich in electrons. Another example of a reaction that fits



this description is the Stevens rearrangement.

The Wittig rearrangement usually involves the base-induced isomerization of a benzyl alkyl ether to an alcohol. For example, dibenzyl ether has been rearranged by such strong bases as phenyllithium (2) or potassium amide (3) to 1,2-diphenylethanol. It is



assumed that the base removes an α-hydrogen of a benzyl group giving a carbanion which rearranges to the alcoholate ion followed by conversion to the alcohol in the workup.

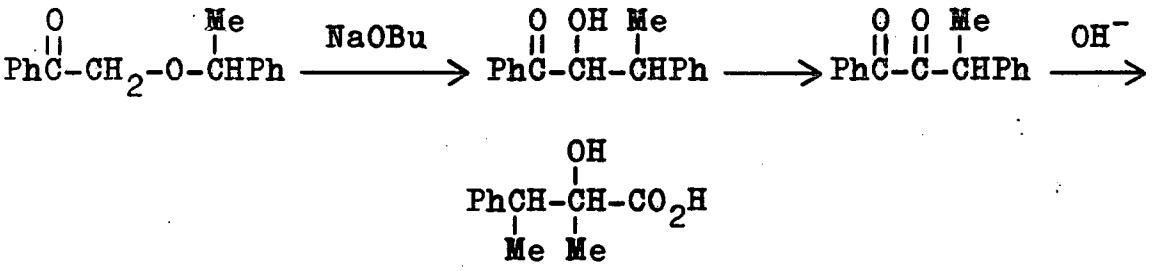
A variety of benzyl ethers have been rearranged in which the migrating groups include methyl (2), s-butyl (3,4), allyl (3), t-butyl, adamantyl (5), cyclopropylcarbinyl, and cyclobutyl (6). Ethers with groups such as α-cyanobenzyl (7), α-methylbenzyl (8,9), benzhydryl (4,5,10,11,12,18) fluorenyl (7,13,18), desyl (14), and α - and γ-pyridyl (15,16) have also been studied.

In some cases, attempts to induce the base catalyzed ether-carbinol rearrangement have led to products resulting from ether cleavage (3,12,17). Generally, these products are the aldehyde and the conjugate acid of $R:^-$ which result from an independent

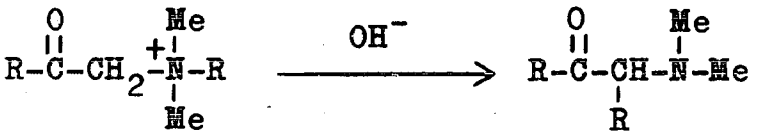
$$Ph\text{-}\overset{O\text{-}R}{\overset{|}{C}}H_2 \xrightarrow{KNH_2} Ph\text{-}\overset{\curvearrowright R}{C}H\text{-}O \longrightarrow PhCH{=}O + R:^- \xrightarrow{H^+} R\text{-}H \quad (1)$$

β-elimination reaction leading to these cleavage products (equation 1). A second type of β-elimination is encountered in the conversion of benzyl ethyl ether to benzyl alcohol and ethylene by propylsodium (11) and potassium amide (3). The reaction of sodium butoxide with phenacyl 1-phenylethyl ether resulted in a double

rearrangement (electrophilic rearrangement followed by benzylic change) leading to the formation of α-hydroxy-$\alpha\,\beta$-diphenylbutyric acid (18). The formation of this acid was suggested to occur as depicted in the sequence below which is analogous to the observations of Cast, Stevens and Holmes (7) for the action of base on benzyl phenacyl ether.



The closely related Stevens rearrangement has been studied in considerable detail. In this electrophilic 1,2 rearrangement a quaternary ammonium salt in which one of the groups bears a carbonyl carbon is converted by base to a tertiary amine in which one of the alkyl groups has migrated from nitrogen to the carbon bearing the carbonyl carbon. Thus, it was found that

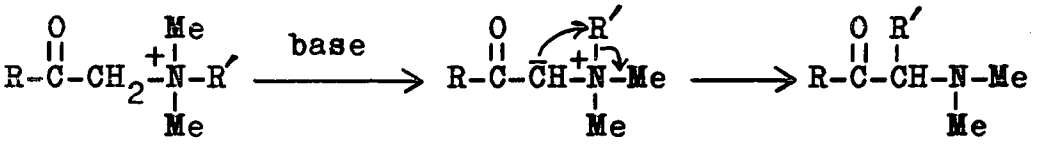


dimethylphenacyl-1-benzylammonium bromide when treated with dilute sodium hydroxide gave dimethylaminobenzyl-acetophenone (19). The intramolecular nature of this

rearrangement was established when a mixture of phenacyl-m-bromobenzyldimethylammonium and p-bromophenacylbenzyl-dimethylammonium bromides was induced to rearrange by the action of sodium ethoxide (20). No "crossover" products were isolated and also each one of these quaternary salts was shown to rearrange at comparable rates. At first it was proposed (20) that the migrating group became detached from nitrogen as a cation. However, from a study of the relative rates of rearrangement of a series of ammonium salts substituted in the para position of the migrating benzyl group, the order was found to be $NO_2 >$ halogen $>$ Me, H $>$ OMe (21). This order is consistent with the decreasing stability of a benzyl carbon bearing a negative charge as is the case with the S_N2 displacements on corresponding benzyl halides by basic ions (22). Had the migrating benzyl group been cationic in character the reverse order of rates might have been expected. Therefore, an internal nucleophilic displacement mechanism was suggested.

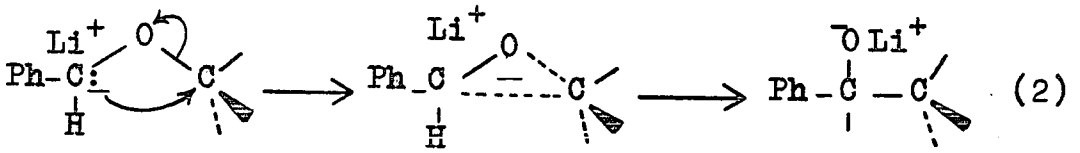
Further confirmation of the intramolecular nature of the Stevens rearrangement was obtained when the rearrangement of optically active α-methylbenzylphenacyldimethylammonium bromide gave a product where almost no racemization of the asymmetric center took place (2,3). Other studies of the rearrangement of the above-mentioned

quaternary salt (18,24) confirmed the low degree of racemization during the reaction and further revealed that the group containing the asymmetric carbon had migrated with retention of configuration. This stereochemical evidence together with the kinetic data mentioned in the previous paragraph is best rationalized by an intramolecular nucleophilic displacement (S_Ni) mechanism proposed by Hauser (3).

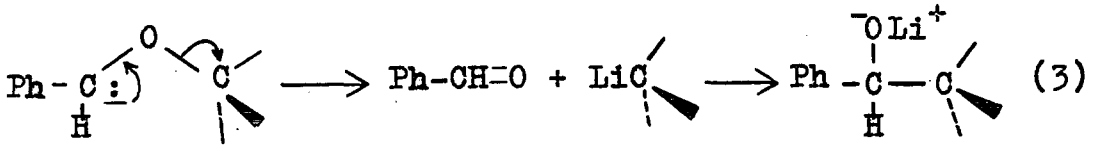


In contrast to the Stevens rearrangement, evidence from studies of the Wittig rearrangement have provided data which do not permit a clear-cut definition of the mechanism.

During the past twenty-five years, the organolithium induced isomerization of benzyl alkyl ethers to alcohols has been investigated by Wittig and his co-workers (2,10,13,25,26). They considered the rearrangement to be an intramolecular nucleophilic substitution reaction (S_Ni) in which a carbanion displaced an


(2)

alkoxide, the net result being transfer of the migrating group without its bonding electrons. This interpretation seemed reasonable as it is in accord with the analogous Stevens rearrangement (1,27). An alternative mechanism for the rearrangement involves a β-elimination followed by recombination of the resulting fragments. The earlier



(3)

workers (2) had rejected this latter mechanism because no evidence for "trapping" of the intermediate carbonyl moiety by excess metalating base could be obtained. Thus, Hauser (3) showed that during the butyllithium-induced isomerization of dibenzyl ether to benzylphenylcarbinol, no isolable amount of benzylbutylcarbinol was formed.

However, recent evidence has been provided which is best interpreted by the process depicted in equation 3. It was noted that varying nominal amounts of methylphenylcarbinol were formed from the methyllithium induced isomerization of dibenzyl ether in a series of solvent mixtures (5). Nevertheless, the failure to isolate any methylphenylcarbinol resulting from trapped benzaldehyde when the migrating group was an n-alkyl or sec-alkyl (28) denied an unambiguous interpretation that

cleavage-recombination occurs in all of these benzyl alkyl ether rearrangements.

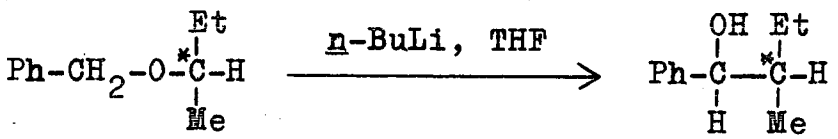
Some studies have been directed toward the demonstration of the alternative S_Ni mechanism (equation 2) based on the hypothesis that the migrating group might develop some cationic character depending upon the relative extent of bond making and breaking in the transition state (5). Thus, in a study of the relative reactivities of three t-alkyl benzyl ethers it was found that both t-butyl and 1-adamantyl benzyl ether were isomerized to the alcohols in high yield under conditions where 1-apocamphyl benzyl ether was not. Since it seemed unlikely that these observations were the result of expulsion of highly basic tertiary carbanions (equation 3), Lansbury (5) favored the S_Ni process in these cases.

As a further test of the possibility of cationic character in the transition state during the S_Ni process (equation 2), Lansbury (6) studied the methyllithium-induced rearrangement of cyclopropylcarbinyl and cyclobutyl benzyl ethers. Cyclopropylcarbinyl and cyclobutyl systems, particularly the former, are exceedingly reactive in cationic processes and such reactions always lead to a mixture of cyclobutyl, cyclopropylcarbinyl and allylcarbinyl derivatives, the proportions depending on whether or not the reaction is reversible (29,30). However, if the

rearrangement were to follow a sequence involving carbanionoid intermediates (equation 3), the cyclobutyl group would not be expected to isomerize (29,32) but emerge intact in the product carbinol. The cyclopropylcarbinyl anion, however, would be expected to isomerize extensively to the allylcarbinyl structure (33). When cyclobutyl benzyl ether was rearranged the only product was cyclobutylphenylcarbinol leading at least to the conclusion that the migrating group does not develop any significant positive character in the transition state. In the case of cyclopropylcarbinyl benzyl ether, a high yield of cyclopropylcarbinylphenylcarbinol was observed. Although the expected isomerization of the cyclopropylcarbinyl group to the allylcarbinyl system did not take place, the result is nonetheless inconsistent with a cationic S_Ni mechanism (29,30) and readily accounted for by a carbanionoid cleavage-recombination mechanism. One might argue that the failure to observe any significant formation of an allylcarbinyl derivative precludes the development of carbanionoid character in the cyclopropylcarbinyl group. However, the stability under certain conditions of the cyclopropylcarbinyl anion has been demonstrated (31) recently through the preparation of cyclopropylcarbinyllithium without rapid isomerization to allylcarbinyllithium. It was concluded (6) that most

Wittig rearrangements are best considered a fragmentation-recombination process (equation 3), but the S_Ni process (equation 2) may be more favorable for the rearrangement of the t-alkyl ethers. It should be added that the S_Ni process for the Wittig rearrangement in the above cyclobutyl and cyclopropylcarbinyl cases is not necessarily precluded on the basis of the results described above. In those cases the S_Ni process might be operative if the migrating group remains completely neutral in the transition state.

Further evidence that the mechanism of the Wittig rearrangement might best be accommodated by a fragmentation-recombination scheme was gained through studies of the stereochemical course of this rearrangement (3,4,8,9). It was shown by Schollkopf (4) that the butyllithium induced rearrangement of optically active benzyl s-butyl ether in tetrahydrofuran gave the product carbinol in which the asymmetric center of the migrating group (C*) was found to have been largely racemized. However, the



(L) (L and D,L)

optical form in excess was the same as that in the starting ether and the degree of retention of configuration

of the asymmetric center was estimated to be 58.5%. A higher degree of retention (65.5%) was attained when the rearrangement was conducted in the less polar solvent, pentane. Racemization was shown (4) not to occur before rearrangement by recovery of optically active starting material after partial reaction. Also, the product carbinol showed no loss of optical activity when subjected to both reaction and workup conditions showing that racemization did not occur after the rearrangement.

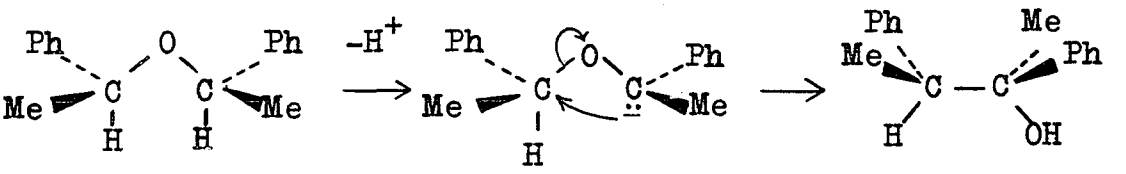
In another case, the butyllithium induced isomerization of optically active s-butyl benzhydryl ether gave the expected alcohol with only 5% of the optical activity retained (4).

From the observation that a low degree of optical activity is retained, Schollkopf concluded that the reaction involves a series of steps similar to equation 3, rather than a concerted intramolecular displacement, since the latter transformation should proceed with essentially complete retention (4). Schollkopf's conclusions would appear to be supported by the rearrangement (7) of (-)-9-fluorenyl-α-methylbenzyl ether to completely racemic 9-α-methylbenzyl-fluoren-9-ol. Under various reaction conditions (sodium butoxide in butanol at 110° or phenyllithium at 15°) the product showed no rotation in either alcohol or chloroform.

In a preliminary study by Weinheimer (8) of the rearrangement of meso and d,l bis (α-methylbenzyl) ethers, the Schollkopf mechanism (equation 3) did not seem attractive. However, the Schollkopf mechanism was to find support in a later study by Sifford (9) of the optically active forms of these ethers (page 12). A predominance of stereospecificity was observed (8) when, in the case of meso bis (α-methylbenzyl) ether, the carbinol formed was erythro 2,3-diphenyl-2-butanol while the d,l ether led to the threo alcohol. If the reaction involved the ion-pair intermediate then the formation of an equilibrium mixture of the diastereomeric carbinols would have been observed.

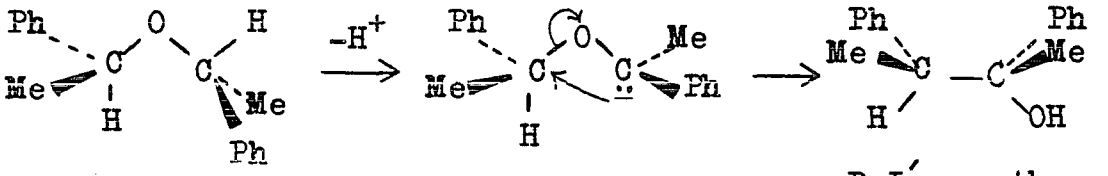
A further consequence of the results from the Wittig rearrangement of the bis (α-methylbenzyl) ethers was the requirement that an inversion of configuration had occurred. This inversion could have occurred in either the migrating group or the ionized carbon atom. Since a high degree of retention of configuration of the migrating group had been observed in the Stevens rearrangement and, likewise, the partial retention in the isomerization of s-butyl benzyl ether discussed above, Weinheimer (8) preferred to regard the site of inversion as the ionized carbon atom.

The argument for this inversion follows from the fact that the meso ether would be expected to give threo-2,3-diphenyl-2-butanol in the absence of any inversion as shown in the equation below. By the same course, the d,l ether should give the erythro alcohol.



meso threo

However, since upon rearrangement the meso ether actually gave erythro-2,3-diphenyl-2-butanol, inversion must have occurred during the reaction. In the light of this

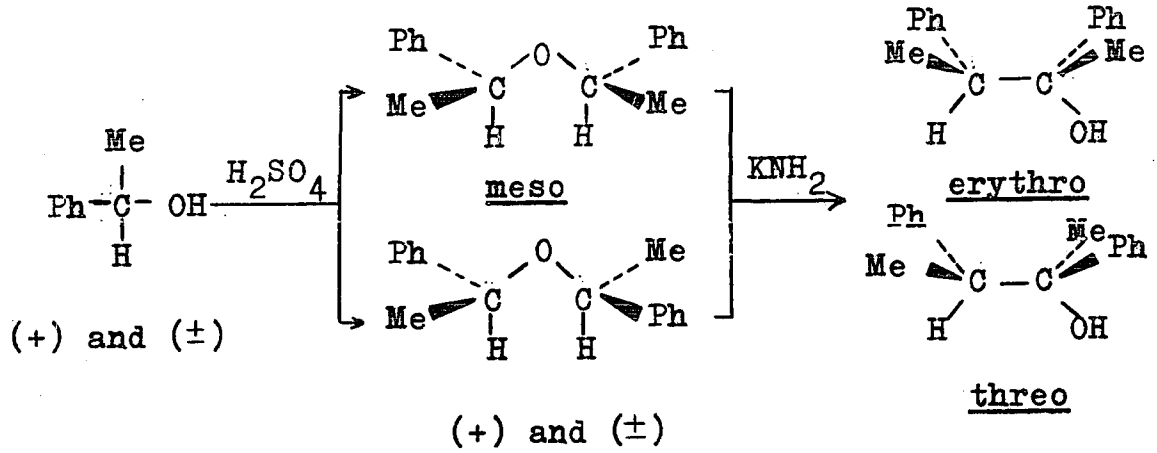


meso D,L erythro

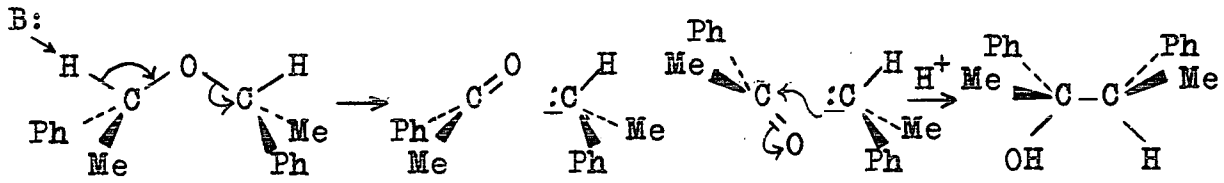
inversion of configuration together with the observed predominance of stereospecificity, Weinheimer (8) favored the interpretation of the rearrangement as involving a concerted process of inversion of the carbanion and rearrangement to the alcoholate ion.

As a result of a stereochemical study by Sifford (9) it was concluded that the operation of both the fragmentation-recombination mechanism and the S_Ni process seemed to be the best rationale for the cases studied. It was observed that in the potassium amide induced isomerization of (-)-benzyl-α-methylbenzyl ether, the asymmetric carbon atom migrated with 64% of the optical activity retained when liquid ammonia was used as the solvent. In refluxing ether a still higher degree of optical activity (70%) was retained. In both cases the optical form in excess in the product was the same as that in the starting ether. The relatively high degree of retention of configuration in the migrating group suggests that the reaction may occur at least partly by an intramolecular S_Ni mechanism, and not exclusively by the ion-pair mechanism as proposed by Schollkopf (4). However, the racemized portion of the product may well have been formed by the mechanism he suggested.

A stronger case for the Schollkopf ion-pair mechanism was demonstrated by Sifford (9) when a mixture of the diastereomeric bis (α-methylbenzyl) ethers prepared from (+)-α-methylbenzyl alcohol (partially active) was rearranged using potassium amide in liquid ammonia. The product diastereomeric carbinols were



separated by chromatography and, as anticipated, the threo modification showed a high degree of retention of optical activity (74%). Surprisingly, the erythro modification also showed some optical activity (9.7% of that of the starting ether). Furthermore, it was noted that the active erythro form had the same configuration in the migrating group as present in the optically active ether. It can be assumed that the active erythro alcohol must arise from the d,l form of the ether and, hence, a mechanism was proposed which involves a fragmentation-recombination process followed by a reorientation of the acetophenone fragment relative to the α-methylbenzyl carbanion, which retains its configuration during this process:



D and D,L (+)-erythro

If the carbanion can maintain asymmetry during the reorientation of the carbonyl moiety, then it should also be able to do so during the direct recombination involved in the formation of the (+)-threo alcohol. For this reason then, the single process of fragmentation-recombination is preferred to the dual course requiring in addition, the operation of the S_Ni mechanism.

The present work was undertaken in order to examine further the stereochemistry of the migration of the α-methylbenzyl group in optically active benzyl-α-methylbenzyl ether and to examine the possibility of racemization of the ether under the reaction conditions.

DISCUSSION

As a means of studying the stereochemical course of the Wittig rearrangement, Sifford (9) selected benzyl-α-methylbenzyl ether based on the expectation of a high degree of stereospecificity in the migration of a benzylic group. It was found (9) that this ether could be synthesized in its optically active form through the Williamson method. Thus, (-)-benzyl-α-methylbenzyl ether was readily prepared in excellent yield from (-)-α-methylbenzyl alcohol and benzyl chloride in liquid ammonia using potassium amide as the base. The active ether was shown to have undergone minimal racemization during its preparation through hydrogenolysis of the ether to the active alcohol from which it was prepared. In addition, the rotation of optically pure (-)-benzyl-α-methyl-benzyl ether was estimated to be a minimum of 85.3° from the results of the hydrogenolysis experiment.

Sifford (9) found that the Wittig rearrangement of (-)-benzyl-α-methylbenzyl ether (potassium amide-liquid ammonia) produced a mixture of diastereomeric

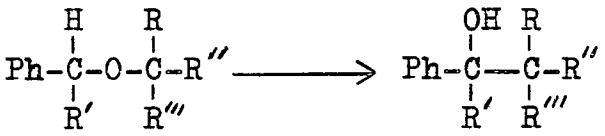
1,2-diphenyl-1-propanols in which the migrating group was estimated to have retained 64% of its optical activity. Migration of the α-methylbenzyl group had occurred with predominant retention of configuration. This estimate was based upon the optical purity of the D-(+)-α-methyldeoxybenzoin from oxidation of the mixture of optically active diastereomeric carbinols isolated from the rearrangement. However, the question of possible racemization of the optically active ether prior to rearrangement remained unsettled. The first part of the present work was undertaken in order to examine this possibility.

Optically inactive (±)-benzyl-α-methylbenzyl ether prepared by the method developed by Sifford (9) for the optically active ether was subjected to the conditions used by Sifford for the rearrangement (potassium amide in liquid ammonia). The reaction was found to be essentially complete in fifteen minutes insofar as only a trace of the starting ether could be detected by gas chromatography. A continued search for conditions necessary to provide a significant quantity of unreacted ether revealed that it was essential to quench the reaction (addition of water) after only three minutes. The optically active ether was prepared according to the method of Sifford (9) and the sample used subsequently for the rearrangement showed $[\alpha]_D^{25}$ - 3.81. Treatment of

the optically active ether for three minutes with potassium amide in liquid ammonia provided a sample of unreacted ether (purified by chromatography on alumina) which showed α_D^{25} - 3.83°. Thus, it was shown that racemization of the ether prior to rearrangement was not a factor in the loss of optical activity during the potassium amide induced isomerization of optically active (-)-benzyl-α-methylbenzyl ether. The optically active ether was also shown to be stable to the alumina chromatography.

The Wittig rearrangement of optically active benzyl-α-methylbenzyl ether produces a mixture of diastereomeric 1,2-diphenyl-1-propanols; the rotation of the two modifications are known, and are different (34). Thus, Sifford (9) evaluated the degree of racemization from the optical purity of the ketone obtained from the mixture of diastereomeric alcohols by oxidation under conditions known not to racemize the ketone (34). In the present work a method for evaluating the stereochemical course of the rearrangement directly from the rotation of the mixture of the product carbinols was examined. Such a method would have the advantage of providing a means of studying the migration of an optically active group in the Wittig rearrangement where the product carbinols were a mixture of diastereomeric

tertiary alcohols, the general case of which is depicted below.

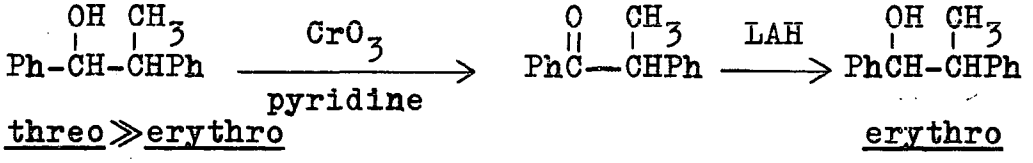


threo and erythro

Utilization of the method would depend on such factors as the rotation of each of the diastereomeric carbinols in their pure form and also on the accurate determination of their composition in the product mixture. Application of the method designed to evaluate the level of retention of optical purity in the case of optically active benzyl-α-methylbenzyl ether required only to find an appropriate method to determine the composition of the mixture of product isomers since the rotation of each optically pure isomer is reported (34). It was hoped that this could be accomplished conveniently by quantitative gas chromatographic analysis.

Each of the diastereomeric 1,2-diphenyl-1-propanols were synthesized independently in order to study their gas chromatographic behavior. The synthesis of threo-1,2-diphenyl-1-propanol free of the erythro modification was accomplished through a Grignard reaction of phenylmagnesium bromide with hydratropic aldehyde.

The resultant product was predominately the threo alcohol, the racemate predicted on the basis of the well-known rule of asymmetric induction (Cram's rule) (35). Complete purification of the threo alcohol involved the preparation of the p-nitrobenzoate ester of the product followed by six recrystallizations giving finally the ester having m.p. 145.5-147°. Saponification of the ester with alcoholic potassium hydroxide afforded a sample of the liquid threo-alcohol in pure form. The erythro isomer was prepared by the lithium aluminum hydride reduction of α-methyl-deoxybenzoin which was obtained by means of a pyridine-chromium trioxide oxidation of the mixture of alcohols obtained in the above reaction. Several recrystallizations afforded pure solid erythro-1,2-diphenyl-1-propanol m.p. 52-54°.



threo ≫ erythro

erythro

Mixtures of the authentic diastereomeric 1,2-diphenyl-1-propanols were tested on a large number of gas chromatography columns utilizing stationary phases such as LAC-296, Carbowax 20 M, Apiezon L, and XE-60. None of these gave satisfactory separation of the racemates nor did varying the ratio of the stationary phase

to the solid support contribute to their resolution. Finally, it was found that excellent separation of the diastereomers could be realized through the utilization of 5% QF-1 on the support, Gas Chrom Z. This column gave cleanly separated, symmetrical peaks and each of the authentic samples of the diastereomeric carbinols was subsequently shown to be homogeneous.

When optically inactive benzyl-α-methylbenzyl ether is rearranged using Sifford's conditions (potassium amide in liquid ammonia), the mixture of product carbinols consists of 69% of the threo form as estimated from gas chromatography (Micro Tec). In the present work, the data recorded by Sifford (9) was employed in a calculation (of the type discussed below) designed to arrive at an estimate of the composition of the mixture of the two alcohols obtained in his work. Sifford obtained a mixture of optically active 1,2-diphenyl-1-propanols displaying $[\alpha]_D^{25}$ - 12.1°. Other values on which the calculated composition is based are 34.4% for the optical purity of the starting ether, 64% for the level of retention of optical activity in the rearrangement and the reported (34) rotations of -68.8° and -47.2° for the respective rotations of optically pure erythro and threo alcohols. The above quantities can then be expressed in terms of % threo which takes the form of equation 1.

$$\% T = \frac{R_m \times 10^2 - a\ b\ R_E \times 10^{-2}}{(a\ b \times 10^{-4})\ (R_T - R_E)} \quad \text{(Equation 1)}$$

% T = % of the threo form in the product mixture of the diastereomeric carbinols.

a = % optical purity of the starting ether.

b = % retention of optical activity in the reaction.

R_m = rotation of the product mixture of the diastereomeric carbinols.

R_T = rotation of optically pure threo-1,2-diphenyl-1-propanol (34).

R_E = rotation of optically pure erythro-1,2,-diphenyl-1-propanol (34).

Solution of equation 1 employing the above data gives a value of 65% threo which is in fair agreement with that estimated from gas chromatography as discussed above. It may seem that this apparent agreement might be taken to indicate that the level of optical activity retained in each alcohol is the same. However, sample calculations showed that when dramatic differences in optical purity were assigned to each of the alcohols, the calculated rotation of the mixture of alcohols was seen to vary only slightly. This is presumably due to the relatively small difference between the rotations of each of the optically pure alcohols.

It is unlikely that the observed ratio of the diastereomeric carbinols is the result of a rapid equilibrium between the pair of racemates under the reaction conditions. It is well substantiated that, in general, the erythro form of a pair of given racemates is thermodynamically more stable than the threo form (37). That the thermodynamically less stable threo isomer is observed to be the form in excess in the product mixture, therefore, seems to preclude the possibility of a pair of rapidly equilibrating forms where the erythro form would be expected to predominate. However, if the rate of equilibrium between the two forms is appreciably less than the rate of the rearrangement then, in this case, interconvertability of the two racemates under the reaction conditions might indeed be a factor in determining the product composition at the conclusion of the reaction. This possibility was tested experimentally and precluded by the observation that an authentic mixture of diastereomeric 1,2-diphenyl-1-propanols was recovered unchanged in composition after exposure to the reaction conditions.

With Sifford's (9) observation of the relatively high degree of retention in the α-methylbenzyl group during the potassium amide induced isomerization of (-)-benzyl-α-methylbenzyl ether, it was decided to investigate the stereochemistry of this rearrangement

in other solvent systems. Schollkopf (4) observed a somewhat higher level of retention of optical activity (17% vs. 31%) in the migration of the s-butyl group of the corresponding benzyl ether when the solvent was changed from tetrahydrofuran to pentane. Based on this observation, it was anticipated to observe a higher level of retention in the Wittig rearrangement of (-)-benzyl-α-methylbenzyl ether with potassium amide in hexane.

Preliminary studies with inactive benzyl-α-methylbenzyl ether using potassium amide in refluxing hexane revealed that the formation of the diastereomeric 1,2-diphenyl-1-propanols was indeed a relatively slow process. Approximately two days were required to bring the reaction to near completion as compared with 15 minutes in liquid ammonia at -33°. This marked decrease in rate is at least partially attributable to the extreme insolubility of potassium amide in hot hexane. Since under these conditions the reaction is essentially heterogeneous, it was not surprising to observe varying rates from run to run. In this case the rate would in part depend upon such factors as the state of subdivision of the potassium amide and rate of stirring, factors which would not likely be duplicated in subsequent reactions. In all cases, it was necessary to separate the mixture of product carbinols from a small amount of unreacted

ether by column chromatography on alumina prior to a final purification of the carbinols by a short-path distillation. It therefore became necessary to investigate the possibility that the chromatography might in some way change the composition of the racemates. When a mixture of pure threo-1,2-diphenyl-1-propanol and benzyl-α-methylbenzyl ether was chromatographed on alumina the ether was eluted in the early fractions using hexane as the eluant. All of the threo isomer was then washed from the column using neat ether. A gas chromatogram of the combined fractions containing the carbinol showed that none of the alternate erythro isomer had been formed. Therefore, it was expected that the alumina chromatography would in no way affect the composition of the mixture of diastereomeric 1,2-diphenyl-1-propanols. Also, since the boiling points of both racemates are nearly the same it would be extremely unlikely that a short-path distillation would result in a composition change.

Optically active benzyl-α-methylbenzyl ether was prepared from active α-methylbenzyl alcohol by the Williamson method. As anticipated from the results of Sifford (9), only a slight lowering of optical activity was encountered during the preparation. Thus, from

alcohol of 27.9% optical purity, ether was obtained having an optical purity of 26.9%.

Rearrangement of optically active ether (optical purity 29.1%) was carried out with potassium amide in refluxing hexane for 35.25 hours. After this time a gas chromatographic analysis of the crude reaction product showed the presence of only a trace of unreacted benzyl-α-methylbenzyl ether. The areas under the peaks for the pair of diastereomeric carbinols corresponded to 60% for the threo form and 40% for erythro. The crude reaction product was chromatographed on alumina in order to separate the mixture of optically active carbinols from unreacted ether. As expected, the composition was unchanged following the chromatography. After a short-path distillation of the product alcohols, the mixture showed $[\alpha]_D^{25}$ - 15.38°. The composition of the distilled mixture did not differ from that obtained on the crude reaction product. The level of retention of optical activity in the reaction may now be calculated using equation 1 expressed in terms of % retention of optical activity:

$$b = \frac{R_m \times 10^4}{a \quad (\% T \times 10^{-2}) \quad (R_T - R_E) + R_E} \quad \text{(Equation 2)}$$

where the symbols have the same meaning as defined in equation 1. For the rearrangement of (-)-benzyl-α-methylbenzyl ether with potassium amide in refluxing hexane, the level of retention of optical activity in the reaction as estimated from equation 2 amounts to 95%. Consistent with past observations (4,9), the optical form in excess is the same as that in the starting ether. It is noteworthy that this level of retention is much higher than any reported for previous stereochemical studies of the Wittig rearrangement.

The mixture of optically active diastereomeric 1,2-diphenyl-1-propanols obtained in the above rearrangement was oxidized to the corresponding ketone by chromic acid. Since this method had been shown previously (34) to not racemize the resulting ketone, the configuration and optical purity of the α-methylbenzyl group in this compound could be compared with those of the same group in the starting ether. Thus, it is possible to check the level of retention in the rearrangement as reflected by the diastereomeric composition and rotation of the mixture of product carbinols against that reflected by the optical purity of the ketone. Starting with D-(-) ether of 29.1% optical purity rearrangement and oxidation led to D-(+)-α-methyldeoxybenzoin of 24.9% optical purity. This corresponds to 86% retention of optical

purity, and predominant retention of configuration in the rearrangement step.

Clearly, there exists a relatively small but significant discrepancy between the values estimated for the level of optical activity retained as derived from the two independent methods. Therefore, it was decided to reinvestigate the possibility of a small degree of racemization during the chromic acid oxidation of the diastereomeric carbinols. Accordingly, (+)-α-methyldeoxybenzoin of 24.9% optical purity when stirred for 7.5 hours with the oxidation mixture used to convert the diastereomeric carbinols to the ketone, the recovered ketone had an optical purity of 23.6%. This corresponds to a small degree of racemization amounting to 5.2%. Allowing for this small loss of activity in the ketone, the value for the level of retention in the rearrangement as reflected by the optical purity of the ketone becomes 91.2%. This corrected value, then, agrees, within experimental error, with that estimated from the rotation and composition of the product carbinols.

On the basis that the non-homogeneous conditions of the rearrangement with potassium amide in hexane might be a factor affecting the high degree of retention observed, it was decided to investigate the rearrangement using instead the completely hexane soluble base,

n-butyllithium. A preliminary run of the rearrangement of (±)-benzyl-α-methylbenzyl ether with excess n-butyllithium in refluxing hexane was followed by observing the gas chromatograms of aliquots which were removed periodically while the reaction was in progress. This experiment showed that the rate of the reaction was about double that when potassium amide was used, requiring about 15 hours to attain 50% completion of the reaction and 27 hours for 90% completion. Thus, from this information, one can choose a suitable reaction time which would permit the isolation of unreacted ether in addition to the product carbinols. It was hoped to separate significant quantities of the unreacted ether from the product carbinols in order to examine the optical stability of the ether as well as the stereochemical course of the rearrangement. However, the reaction was complicated by the presence of an unidentified peak in the gas chromatogram appearing close to and slightly ahead of the peak corresponding to unreacted ether. Also, there remained the possibility of configurational interconversion between the pair of racemates produced in the rearrangement. However, it was shown that when pure erythro-1,2-diphenyl-1-propanol was treated with n-butyllithium in hexane, no threo alcohol was produced. Therefore,

it was anticipated, as in the case when potassium amide was used, that the composition of the product carbinols would remain unchanged under the reaction conditions.

Optically active (-)-benzyl-α-methylbenzyl ether of 25.0% optical purity was rearranged with excess (3:1) n-butyllithium in refluxing hexane for about 12 hours. The crude reaction product was chromatographed on alumina. Flushing the column with hexane afforded the unreacted ether contaminated with the unidentified material and after two short-path distillations a sample of unreacted ether was obtained which showed an optical purity of 15.9%. However, since gas chromatography of this sample showed that the impurity was present to the extent of about 40% it may be assumed that no loss of optical activity in the starting ether occurred if the impurity itself is optically inactive. However, this assumption was not checked out experimentally.

The mixture of diastereomeric carbinols was flushed from the alumina column with ether affording material whose infrared spectrum showed carbonyl absorption in addition to the expected hydroxyl absorption. Therefore, this material was chromatographed on alumina (10% ether in hexane). The first

two fractions afforded material whose weight constituted 12% of the total weight of material chromatographed. This material gave an infrared spectrum essentially identical with that of an authentic specimen of α-methyldeoxybenzoin. Gas chromatographic behavior of the material was identical with authentic α-methyldeoxybenzoin although traces of two other compounds were evident in the gas chromatogram. The ketone, α-methyldeoxybenzoin, is presumed to arise from air oxidation of the product carbinols. The chromatographic fractions 3 through 11 afforded a heavy liquid corresponding to 36% of the total weight of chromatographed material. Gas chromatography gave peaks corresponding to the erythro and threo racemates along with the two small peaks which were present in the sample of α-methyldeoxybenzoin found in fractions 1 and 2. Finally, a pure sample of the pair of diastereomeric carbinols was isolated from fractions 12 through 31 (14.5% of the total material chromatographed) which showed $[\alpha]_D^{25}$ - 12.97°. The composition of this sample showed 47.07% of the threo racemate by gas chromatography (Barber-Colman). The chromatography on alumina did not alter the composition of the racemates. Identical values for the composition of the racemates were obtained by gas chromatography before and after the column chromatography. Using equation 2, it was calculated that the level of retention of optical

activity in the rearrangement of (-)-benzyl-α-methylbenzyl ether with n-butyllithium in hexane is 88.5%. Consistent with this value is an estimate of 87% retention based on the optical purity of the ketone obtained from the oxidation of the optically active mixture of diastereomeric carbinols isolated from the rearrangement. Also, consistent with past observations (4,9), it was noted that the optical form in excess in the product carbinols was the same as that in the starting ether.

The results discussed thus far in the present work are summarized in Table I. For the purpose of a mechanistic discussion based on the results in Table I it is first assumed that the main course of the rearrangement follows a fragmentation-recombination process discussed in introduction which has been previously proposed (4,5,6,9). It is further assumed that in the fragmentation step of the rearrangement, the bond of the abstracted methylene proton, the bond between the methylene carbon and the ether oxygen, and the bond between the ether oxygen and the asymmetric carbon all are coplanar. This model is analogous to that proposed for the activated complex in an E 2 reaction (38). For benzyl-α-methylbenzyl ether, two such activated complexes are depicted in I_a and I_b and differ mainly with respect to which methylene proton,

TABLE I

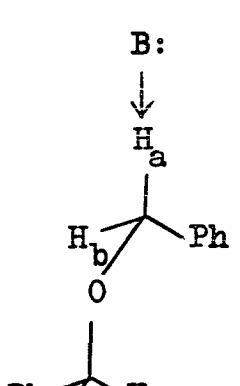
CONDITIONS AND RESULTS IN THE REARRANGEMENT OF (-)-BENZYL-α-METHYLBENZYL ETHER

Base	Solvent	T(°C)	% threo-1,2-Diphenyl-1-propanol	% Retention
KNH_2	$NH_3(l)$	-33	69	64[a]
KNH_2	Hexane	65	60	95[b]
n-BuLi	Hexane	65	47	88.5[b]

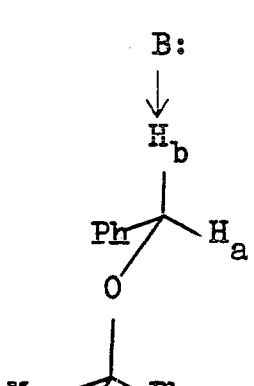
[a]Result determined by Sifford (9).

[b]Based on rotation and composition of the mixture of product 1,2-diphenyl-1-propanols.

H_a or H_b, is in suitable position during attack by base, B:. It should be noted that activated complexes I_a and I_b are not conformers but instead are related diastereomerically because of the incorporation of B:. In addition to fulfilling the condition of coplanarity mentioned above, the bulky phenyl groups are arranged in I_a and I_b so that there is a maximum of distance between them. Examination of these two activated complexes leads to the conclusion that the energy of activation leading to I_b is probably greater than that leading to I_a. This conclusion is based on the likelihood of a more or less severe 1,3-phenyl-methyl steric interaction in I_b whereas in I_a only 1,3-phenyl-hydrogen interaction is encountered.

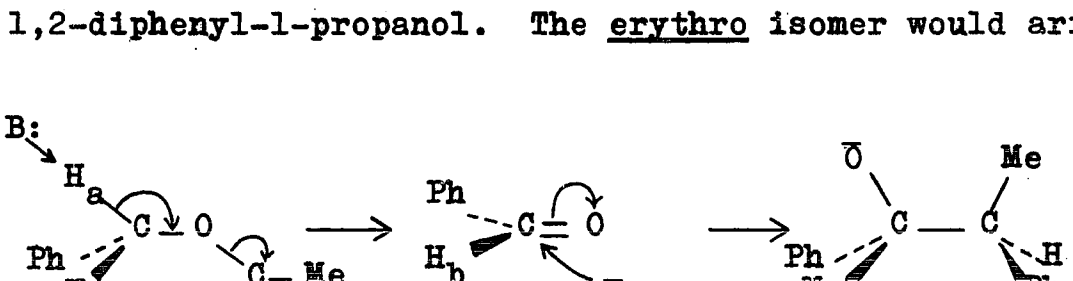


I_a



I_b

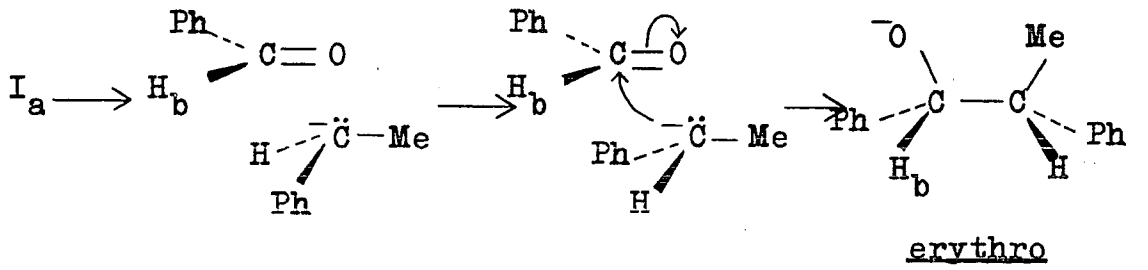
The expected diastereomer resulting from the fragmentation and direct recombination of activated complex I_a is the thermodynamically less stable threo-1,2-diphenyl-1-propanol. The erythro isomer would arise



I_a

from the fragmentation and direct recombination of activated complex I_b. If this process (concurrent fragmentation-direct recombination of both I_a and I_b) were the exclusive course in the rearrangement, the

expected result should be at least a predominance of the threo isomer with complete retention of optical purity. In Table I the second case seems to most nearly approach this situation. The first case, where there is a somewhat greater amount of the threo isomer, might be taken to reflect an enlarged energy difference between I_a and I_b due to the low reaction temperature. In addition, the first case differs from the second with respect to a somewhat greater level of racemization. Within the framework of the present mechanism, this demands a complete inversion of the α-methylbenzyl fragment prior to recombination. It should be pointed out that this inversion would lead to the erythro form. If the fragments are sufficiently



erythro

free to undergo random reorientation before recombining, one might anticipate a more or less equal composition of diastereomeric carbinols with complete racemization because all possible orientations of the fragments are possible. This process is called upon to accommodate the racemized portion of the rearrangement in the first

case in Table I. However, in view of the high level of retention of configuration in even the first case, reorientation of the fragments prior to recombination is a minor process at least in the first two cases.

Surprisingly, the third case in Table I shows a high level of retention without the expected predominance of the threo isomer. In view of the present mechanism this observation would seem to demand extensive "flipping" of the carbonyl moiety and very little inversion of the α-methylbenzyl group prior to recombination, with the result that the α-methylbenzyl group upon recombination would have an equal chance of meeting either face of the carbonyl fragment. This would accommodate the observed approximately 50:50 ratio of threo and erythro alcohols in the product mixture together with a high level of retention in the rearrangement. It is speculated that this unusual mechanism may be rationalized by the formation of a relatively stable organolithium compound immediately following fragmentation with sufficient lifetime to permit the extensive flipping of the carbonyl fragment prior to recombination. It has been shown (39) that under certain conditions an optically active organolithium compound can be prepared in pentane displaying up to 83% retention of optical activity in its carbonated product.

Since a completely S_Ni process as discussed in the introduction demands complete retention of configuration, the first case in Table I cannot be accommodated entirely by this mechanism although the unracemized portion of the reaction could conceivably follow this path. Furthermore, since it is not possible to accurately predict the composition of the diastereomeric alcohols within the framework of an S_Ni process one cannot preclude this mechanism on the basis of the composition data in Table I. However, the fragmentation-recombination scheme satisfactorily accounts for all results.

EXPERIMENTAL

All melting points and boiling points are uncorrected.

Optical rotations were obtained with a Gaertner L-320 Polarimeter.

Gas chromatographic analyses used to determine the composition of mixtures of diastereomeric 1,2-diphenyl-1-propanols were performed on a Micro Tek model 1600 gas chromatograph utilizing a hydrogen flame detection system. The seven foot by 1/8 inch O.D. stainless steel column was packed with 5% QF-1 on 100-120 mesh Gas Chrom Z and operated at 143°. The inlet and detector temperatures were 257° and 218° respectively and the helium carrier gas was delivered at a pressure of 50 p.s.i. The area under the peaks was measured with a polar planimeter. The ratio of the areas corresponded, within experimental error, (± 3%) to the mole fraction ratio of authentic samples of known composition; thus a correction factor was not needed. The Barber Colman model 15 gas chromatograph

equipped with an argon detector was used to determine the composition of the diastereomeric carbinols in the experiment where n-butyllithium was employed. The 8 foot by 2 mm. I. D. pyrex U-shaped column was packed with 5% QF-1 on 80-100 mesh Gas Chrom Z and operated at 115°. The inlet and detector temperatures were 203° and 230° respectively and the argon carrier gas was delivered at a pressure of 60 p.s.i.

A standard mixture consisting of threo and erythro isomers in the ratio 2.19 gave peaks displaying the area ratios of 3.08. Thus, the factor 0.711 was employed to reduce the observed ratios in other mixtures to actual values.

Preparation of (±)-Benzyl-α-Methylbenzyl Ether. -- To a 3-necked flask equipped with stirrer and containing 2.5 l. of liquid ammonia was added 60.5 g. (1.55 mole) of potassium metal. About 0.5 g. of ferric nitrate was added in order to catalyze the formation of potassium amide. When the amide formation was complete, a solution of 189 g. (1.55 mole) of (±)-α-methylbenzyl alcohol in 300 ml. of ether was added to the stirring mixture of potassium amide in liquid ammonia over a period of one hour. After the addition was complete 294 g. (2.32 mole) of benzyl chloride was added in 0.5 hour. The mixture was allowed to stir

for 6 hours after which time most of the ammonia had evaporated. The mixture was hydrolyzed by slow addition of 300 ml. of water with vigorous stirring. After filtering the reaction mixture, the layers were separated and the aqueous phase was extracted with three 50 ml. portions of hexane. The combined organic phase was washed with water, 4 N hydrochloric acid, again with water and then dried. After removal of the solvent and excess benzyl chloride, distillation gave 179.4 g. of the colorless ether, b.p. 119-124° at 2.5-2.9 mm.; n_D^{25} 1.5495. The lower boiling material (121.4 g.) was redistilled giving two fractions of the colorless ether: i 62.06 g., b.p. 129-130° at 4.2 to 4.4 mm.; n_D^{25} 1.5499 and ii 36.01 g., b.p. 129-130.5° at 4.1 mm.; n_D^{25} 1.5503. The combined weight of all these fractions represents 84.5% yield of the ether.

Preparation of (-)-Benzyl-α-Methylbenzyl Ether. -- To 0.0735 mole of potassium amide (from 2.88 g., 0.0735 mole of potassium in 500 ml. of liquid ammonia was added a solution of freshly distilled α-methylbenzyl alcohol [9.0 g., 0.0735 mole, α_D^{25} - 6.12° (0.5 dm., neat)] in 40 ml. of ether over a five minute period. To the stirred mixture was added 37.2 g. (0.294 mole) of benzyl chloride all at once. When the ammonia had evaporated (2 hours) 100 ml. of water was added. After

filtering the reaction mixture the layers were separated and the aqueous phase was washed with 3 portions of ether. The combined ethereal solution was washed with water, 1 N hydrochloric acid, again with water and dried. After removal of the solvent and excess benzyl chloride the crude ether was distilled and three fractions of the purified ether were collected: i 2.313 g., b.p. 110-120° at 1 mm., n_D^{25} 1.5459, α_D^{25} - 11.50° (0.5 dm., neat), ii 5.153 g., b.p. 113-115° at 0.8 to 0.9 mm., n_D^{25} 1.5489, α_D^{25} - 11.42° (0.5 dm., neat) and iii 3.969 g., b.p. 116-120° at 0.9 to 1.0 mm., n_D^{25} 1.5490, α_D^{25} - 11.30° (0.5 dm., neat). The combined weight of these three fractions represents a 73.3% yield of the purified ether.

Rearrangement of (±)-Benzyl-α-Methylbenzyl Ether in Liquid Ammonia at -33°. -- The ether (5.00 g., 0.0236 mole) in 10 ml. of ethyl ether was added to 0.0472 mole of potassium amide (from 1.84 g. of potassium) in 300 ml. of liquid ammonia. After stirring the mixture for 15 minutes, 6 g. of ammonium chloride was added followed by 25 ml. of ethyl ether and 20 ml. of water. After the ammonia had evaporated the remaining mixture was filtered and the layers were separated. The aqueous phase was extracted once with ethyl ether and the combined ethereal phases were dried briefly over anhydrous

potassium carbonate. Removal of the solvent left a yellow liquid whose infrared spectrum showed the presence of alcohol. Gas chromatography of the crude reaction product gave peak areas for the mixture of diastereomeric 1,2-diphenyl-1-propanols corresponding to 69.1% threo and 30.9% erythro. Only a trace of the starting ether was present as indicated by the gas chromatogram.

Test of Optical Stability of (-)-Benzyl-α-Methylbenzyl Ether with Potassium Amide. -- The ether [5.605 g., 0.0264 mole, α_D^{25} - 3.81° (0.5 dm, neat)] in 20 ml. of ethyl ether was added all at once to 0.0528 mole of potassium amide (from 2.07 g. of potassium) in about 250 ml. of liquid ammonia. After the reaction mixture had stirred for three minutes, 6 g. of ammonium chloride was added followed by 25 ml. of distilled water. The ammonia was allowed to evaporate at room temperature and the liquid which remained was filtered. The layers were separated and the aqueous phase was washed 3 times with 25 ml. portions of ethyl ether. The combined ethereal solution was washed 8 times with 25 ml. portions of water and dried for one hour over anhydrous sodium sulfate. After removing the solvent there remained 3.854 g. of a clear, yellow liquid. The infrared spectrum of this specimen indicated that both ether and alcohol

were present. A sample of 2.862 g. of this liquid was chromatographed on 20 g. of alumina using 600 ml. of hexane as the eluant. Evaporation of the hexane afforded 1.833 g. of the ether as a light yellow liquid. After two distillations, the colorless liquid showed α_D^{25} - 3.83° (0.5 dm, neat).

threo-1,2-Diphenyl-1-propanol. -- This compound was prepared according to a method previously described (35). To the Grignard reagent prepared from 391 g. (2.5 mole) of bromobenzene and 60.5 g. (2.5 mole) of magnesium in 250 ml. ether was added dropwise 268 g. (2.0 mole) of hydratropaldehyde diluted with an equal volume of ether. Vigorous stirring was continued for 9 hours after the addition was complete. Then the reaction mixture was hydrolyzed by dropwise addition of an aqueous solution of 160.5 g. (3 moles) of ammonium chloride. The mixture was filtered through a Buchner funnel and the filter cake was washed twice with ether. The combined ethereal phases were dried over anhydrous sodium sulfate and the ether was removed. The residue was distilled under reduced pressure and 331 g. of a clear, colorless liquid b.p. 125-128° (0.75 mm.) was collected. The infrared spectrum of this liquid showed a band at 3450 cm^{-1} characteristic of the hydroxyl

group. The distilled material represents 78% yield of 1,2-diphenyl-1-propanol.

Pure threo-1,2-diphenyl-1-propanol was separated from the mixture of diastereomeric alcohols obtained from the Grignard reaction according to a method previously described (35). A solution of 106 g. (0.5 mole) of the mixture of diastereomeric 1,2-diphenyl-1-propanols and 93 g. (0.5 mole) of freshly prepared p-nitrobenzoyl chloride in 500 ml. of pyridine was allowed to reflux for 4 hours. The mixture was cooled and poured into a mixture of ice and dilute sulfuric acid. The precipitate was collected on a funnel, washed twice with water and allowed to air dry overnight. After six recrystallizations from ethanol-ethyl acetate there was obtained 78.5 g. of ester of the threo isomer, m.p. 145.5-147°. Lit. 143-144° (35).

The p-nitrobenzoate ester was hydrolyzed in a methanol-water (1:1) solution containing 24.6 g. (0.440 mole) of potassium hydroxide. After refluxing the solution for 17 hours, the reaction mixture was cooled and extracted three times with ether. The combined ethereal phases were washed once with dilute hydrochloric acid, twice with water and allowed to stand over anhydrous sodium sulfate. The ether was removed and the residue was distilled under reduced pressure.

Three fractions were collected from the vacuum distillation: i 11.8 g., b.p. 116-118.8° (0.30-0.35 mm.), n_D^{25} 1.5711; ii 15.9 g., b.p. 129.5° (1.1 mm.), n_D^{25} 1.5718; iii 10.7 g., b.p. 130° (1.1 mm.), n_D^{25} 1.5721. The infrared spectrum of fraction i showed a strong band at 3430 cm^{-1} characteristic of the hydroxyl group. Also, fraction i showed a single peak in its gas chromatogram which was obtained under conditions sufficient to detect the presence of any of the diastereomeric erythro-1,2-diphenyl-1-propanol. Fractions ii and iii were essentially identical with fraction i with respect to the infrared spectra and gas chromatograms of samples of these fractions.

α-Methyldeoxybenzoin. -- This compound was prepared by the chromium trioxide-pyridine oxidation (36) of a mixture of diastereomeric 1,2-diphenyl-1-propanols. To 300 g. of pyridine was added 30.0 g. (0.3 mole) of chromium trioxide in portions with stirring. The reaction flask was immersed in a bath whose temperature was maintained at a temperature below 20°. When approximately half of the chromium trioxide had been added a yellow precipitate of the pyridine-chromium trioxide complex began to appear. After all of the chromium trioxide had been added,

a 10% pyridine solution of 21.2 g. (0.1 mole) of 1,2-diphenyl-1-propanol was introduced while keeping the temperature of the reaction vessel below 30°. After about 0.5 hours the reaction mixture became black. The mixture was stirred for 24 hours at room temperature. After pouring the reaction mixture into approximately one liter of water the whole was extracted three times with a 1:1 ether-benzene solution. The combined organic phases were dried briefly with anhydrous sodium sulfate and the solvent was removed by distillation. An infrared spectrum of the crude reaction product showed absence of hydroxyl absorption and the presence of a band at 1685 cm^{-1} characteristic of the aryl ketonic carbonyl moiety. The material solidified on standing and after a single recrystallization from ethanol showed m.p. 52.5-54°. This product was used without further purification.

erythro-1,2-Diphenyl-1-propanol. -- This compound was prepared according to a method previously described (35). A solution of 11.0 g. (0.052 mole) of α-methyldeoxybenzoin in 50 ml. of dry ether was added dropwise to a well-stirred mixture of 0.68 g. (0.018 mole) of lithium aluminum hydride and 50 ml. of dry ether. The mixture was then refluxed for 30 minutes, cooled and treated with 1 N sulfuric acid and

shaved ice. The layers were separated, the organic layer was washed successively with ice-water, sodium carbonate solution, water and the solution was then dried over anhydrous sodium sulfate. The solvent was distilled and there remained an oil which was distilled (b.p. 145-147° at 3 mm.) through a short-path modified Claisen apparatus giving 10.92 g. (99% yield) of a mixture of diastereomeric 1,2-diphenyl-1-propanols. An infrared spectrum of the distilled material showed a band at 3430 cm^{-1} corresponding to hydroxyl absorption. The band at 1685 cm^{-1} indicative of aryl ketonic carbonyl absorption was absent.

The product solidified after standing in the cold overnight. Three recrystallizations from pentane gave 5.1 g. of erythro-1,2-diphenyl-1-propanol, m.p. 52-54° (35) which was shown to be homogeneous by gas chromatography.

Rearrangement of (-)-Benzyl-α-Methylbenzyl Ether in Refluxing Hexane. -- Potassium amide (0.06 mole) was prepared in the usual fashion from 2.32 g. of potassium in about 150 ml. of liquid ammonia. After the formation of the potassium amide was complete 250 ml. of hexane was added and the ammonia was allowed to evaporate. The mixture was brought to reflux and the ether [6.36 g., 0.030 mole, α_D^{25} - 12.40° (0.5 dm,

neat)] in about 5 ml. hexane was added all at once with vigorous stirring. The reaction mixture was refluxed on the steam bath for 35 hours, 100 ml. of water was added and the mixture was filtered. The layers were separated and the aqueous phase was washed four times with 15 ml. portions of hexane. The combined hexane solution was washed once with 25 ml. water, once with 25 ml. 4 N hydrochloric acid and four times with 25 ml. portions of water. After drying the hexane solution over anhydrous sodium sulfate and removing the solvent there remained 5.76 g. of a reddish-orange liquid. Gas chromatography of a sample of the crude reaction product gave three major peaks corresponding to the mixture of diastereomeric 1,2-diphenyl-1-propanols and unreacted (-)-benzyl-α-methylbenzyl ether. The areas under the two peaks corresponding to the diastereomeric 1,2-diphenyl-1-propanols were measured with a polar planimeter and estimated to represent 60.0% threo and 40.0% erythro. The alcohols were isolated by column chromatography on neutral alumina. As mentioned earlier the ether was eluted first with hexane. A quantitative gas chromatographic analysis following alumina chromatography showed that the composition of the mixture of diastereomeric 1,2-diphenyl-1-propanols was unchanged. After a short-path

distillation the alcohols showed $[\alpha]_D^{25}$ - 15.38° (α_D^{25} - 3.12°, 1 dm., c = 20.26, $CHCl_3$).

Configurational Stability of a Mixture of Diastereomeric 1,2-Diphenyl-1-propanols toward Potassium Amide in Liquid Ammonia. -- To 0.17 mole of potassium amide (from 6.64 g., 0.17 mole of potassium) in 300 ml. of liquid ammonia was added 18.0 g. (0.085 mole) of a mixture of diastereomeric 1,2-diphenyl-1-propanols in 20 ml. ether the composition of which was 60% threo and 40% erythro as determined by gas chromatography. After stirring the mixture for 4 hours, 18 g. of ammonium chloride was added in small portions followed by the addition of 90 ml. of water. The remaining ammonia was allowed to evaporate and the mixture was filtered and extracted twice with 25 ml. portions of ether. The ethereal solution was washed once with 1 N hydrochloric acid, twice with water and dried briefly over anhydrous sodium sulfate. Removal of the solvent left 16 g. of the mixture of diastereomeric 1,2-diphenyl-1-propanols as a heavy liquid (88% recovery). The composition of the product alcohols was determined by gas chromatography and found to be unchanged relative to the composition of the starting mixture.

Oxidation of the Mixture of Diastereomeric 1,2-Diphenyl-1-propanols Obtained from the Wittig Rearrangement of (-)-Benzyl-α-Methylbenzyl Ether with Potassium Amide in Hexane. -- The mixture of diastereomeric 1,2-diphenyl-1-propanols (1.93 g., 9.10 mmole) in 21 ml. of benzene was added in 3.3 hours with stirring to a mixture composed of 5.71 g. (29.4 mmole) of potassium chromate, 6.3 ml. of sulfuric acid, 3.5 ml. of acetic acid, 21 ml. of water and 10 ml. of benzene. After stirring at room temperature for 2.5 hours, the mixture was filtered, the layers were separated and the aqueous phase was extracted twice with benzene. The combined benzene solution was washed with water, brine, saturated sodium carbonate, again with brine and dried over anhydrous sodium sulfate. Removal of the solvent left 1.56 g. (81.6%) of (+)-α-methyldeoxybenzoin as a heavy yellow liquid. The infrared spectrum of this material showed a trace of hydroxyl (3344 cm^{-1}) and a strong band for the aryl ketonic moiety (1669 cm^{-1}). After three short-path distillations the (+)-α-methyldeoxybenzoin, homogeneous by gas chromatography, showed $[\alpha]_D^{25}$ + 51.3° (α_D^{25} + 3.22°, 1 dm., c = 6.28, $CHCl_3$) and m.p. 40.8-48.9°.

Test of the Optical Stability of (+)-α-Methyldeoxybenzoin. -- The ketone [0.212 g., 1.0 mmole, $[\alpha]_D^{25}$ + 51.3° (α_D^{25} + 3.22°, 1 dm., c = 6.28, $CHCl_3$)] in 10 ml. of benzene was added in 30 minutes with stirring to a mixture composed of 5.71 g. (29.4 mmole) of potassium chromate, 6.3 ml. of sulfuric acid, 3.5 ml. of acetic acid, 21 ml. of water and 10 ml. of benzene. After stirring at room temperature for 7.5 hours, the reaction mixture was filtered and the layers were separated. The aqueous phase was extracted with benzene and the benzene solution was washed once with brine, once with saturated sodium carbonate and three more times with brine. After drying and removing the benzene there was left 0.17 g. of the (+)-α-methyldeoxybenzoin as a heavy, slightly yellow liquid. This amount represents a recovery of 80.2%. After a short-path distillation the ketone solidified and showed $[\alpha]_D^{25}$ + 48.6° (α_D^{25} + 3.54°, 1 dm., c = 7.285, $CHCl_3$). The distilled ketone was shown to be homogenecus by gas chromatography and its infrared spectrum was identical with that of an authentic specimen of α-methyldeoxybenzoin.

Rearrangement of (±)-Benzyl-α-Methylbenzyl Ether with n-Butyllithium in Refluxing Hexane. -- The ether (22.26 g., 0.105 mole) in 50 ml. of hexane

was added all at once to 250 ml. (0.41 mole) of a 1.64 N hexane solution of n-butyllithium diluted with 100 ml. of hexane. The whole was brought to reflux with stirring and after 10 minutes, the reaction mixture became red-orange. Periodically, 1 ml. samples of the reaction mixture were withdrawn and hydrolyzed with 1 ml. of water. Gas chromatographic analyses of the aliquots showed that after 6 hours a significant quantity of unreacted ether remained and after 27 hours only a trace was left. The gas chromatograms also displayed a significant peak of unknown identity which appeared just before the peak corresponding to unreacted ether. The peaks for the mixture of diastereomeric alcohols showed a composition of approximately equal amounts of both forms.

Rearrangement of (-)-Benzyl-α-Methylbenzyl Ether in Hexane Solution with n-Butyllithium. -- The ether [3.29 g., 0.0155 mole, α_D^{25} - 10.64° (0.5 dm, neat)] in 11 ml. of hexane was added all at once to 28.4 ml. of a 1.64 N hexane solution of n-butyllithium diluted with 70 ml. of hexane. The whole was brought to the boiling point and almost immediately a clear, light yellow-green color developed. After the solution had been allowed to reflux for 6.5 hours, 70 ml. of water was added and the layers were separated. The aqueous

phase was extracted three times with 10 ml. portions of hexane. The combined hexane solution was washed once with 25 ml. of water, once with 25 ml. of 4 N hydrochloric acid and three times with 25 ml. portions of water. After drying and removal of solvent there was left 3.10 g. of a light yellow liquid of which the infrared spectrum showed the presence of alcohol (3500 cm^{-1}), ether (1096 cm^{-1}) and a trace of carbonyl (1684 cm^{-1}). The product carbinols were separated from unreacted (-)-benzyl-α-methylbenzyl ether by chromatography on 88 g. of alumina affording 1.26 g. (39%) of the mixture of diastereomeric 1,2-diphenyl-1-propanols as a slightly yellow, heavy liquid. Gas chromatographic analysis of the product carbinols revealed the presence of small amounts of impurities. The product carbinols were therefore rechromatographed affording a mixture of diastereomeric 1,2-diphenyl-1-propanols which was shown to be homogeneous by gas chromatography and unchanged in composition compared with the crude reaction product. This sample showed $[\alpha]_D^{25}$ - 12.97° (α_D^{25} - 0.95°, 1 dm., c = 7.32, $CHCl_3$). The composition of the mixture of diastereomeric 1,2-diphenyl-1-propanols was estimated by quantitative gas chromatography (Barber-Colman) giving peak areas corresponding to 53% for the erythro form and 47% for threo.

The early fractions from the alumina chromatography of the crude reaction product contained unreacted (-)-benzyl-α-methylbenzyl ether which showed α_D^{25} - 4.24° (0.5 dm, neat). After a second chromatography followed by a short-path distillation, the ether showed α_D^{25} - 6.77° (0.5 dm, neat). A gas chromatographic analysis of a sample of this material showed the presence of an impurity which was estimated to comprise approximately 40% of the sample. Assuming that the impurity is optically inactive, the rotation of the recovered ether can be assumed to be identical with that of the starting ether.

Configurational Stability of erythro-1,2-Diphenyl-1-propanol with n-Butyl Lithium in Hexane. -- To a hexane solution of 0.212 g. (1 mmole) of erythro-1,2-diphenyl-1-propanol (homogeneous by gas chromatography) was added 2 ml. of a 1.64 N (3.28 mmole) hexane solution of n-butyl lithium. The whole was brought to reflux and allowed to stir for 25.5 hours after which time 25 ml. of water was added. The layers were separated and the aqueous phase was extracted three times with hexane. The combined hexane phases were washed once with water, once with 4 N hydrochloric acid and again with water. After drying the hexane solution and removing most of the hexane, a gas

chromatographic analysis showed no detectable amount of the threo modification.

Oxidation of the Mixture of Diastereomeric 1,2-Diphenyl-1-Propanols Obtained from the Wittig Rearrangement of (-)-Benzyl-α-Methylbenzyl Ether with n-Butyl Lithium in Hexane. -- The mixture of 1,2-diphenyl-1-propanols (0.566 g., 2.67 mmole) in 10 ml. of benzene was added in 2 hours with stirring to a mixture composed of 8.75 g. (29.4 mmole) of sodium dichromate, 6.3 ml. of sulfuric acid, 3.5 ml. of acetic acid, 21 ml. of water and 10 ml. of benzene. After stirring at room temperature for one hour, the layers were separated and the aqueous phase was extracted twice with benzene. The combined benzene solution was washed twice with brine, twice with saturated sodium carbonate and again with brine. After drying and removing the solvent there remained 0.434 g. (77.5%) of (+)-α-methyldeoxybenzoin as a yellow oil. The product was purified by two short-path distillations giving solid (+)-α-methyldeoxybenzoin $[\alpha]_D^{25}$ + 44.8° (α_D^{25} + 3.91°, 1 dm., c = 8.73, $CHCl_3$).

SUMMARY

The stereochemical course of the Wittig rearrangement of optically active (-)-benzyl-α-methylbenzyl ether has been examined under three different sets of reaction conditions. A method for evaluating the level of retention in the rearrangement based on the rotation and composition of the product diastereomeric 1,2-diphenyl-1-propanols has been developed. An extremely high level (95%) of retention of optical activity in the rearrangement has been observed using potassium amide in hexane. The mechanism of the rearrangement has been discussed in terms of a previously suggested fragmentation-recombination scheme and is preferred to a dual course requiring in addition the operation of an S_Ni process.

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PART II

OLEFINS FROM THE HYDROBORATION OF ENAMINES

INTRODUCTION

The hydroboration reaction (1) has received much attention during the past ten years mainly because of its great utility in the area of synthetic organic chemistry. In broad terms, the reaction involves the addition of diborane to a carbon-carbon double bond resulting in the formation of an alkylborane, a useful intermediate which may readily be oxidized to an alcohol or a ketone.

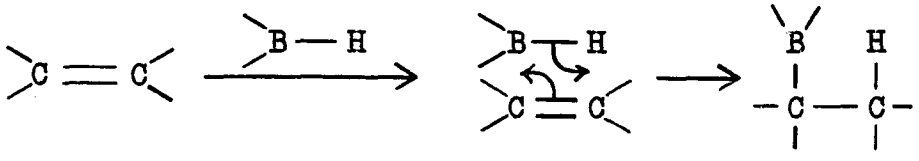
Diborane, a colorless gas at room temperature, is prepared conveniently by the action of boron trifluoride on sodium borohydride in diglyme. It is

$$3\ NaBH_4 + 4\ BF_3 \longrightarrow 2\ B_2H_6 + 3\ NaBF_4$$

sparingly soluble in diglyme but readily soluble in tetrahydrofuran where it exists as the tetrahydroduran solvated monomeric borine (BH_3) (2). In general, two techniques are employed in the hydroboration

reaction involving either the generation of diborane in the reaction vessel containing a solution of the olefin (in situ) or the introduction of pure diborane generated externally into a solution of the olefin (ex situ).

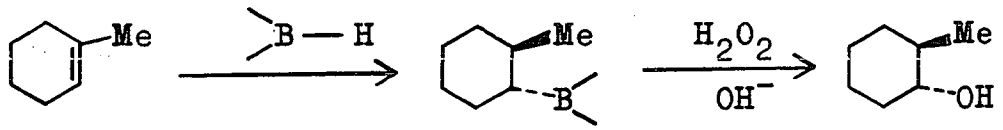
The reaction has been thoroughly reviewed in the book "Hydroboration" by H. C. Brown (1). Some of the salient features of the reaction are now briefly touched upon. The addition of diborane to an olefin in all cases proceeds in a cis-fashion. The mechanism of the addition is usually depicted as involving a 4-centered transition state. With unsymmetrically



substituted olefins the boron atom is for the most part directed to the least substituted carbon atom of the double bond. The hydroboration of unhindered olefins results in the production of a trialkylborane; hindered olefins usually produce mono- or dialkylboranes depending upon the degree of hindrance.

The alkylboranes are usually not isolated as such but are oxidized to an alcohol with alkaline hydrogen peroxide following the hydroboration. In all cases studied the oxidation results in the

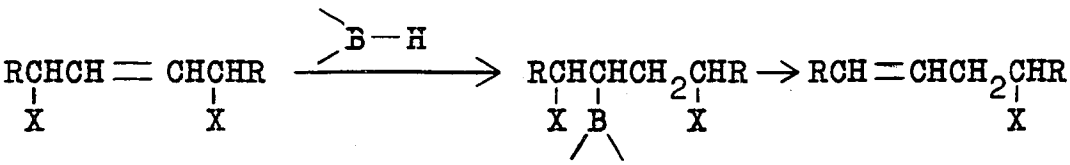
replacement of the boron atom by a hydroxyl group with retention of configuration. Thus, the hydroboration-oxidation sequence when carried out with 1-methylcyclohexene gives only trans-2-methylcyclohexanol. Since



during the hydroboration, the boron atom becomes attached to the least substituted carbon atom of the double bond, the result is an overall anti-Markownikoff cis hydration of the olefin.

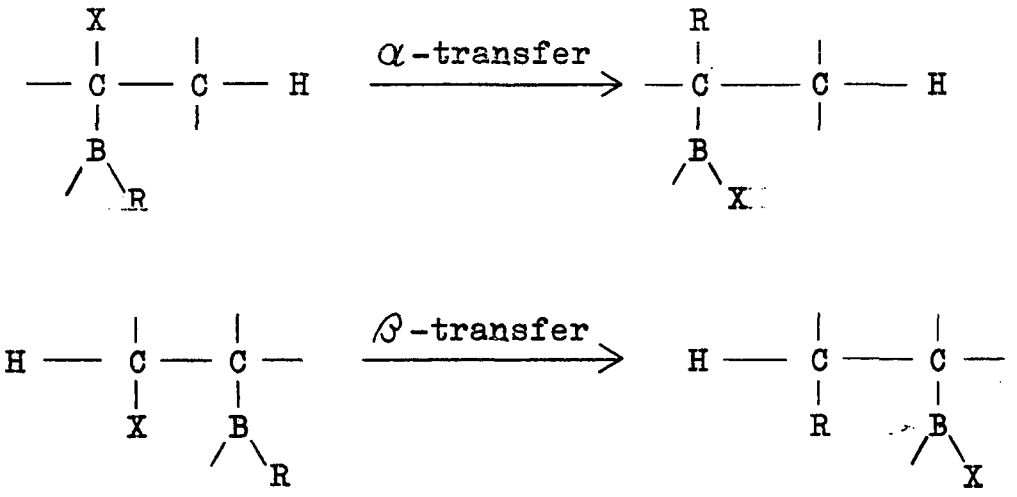
Recently, efforts have been directed toward increasing the utility of the hydroboration reaction through the study of olefins in which one unsaturated carbon bears a hetero atom, as in enol ethers (8,9), enol acetates (10,11,12), enamines and vinyl halides (3,4,5). The hydroboration of vinyl chloride (3) represents an early example of this area of research and resulted mainly in the formation of an unstable vicinal chloroalkylborane which rapidly underwent elimination generating ethylene. Similar results were observed during the hydroboration of 3-chlorocyclohexene (4). Although not a vinyl halide, this compound provided in part an unstable vicinal chloroalkylborane

which eliminated to form cyclohexene. More recently, the hydroboration of 1,4-dialkyl-1,4-dihalo-2-butenes (5) provided further confirmation for facile elimination in vicinal haloalkylboranes producing 4-haloalkenes in this case.



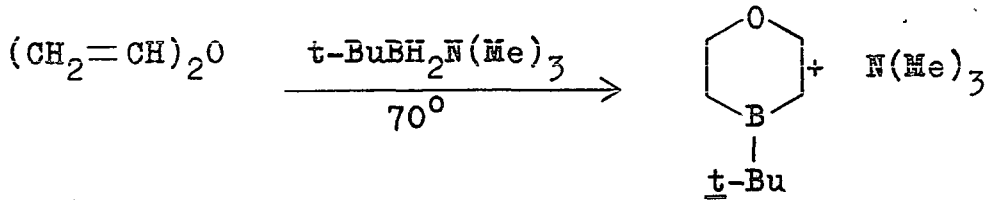
In contrast to vinyl halides the hydroboration of enethiol and enol ethers presents a more complicated picture in that the intermediate borane undergoes a variety of reactions. The important difference between these cases and those involving the vinyl halides is that elimination seems not to be the exclusive course. The variety of products has been attributed to the operation of transfer reactions within the intermediate borane (6,7,8). "Transfer" involves exchange of either hydrogen or of an alkyl residue for the hetero atom within the alkylborane. If hydrogen is exchanged, an unsubstituted borane results, and if the alkyl residue is exchanged, dimers result. The transfer reactions are of two types depending upon whether the boron atom becomes fixed to the carbon bearing the hetero atom or to the carbon <u>beta</u> to the hetero atom. In broad terms, the transfer reactions

for the alkylboranes derived from enethiol ethers (6,7) are depicted below. Analogous results are obtained



X = PhS-; R = H or substituted carbon

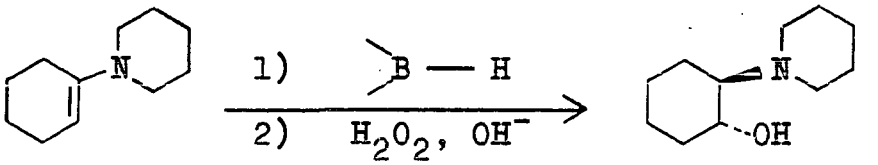
with enol ethers (8). Thus, the hydroboration-oxidation sequence of β-ethoxystrene (8) leads to 1-phenylethanol, 2-phenylethanol, 1-phenyl-2-ethoxyethane, 1-phenyl-1-hydroxy-2-ethoxyethane. The first two compounds result from hydrogen transfer, the third from debenzylation and the last is the "normal product." Also, a small amount of styrene was isolated, the result of elimination. These results are discussed in terms of competitive transfer and elimination schemes. An exception to the instability of the boranes formed from the hydroboration of these enol systems was seen when the hydroboration of divinyl ether (9) afforded a stable cyclic adduct.



Related to these investigations are several studies involving the addition of diborane to enol acetates (10,11,12). An early observation disclosed that the alkyl borane formed from the enol acetate of cholestan-3-one (10) treated with acetic anhydride eliminated to give cholest-2-ene. At about the same time, Hassner (11) carried out the hydroboration-oxidation sequence with 1-acetoxycyclohexene and obtained trans-1,2-cyclohexanediol which might be considered a normal product. However, the sequence also afforded some cyclohexanol. Two mechanisms were considered in order to account for this abnormal product, one involving its generation from a possible 1-acetoxyalkylborane intermediate in some unspecified manner; the other calling upon an elimination of the 2-acetoxyalkylborane forming cyclohexene which then suffered hydroboration and oxidation in the usual manner to give cyclohexanol. Olefin formation was the exclusive path when a mixture of 2- and 6-methyl-cyclohex-1-enyl acetate (the former in excess) was

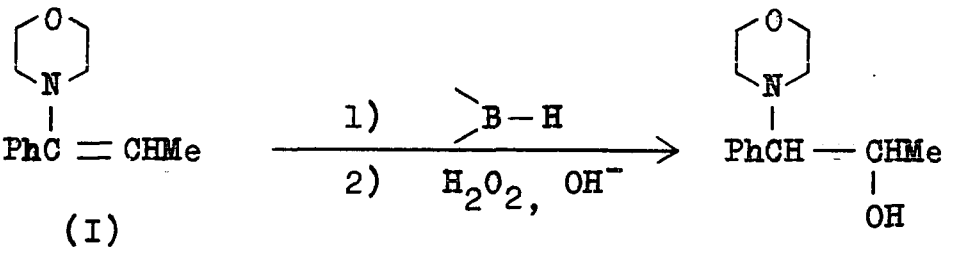
hydroborated and then treated with a carboxylic acid (12). The products were 1- and 3-methylcyclohexene (64% and 17%) and some methylcyclohexane (19%), the latter compound being presumably the result of a spontaneous elimination of the 2-acetoxyalkylborane followed by hydroboration and protonolysis.

A systematic study of the hydroboration of enamines was undertaken in this laboratory by Kelly (13) using the <u>in situ</u> generation of diborane followed by oxidation with alkaline hydrogen peroxide. Enamines derived from ketones and secondary amines afforded high yields of amino alcohols whose stereochemistry is consistent with an anti-Markownikoff <u>cis</u> hydration of the olefin. For example, 1-(1-cyclohexyl) piperidine gave 88% of pure <u>trans</u>-2-(1-piperidine) cyclohexanol. Also, the hydroboration of 4-(1-phenyl-1-propenyl) morpholine (I) gave 88.6% of a sharp melting



1-(4-morpholino) 1-phenyl-2-propanol (II). From the stereospecificity apparent in the previous example this amino alcohol was considered to be either of two possible diastereomers and not a mixture.

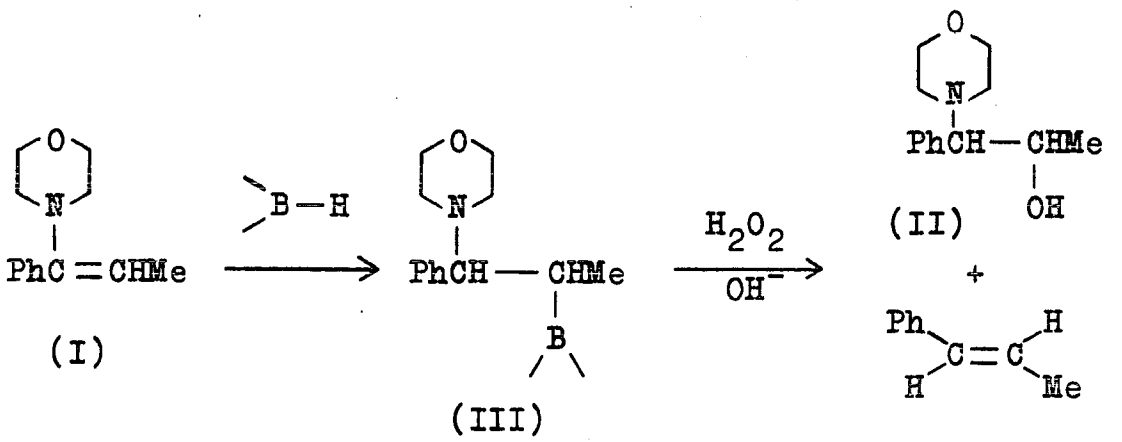
When we repeated the hydroboration of (I) using instead the ex situ technique the expected product (II) was isolated in low yield along with an unexpected product, trans-propenylbenzene. The present work was



undertaken in order to investigate the production of olefins in the ex situ hydroboration of enamines derived from ketones and secondary amines with special emphasis on the stereochemical aspects of their formation.

DISCUSSION

The *ex situ* hydroboration of 4-(1-phenyl-1-propenyl) morpholine (I) followed by treatment of the intermediate aminoalkylborane (III) with alkaline hydrogen peroxide leads to amino alcohol (II) and *trans*-propenylbenzene. Why olefin formation does not occur in the *in situ* hydroboration (13) of enamine (I) is a question which remains unanswered in the present work. Amino alcohol (II) may be considered the normal product from this sequence while *trans*-propenylbenzene is evidently the product of some type of elimination reaction in which both the morpholine and boron moieties are lost. The assignment of *trans*-geometry



(I) (III)

to the propenylbenzene was confirmed by the observation that both the infrared and n.m.r. spectra are identical in all respects to those of authentic trans-propenylbenzene. Both the trans-propenylbenzene isolated in the present work and an authentic sample of the substance displayed a doublet centered at 1.70 p.p.m. (J = 5 c.p.s.) for the three methyl protons, a narrow multiplet having the tallest signal at 6.23 p.p.m. for the two vinyl protons and a narrow multiplet at 7.17 p.p.m. for the aromatic protons. Also, the infrared spectrum showed a strong band at 960 cm^{-1} which is characteristic of out-of-plane deformation of trans-substituted ethylenic double bonds (14).

The results of an examination of alkaline hydrogen peroxide treatments of (III) under various conditions are summarized in Table I. These experiments represent an attempt to find conditions which would afford the olefin as the exclusive product. However, a significant amount of the normal product (II) was formed in each case. Only in three experiments (2, 5, and 8) did the yield of olefin actually exceed the yield of (II). Experiments 7 and 8 gave the unexpected result that when hydrogen peroxide was supplied in a limited amount, the cis-isomer was formed

TABLE I

RESULTS OF A STUDY OF THE EFFECT OF VARIOUS ALKALINE HYDROGEN PEROXIDE TREATMENTS OF (III)

Expt.	H_2O_2/ (I)	NaOH/ (I)	Time Hrs.	Temp. °C	Yield % (II)	Yield % Olefin
1[a]	4	1	12	25	65	33
2[a]	2	1	3	25	27	48
3[a]	2	1	3	0	43	19
4[a]	2	2	3	0	48	42
5[a,d]	2	1	4	25	37	50
6[a]	2	3	3	25	65	21
7[a]	1	1	4.5	70	45	36[e]
8[a]	0.5	0.5	4	25	24	39[f]
9[b]	4.5	1	12	25	55	36
10[c]	4	4	12	25	53	20

[a]Aqueous sodium hydroxide and 30% hydrogen peroxide were combined prior to addition.

[b]Base added first followed by dropwise addition of 30% hydrogen peroxide.

[c]30% hydrogen peroxide was added first and after one hour the base was added.

[d]The oxidation mixture was added slowly (3 hours).

[e]Olefin fraction consists of 85% *trans*- and 15% *cis*-propenylbenzene.

[f]Olefin fraction consists of 50% *trans*- and 50% *cis*-propenylbenzene.

together with the trans-isomer. The significance of this observation will be discussed later.

The isolation of trans-propenylbenzene free of the cis-isomer indicates that the elimination reaction leading to the olefin is highly stereospecific. However, before one can begin an intelligent mechanistic discussion, it is germane to know the stereochemistry of the intermediate aminoalkylborane (III). In order to make a configurational assignment to this compound, a series of stereospecific reactions was employed designed to lead to a product whose stereochemistry would reflect that of the intermediate aminoalkylborane (III).

Since the amino alcohol (II) can be regarded as the result of normal hydroboration-oxidation of the enamine, the configuration of both the enamine and intermediate aminoalkylborane (III) would be determined by establishment of the configuration of the amino alcohol (II). This was done by preparing the quaternary methiodide of the amino alcohol (II) followed by ring closure to the oxide by treatment with sodium hydride. Incidentally, all attempts to induce this intramolecular displacement reaction (inversion) by the normal procedure (freshly prepared silver oxide) failed to afford any oxide. The oxide

formed was shown to have the cis-configuration by comparing its infrared spectrum with those reported (15) for both of the isomeric oxides. The literature value (15) for the so-called "12 μ band" (16) of cis-propenylbenzene oxide is 852 cm^{-1} which compares well with a value of 851 cm^{-1} observed for the oxide synthesized in the present work. Further confirmation of the stereochemistry of the oxide came from a favorable comparison of its n.m.r. spectrum with that of authentic cis-propenylbenzene oxide prepared from the reaction of cis-propenylbenzene with m-chloroperbenzoic acid. The three methyl protons displayed a doublet centered at 1.05 p.p.m. (J = 5.3 c.p.s.), the single benzyl proton appeared as a doublet centered at 3.96 p.p.m. (J = 4.0 c.p.s.) and the five aromatic protons appeared as a singlet at 7.32 p.p.m. As expected from the very high purity of the starting alcohol (II), the oxide formed was free of the trans-isomer as shown by gas chromatography under conditions sufficient to detect trans-oxide. Assignment of cis-configuration to the oxide permits assignment of configurations to the amino alcohol (II), intermediate aminoalkylborane (III) and enamine (I), as outlined in Figure 1.

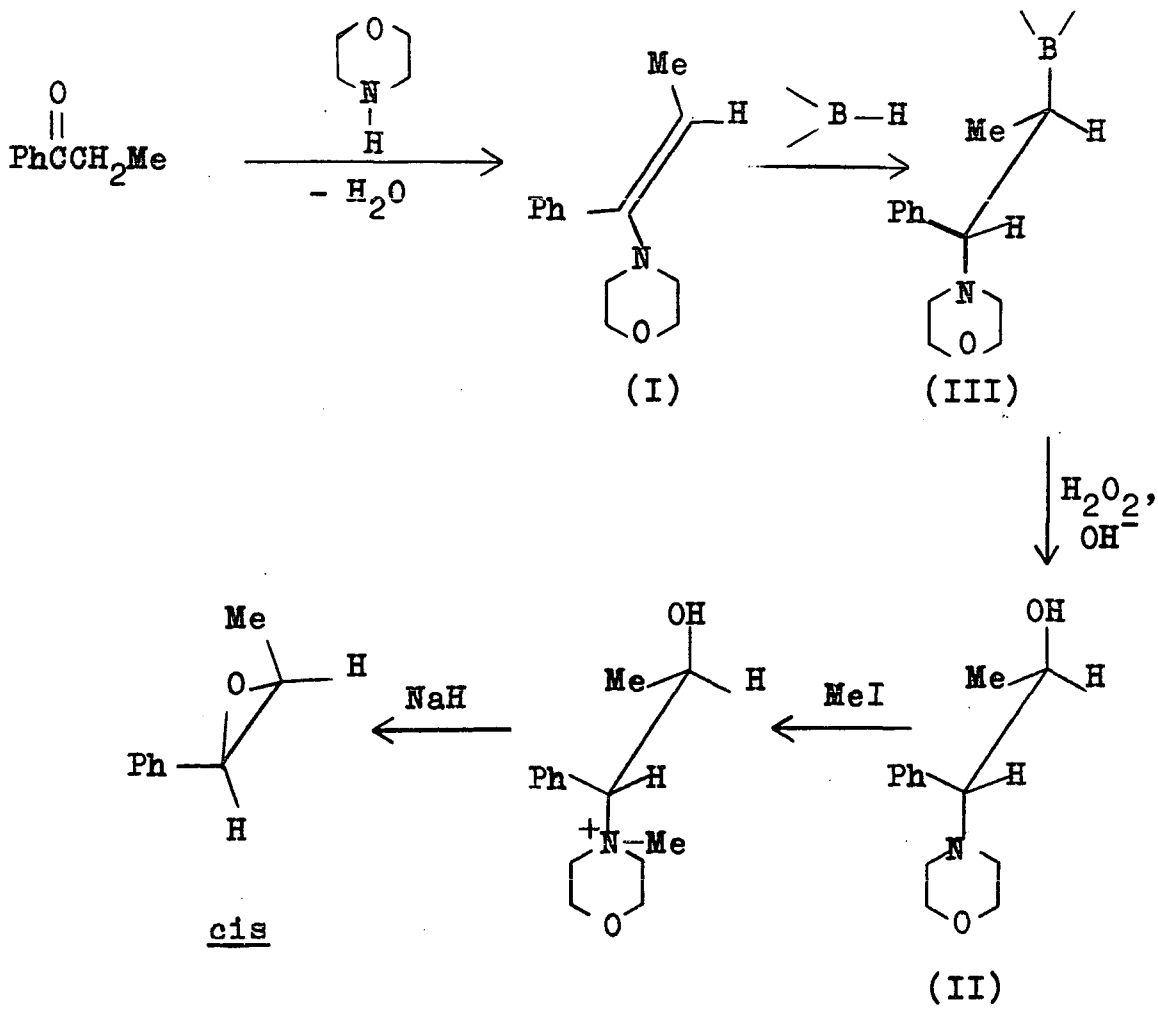


Figure 1. -- Reactions leading to the determination of the stereochemistry of the aminoalkylborane (III).

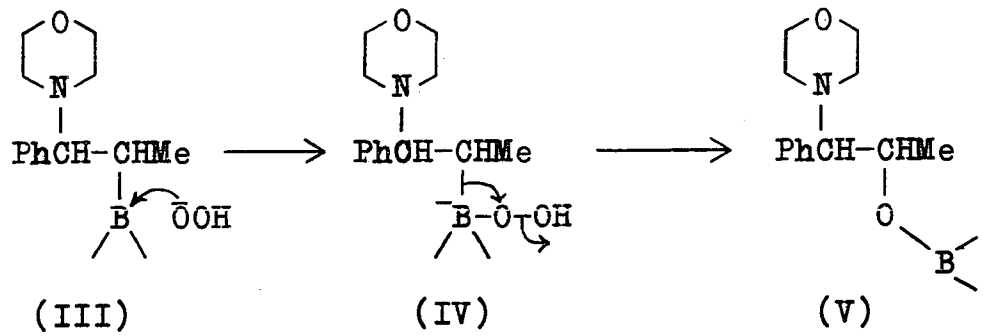
The stereochemistry of the enamine (I) is that depicted in Figure 1 in which the phenyl and methyl groups bear a cis-relationship. It is interesting that the enamine (I) proved to be the isomer having a

carbon skeleton displaying cis-geometry. This isomer is presumably the more stable of the two possible isomers because the conditions employed in its preparation are those leading to the product of thermodynamic control rather than kinetic control. This stereochemical result is reminiscent of that reported by Munk (17) for the preparation of the enamine from deoxybenzoin and morpholine in which the carbon skeleton also proved to have the cis-configuration. The stereochemical results of the work outlined in Figure 1 demands that the aminoalkylborane (III) possess the stereochemistry shown. This is designated as the threo form in the present work. With the stereochemistry of (III) thus defined, one may conclude that the reaction leading to trans-propenylbenzene demands cis-elimination of the morpholine and boron moieties from (III).

The normal product (II) may be considered to arise from (III) via a mechanism similar to that proposed for the alkaline hydrogen peroxide oxidation of benzeneboronic acid (17) and for a dialkylborinic acid (18). The aminoalkylboronate ester (V) is then rapidly hydrolyzed to the amino alcohol (II).

Before plunging into a mechanistic discussion of the novel cis-elimination reaction leading to the

$$H_2O_2 + OH^- \rightleftharpoons HO_2^- + H_2O$$

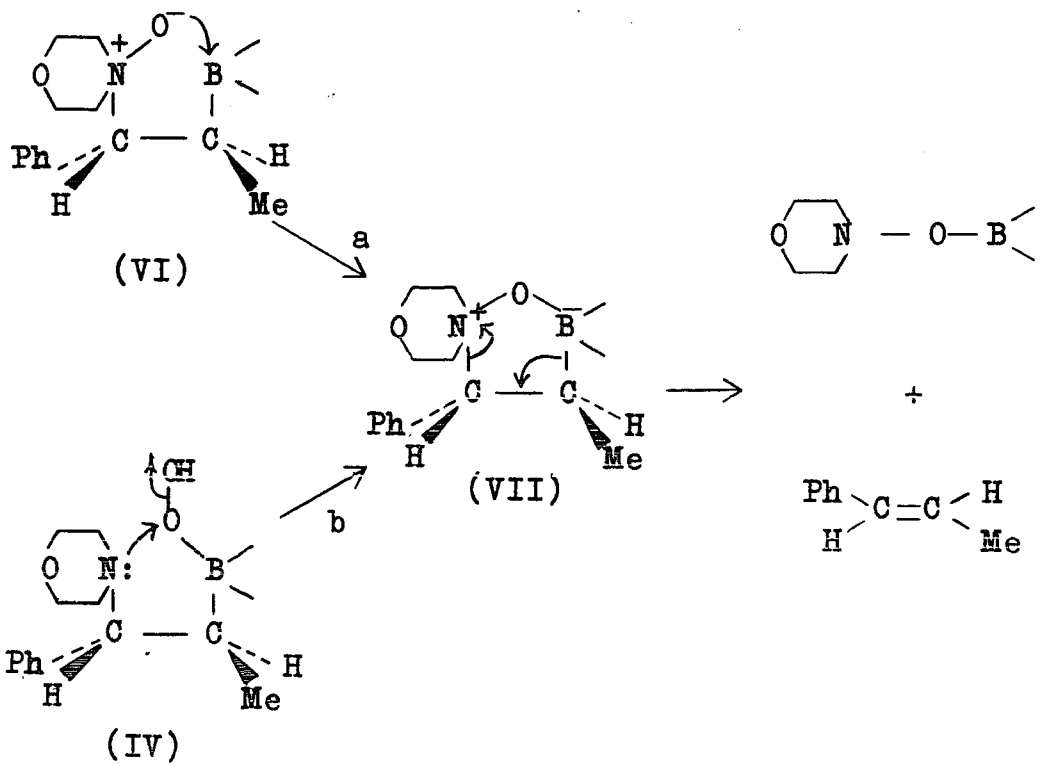


(III) (IV) (V)

olefin, it should be pointed out that it is unlikely that the aminoalkylborane (III) suffers elimination prior to alkaline hydrogen peroxide treatment. This argument follows from the observation that when the reaction was interrupted prior to oxidation the aminoalkylboronic acid (VIII) (vide infra) was isolated and no olefin was present. Also, no simple alcohols were ever isolated, although they would be expected to result from the hydroboration of the olefin which would be expected to occur (especially in the presence of excess diborane) had the olefin been present in the reaction mixture during the hydroboration step.

Two mechanisms considered as reasonable for the formation of trans-propenylbenzene are now discussed. Consideration is restricted to the possible influence of the β-nitrogen on the course of oxidation,

since the evidence cited above clearly indicates that olefin formation occurs in this step, and is of course observed only because the nitrogen function is present. Since eliminated groups are cis, a cyclic mechanism appears most reasonable. First, (path a) let us assume that the amine oxide (VI) may be formed from the reaction of (III) with hydrogen peroxide followed by an intramolecular attack of the oxide oxygen atom on the electron-deficient boron atom leading to the presumably unstable borisoxazole (VII). The



borisoxazole (VII) may then collapse as shown to form the products. Path b depicts the intermediate (IV) undergoing (instead of alkyl migration) an intramolecular nucleophilic attack by the lone pair of electrons of the nitrogen atom displacing a hydroxide ion leading to (VII). Although neither path is absolutely precluded, path b is preferred partly for the reason that the formation of tertiary amine oxides is usually carried out under acidic conditions (hydrogen peroxide in acetic acid, for example). The author is familiar with no examples in which alkaline hydrogen peroxide is used to form tertiary amine oxides. Another reason that path b is preferred is that intermediates of type (IV) are implicated in all alkaline hydrogen peroxide oxidations of alkylboranes. In particular, such oxidations of alkylboronic (18) and dialkyborinic acids (19) have been studied in detail. Furthermore, it is known that even under very mild conditions, alkylboranes are very rapidly oxidized by alkaline hydrogen peroxide (20). Therefore, in the case of the aminoalkylborane (III) one might expect at least a high degree of selectivity where the boron atom is oxidized much more rapidly than the nitrogen atom. For these reasons, then, path b is considered to best accommodate the cis-elimination reaction leading to trans-propenylbenzene.

As mentioned earlier, experiments 7 and 8, Table I, resulted in the formation of some cis-propenylbenzene the formation of which was found to be related to the relatively limited amount of hydrogen peroxide present in the reaction mixture. Subsequent experiments confirmed this observation, resulting in the isolation of cis-propenylbenzene containing only a trace of the trans-isomer when no hydrogen peroxide was used. The cis-stereochemistry of the olefin was confirmed by its n.m.r. spectrum which showed signals which were identical with those reported (21) for the same compound. The vinyl methyl group displayed a double doublet centered at 1.84 p.p.m. (J = 7.0 and 1.5 c.p.s.), the vinyl protons appeared as a broad multiplet from 5.3 to 6.6 p.p.m. and the aromatic protons appeared as a narrow multiplet at 7.23 p.p.m. Further confirmation of the cis-stereochemistry was obtained from the observation that the olefin gave the known cis-propenylbenzene oxide upon epoxidation using m-chloroperbenzoic acid. The results of a study of various non-oxidative treatments of the intermediate aminoalkylborane (III) are summarized in Table II. Although an extensive survey of reagents was not undertaken, it is clear that nucleophilic reagents promote the reaction leading directly from

TABLE II

RESULTS OF A STUDY OF THE EFFECT OF VARIOUS NON-OXIDATIVE REAGENTS ON (III)

Expt.	Added Reagent	Added Reagent/(I)	Time Hrs.	Temp °C	Yield % cis-Olefin
1	NaOH	1	4	70	91
2	H_2O	excess	24	70	71
3	NaOAc	2	12	70	69
4	NaOAc	2	9	25	13
5	NaOAc	2	2	70	49
6	HOAc	12	168	70	77
7	HOAc	3	6	70	--[a]
8	none	--	2	100	trace[b]

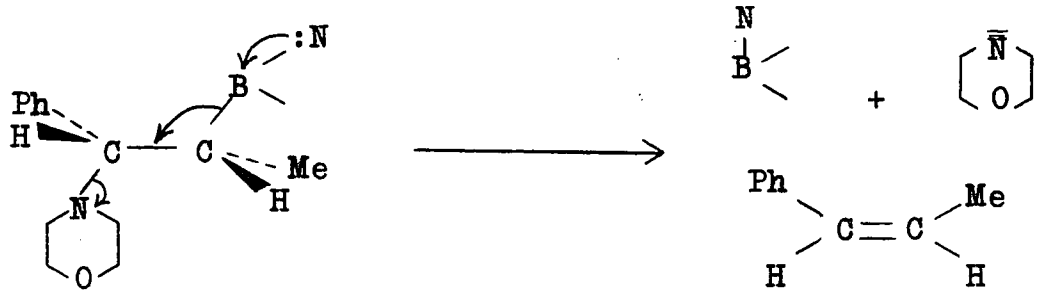
[a]The aminoalkylboronic acid (VIII) (46%) was isolated.

[b]Gas chromatography indicated olefin fraction was a mixture of 50% each of the cis- and trans-isomers.

(III) to the cis-olefin. The highest yield of cis-propenylbenzene was obtained when the product of the hydroboration was refluxed with sodium hydroxide for four hours.

Since the stereochemistry of the intermediate aminoalkylborane (III) has been established as the

threo modification (Figure 1), it is clear that cis-propenylbenzene is the result of a stereospecific trans-elimination of the morpholine and boron moieties. It is assumed that this trans-elimination is initiated by attack of a nucleophilic species on the electron-deficient boron atom concomitant with a trans-elimination analogous to the base-catalyzed E 2 elimination reaction. The high yield of olefin when sodium hydroxide



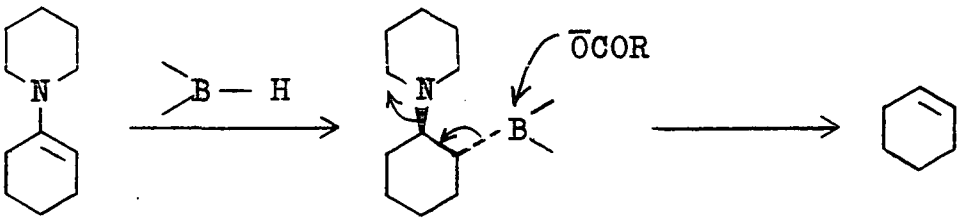
(III)

N: = OH^-, H_2O, OAc^-

was used is due to the efficacy of the hydroxide ion as a nucleophile.

While the present work was in progress, Lewis and Pearce (12) reported high yields (>80%) of olefins from the ex situ hydroboration of both cyclic and acyclic enamines followed by refluxing with acetic or propionic acid in diglyme for an unspecified period of time. These authors proposed a trans-elimination for the olefin formation relying heavily on cyclohexene

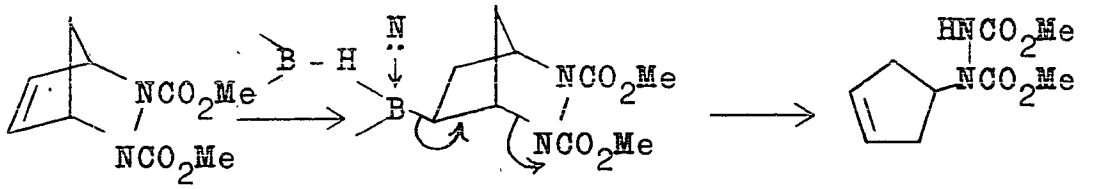
formation from cyclohexenyl piperidine. Since the hydroboration product has <u>trans</u> disposed boron and nitrogen moieties, the elimination in thie case could hardly result from a <u>cis</u>-elimination. However, these



authors made no comment on the stereochemistry of the olefins derived from acyclic enamines.

A similar <u>trans</u>-elimination mechanism was proposed recently (22) to account for the results of the hydroboration-alkaline hydrogen peroxide treatment of 2,3-dicarbomethoxy-2,3-diazabicyclo [2.2.1] hept-5-ene. In addition to the normal product (alcohol), some olefin was observed whose formation was greatly enhanced by the presence of various nucleophilic reagents during the oxidation step. The mechanism for the formation of olefin was presented as depicted below.

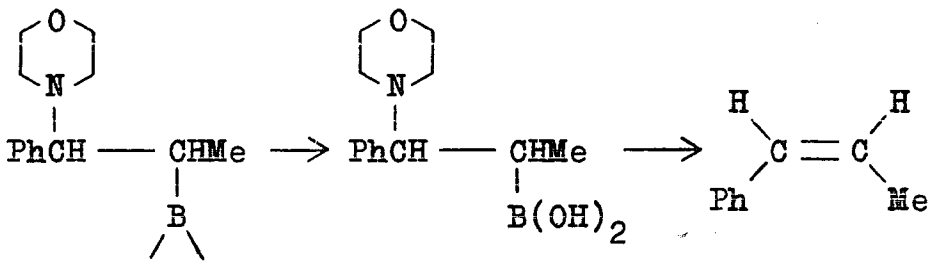
The aminoalkylboronic acid (VIII) was obtained in 46% yield (experiment 7, Table II) by refluxing the intermediate aminoalkylborane (III) with acetic acid for a relatively short time. Apparently, the



N: = THF, OH^-, H_2O, BH_4^-

reaction time in this case was insufficient to allow extensive conversion to olefin, although prolonged treatment leads to high yields of olefin. It should be mentioned that the formation of this boronic acid demonstrates mono-hydroboration of enamine (I).

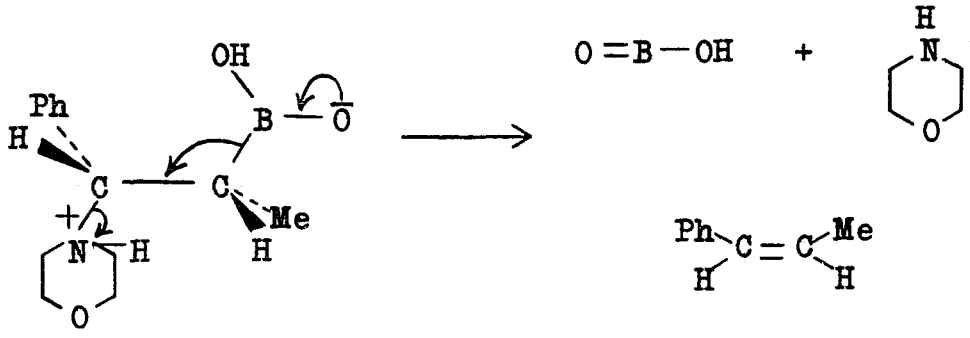
When the aminoalkylboronic acid (VIII) was subjected to the conditions of experiment 2, Table II, 70% of cis-propenylbenzene was obtained. This observation implicates the boronic acid (VIII) as the intermediate leading to the cis-olefin. It is also reasonable



(III) (VIII)

to assume that the boronic acid (VIII), formed by hydrolysis of the aminoalkylborane (III), is the

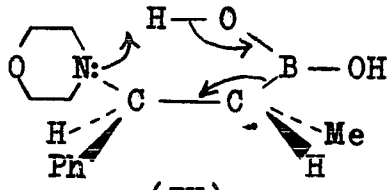
intermediate in the formation of both the amino alcohol (II) and trans-propenylbenzene. The boronic acid (VIII) also gave cis-propenylbenzene by simply heating (VIII) to its melting point (95°) and allowing the product to distill from the melt. The mechanism for this pyrolytic behavior of (VIII) is best considered a trans-elimination as discussed above and can be likened to the decarboxylative β-elimination of β-halo acid anions. Presumably, the zwitterionic form of (VIII) is involved as shown below.



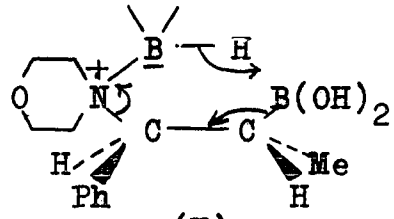
The significance of the observation that only a trace of trans-propenylbenzene was found as an additional product of the experiments in Table II might easily have been overlooked were it not for the results of a rate study employing the conditions of experiment 2. Surprisingly, after 0.5 hours the composition of olefin in an aliquot of the reaction mixture was 33% trans- and 66% cis as determined by gas chromatography. Maximum olefin formation was

observed in an aliquot taken after about 4 hours wherein the olefin mixture consisted of the cis-isomer containing only a trace of the trans-isomer. It seemed curious that most of the trans-olefin was formed during the first half hour of the reaction. It is known that the formation of trans-propenylbenzene is the result of a cis-elimination on the basis of the established threo configuration of the intermediate aminoalkylborane (III) discussed earlier.

As a possible interpretation of the facts discussed above, two types of cis-elimination processes were considered, both involving 6-membered cyclic transition states (IX and X). Transition state (IX)



(IX)



(X)

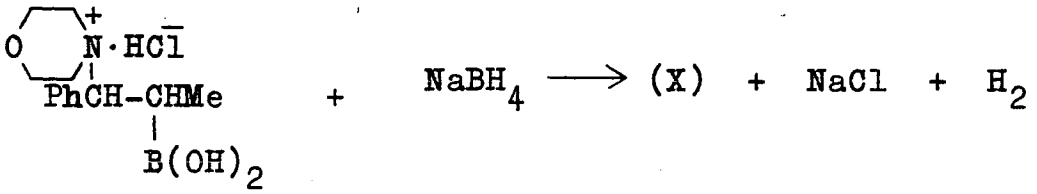
shows the aminoalkylboronic acid (VIII) undergoing an intramolecular cis-elimination. However, one would expect to observe a uniform composition of the isomeric olefins in the early as well as in the later stages of the reaction if parallel intra- and intermolecular processes were occurring in which the rate of the latter is greater than that of the former. Therefore,

the process depicted by (IX) seems to be precluded in the light of the rate study mentioned earlier.

Transition state (X) depicts a process involving an intramolecular 1,6-hydride transfer from the boron atom of an amine borane moiety to that of an alkylborane or boronic acid moiety. Hydride donation from amine boranes is not uncommon; the reducing action of N-methylmorpholine borane toward carbonyl compounds in aqueous media has been noted (21). Process (X) anticipates that during the hydroboration step the borine, in addition to reacting with the double bond, in part becomes coordinated with the nitrogen atom. The extent of this amine borane formation under these conditions is nominal. Only a small amount of crude material showing absorption for the amine borane moiety in the infrared spectrum was isolated from experiments in which the aminoalkylboronic acid (VIII) was prepared. Also confirming this observation is the fact that when enamine (I) was hydroborated using a 1:1 ratio of borine to enamine (I) and then oxidized with alkaline hydrogen peroxide, the amino alcohol (II) was formed in 51% yield. If the morpholine nitrogen competed successfully with the enamine double bond for borine then one would anticipate a substantially lower yield of amino alcohol (II) than that observed.

Indeed, this yield is at least comparable to those cases in which excess borine was employed (Table 1).

In order to explore further the possibility that the mechanism for the formation of trans-propenylbenzene might involve a process such as depicted in (X), an attempt was made to prepare the amine borane by a method other than that involving addition of borine to enamine (I). It was hoped to prepare (X) in good yield via the reaction between the amine hydrochloride of aminoalkylboronic acid (VIII) and sodium borohydride, a method which has been successfully employed (22) for the preparation of pyridine borane from pyridine hydrochloride and sodium borohydride.



(XI)

The amine hydrochloride (XI) was obtained in quantitative yield by passing dry hydrogen chloride through an ether solution of the aminoalkylboronic acid (VIII). Heating this salt to its melting point (131°) afforded cis-propenylbenzene containing no detectable amount of the trans-isomer (by gas chromatography). The

reaction between the amine hydrochloride (XI) and sodium borohydride did not proceed smoothly. Only a small amount of gummy material was isolated whose infrared spectrum showed some absorption characteristic of amine boranes (broad band at 2440 cm^{-1}). However, as much as 36% trans-propenylbenzene was found in the mixture of product olefins when this substance was heated in benzene for 12 hours. Although the above work is not exactly an elegant demonstration of the operation of process (X), the relatively high amount of trans-propenylbenzene seems significant. Since the formation of trans-propenylbenzene does seem related to the presence of the amine borane moiety process (X) is not precluded as a possible mechanism leading to this olefin.

Finally, the possibility that the amine borane might convert the cis-isomer to the trans-isomer by reversible addition to the cis-olefin seems unlikely in view of the mild conditions employed. Only under severe conditions are amine boranes observed to react with olefins (25).

EXPERIMENTAL

All melting points and boiling points are uncorrected.

All solvents used for chromatography were redistilled prior to use. Tetrahydrofuran and diglyme were distilled from lithium aluminum hydride prior to use.

Elemental analyses are by A. Bernhardt, Microanalytical Laboratories, Mulheim (Ruhr), Germany.

N.m.r. spectra were obtained with a Varian A-60 instrument using deuteriochloroform as solvent and tetramethylsilane as internal standard. Chemical shifts are reported in δ -values (p.p.m. from TMS) and are followed by the multiplicity of the signals and corresponding coupling constants. The multiplicity is denoted by the symbols: s, singlet; d, doublet; t, triplet; dd, double doublet, and m, multiplet. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer.

Gas chromatograms were obtained with a Barber-Colman model 15 instrument equipped with an argon detection system. The isomeric propenylbenzenes were separated on a 10' x 3 mm. I.D. pyrex column packed with 5% SE-30 on 80-100 mesh Gas Chrom Z operated at 50°. The detector and inlet temperatures were 200° and 180° respectively, and the argon gas was delivered at a pressure of 80 p.s.i.

Preparation of a Solution of Diborane in Tetrahydrofuran. -- The procedure used for the preparation of tetrahydrofuran solutions of diborane is modeled after one previously described (25). The apparatus used was essentially the same as that described in this reference except that instead of Tygon connections, glass tubing connected with ball and socket joints was used. It is essential to use Apiezon L grease on all glass joints to avoid freezing. Also, a gas scrubber containing a diglyme solution of sodium borohydride was placed in the line leading from the generating vessel to the vessel containing the tetrahydrofuran in order to trap any boron trifluoride etherate that may be carried over.

Briefly, the procedure (25) describes the generation of gaseous diborane by the slow addition

of a 1 M solution of sodium borohydride in diglyme to an excess of boron trifluoride etherate dissolved in diglyme. The diborane is transferred to a vessel containing ice cold tetrahydrofuran. However, it was not possible to prepare the solution of sodium borohydride in diglyme free of solids. The solid material clogged the funnel during the addition step. Smooth generation of diborane was accomplished more conveniently by the slow addition of boron trifluoride etherate (not redistilled) to a stirring suspension of sodium borohydride in diglyme. Although the apparatus should be swept with nitrogen before use, it is not necessary to sweep with nitrogen during the addition of boron trifluoride etherate. To insure complete transfer of diborane, the generating vessel should be swept with a gentle stream of nitrogen after all the boron trifluoride etherate has been added. Heating of the generating vessel at this point should be avoided because this results in the transfer of ethyl ether.

Using the modified procedure as described above, 600 ml. of a tetrahydrofuran solution of diborane was prepared in which the concentration was 1.8 M in borine (81% yield). This solution was obtained by adding 280 ml. (2.22 moles) of boron

trifluoride etherate to 38 g. (1.0 mole) of sodium borohydride suspended in 250 ml. of diglyme. The vessel containing the solution of diborane was capped with a rubber septum and stored in the refrigerator (5° C). After several months, no change in the concentration of borine was observed.

Tetrahydrofuran solutions of diborane were standardized by measuring the volume of hydrogen liberated upon reaction of the diborane with ethylene glycol. Aliquots of the solution were injected into a septum-capped vessel containing a 50% diglyme solution of ethylene glycol. The small vessel was equipped with a sidearm which was connected to a water-filled burette in order to collect and measure the volume of hydrogen liberated.

Preparation of 4-(1-Phenyl-1-propenyl) Morpholine (I). -- This procedure is modeled after one previously described for the preparation of related enamines (26). To 180 ml. of toluene was added 6 g. of Dowex 50 W-X8 ion exchange resin and the mixture was refluxed under a Dean-Stark water separator in order to dry the wet resin. The mixture was cooled and 80.4 g. (0.600 mole) of propiophenone and 104.4 g. (1.2 mole) of morpholine were added all at once. The mixture was allowed to reflux under the separator until the theoretical

amount of water was removed (about 9 days). The mixture was cooled and decanted from the resin. After removal of solvent and excess morpholine the residue was distilled at 15 mm. and 5 fractions were collected: i 50-117°; ii 117-127°; iii 127-134°, 31.324 g.; iv 124-132°, 38.594 g., n_D^{25} 1.5509; v 130-132°, 24.181 g. Fractions i and ii contained unreacted starting materials and solvent. Infrared spectra of the remaining fractions displayed prominent bands at 1630 cm^{-1} (double bond) and 1115 cm^{-1} (ether of morpholine moiety). The combined weight of fractions iii, iv and v corresponds to 77% yield of the enamine. These fractions were bottled separately under nitrogen and stored in the refrigerator.

Hydroboration Followed by Alkaline Hydrogen Peroxide Treatment of 4-(1-Phenyl-1-propenyl) Morpholine (I). -- The hydroboration of this enamine was carried out ex situ. A 250 ml. 3-necked flask fitted with an addition funnel capped with a rubber septum and provided with a gas inlet mounted on the pressure-equalizing side arm was flamed dry in a stream of purified nitrogen. Maintaining a gentle nitrogen flow, the enamine diluted with 15 ml. of dry tetrahydrofuran was added to the flask with a syringe. Also using a syringe, the addition funnel was charged with the appropriate amount of a

standard tetrahydrofuran solution of diborane to correspond to 1.5 to 2 mole ratios of borine to enamine (I). The flask was immersed in an ice bath and the diborane solution was added dropwise during 5 to 35 minutes to the gently stirred (magnetic) solution of the enamine. After all the diborane was added, the ice bath was removed and the flask was kept at room temperature for 35 minutes to overnight while the system was sealed under nitrogen with a mercury valve. Usually, in two hours the light yellow color of the enamine was completely discharged. The mixture was cooled with an ice bath and water was added slowly until hydrogen was no longer evolved. Then a mixture of 30% hydrogen peroxide and aqueous sodium hydroxide diluted with 10 ml. of water was added dropwise to the stirring solution. The quantities of these reagents are indicated in Table I.

At the end of the alkaline hydrogen peroxide treatment, most of the tetrahydrofuran was distilled and the residue was extracted three times with 15 ml. portions of ether. To separate any amine, the combined ether extracts were washed four times with 10 ml. portions of N hydrochloric acid. The ether solution was then washed with water until the washings were neutral to pH paper, dried over sodium sulfate and

the ether removed to give the neutral fraction of the reaction. The neutral fraction was identified as trans-propenylbenzene containing some impurities. The infrared spectrum (neat) displayed a prominent band at 960 cm^{-1} characteristic of out-of-plane deformation of the trans-substituted ethylenic double bond (14), and was identical with that of an authentic specimen. The methyl region of the n.m.r. spectrum of a neat sample had signals at 1.68 d (J = 5 c.p.s.) (3 protons). Vinyl protons appeared at 6.20 m (2 protons) and aromatic protons at 7.15 s (5 protons). The pH of the combined acid washings was adjusted to 10 with 5 N aqueous sodium hydroxide, and the precipitated amine was extracted five times with 10 ml. portions of ether. The combined ether extracts were washed with water until the washings were neutral to pH paper, dried over sodium sulfate and the ether removed to give 1-(4-morpholino) 1-phenyl-2-propanol (II) as a white solid, m.p. 90.2-94°. Prominent bands in its infrared spectrum (KBr) appeared at 3500 cm^{-1} (hydroxyl) and 1115 cm^{-1} (ether of the morpholine group). A recrystallized sample (hexane) of the amino alcohol showed m.p. 93-95°.

Preparation of the Methiodide of 1-(4-Morpholino) 1-phenyl-2-propanol (II). -- The amino alcohol (4.42 g.,

0.0200 mole) obtained from the ex situ hydroboration-alkaline hydrogen peroxide treatment of 4-(1-phenyl-1-propenyl) morpholine (I) was refluxed in 25 ml. of methyl iodide for 191 hours. The solid methiodide (3.039 g., 42% yield) was collected on a funnel and washed with ether. After air-drying, the methiodide showed m.p. 177-178°. Recrystallization of 0.091 g. of the methiodide (ethyl acetate-ethanol) afforded 0.045 g. of an analytical sample whose melting point was unchanged.

Anal. Calcd. for $C_{14}H_{22}NO_2I$: C, 46.29; H, 6.11; N, 3.86. Found: C, 46.14; H, 6.12; N, 3.75.

Treatment of the Methiodide of 1-(4-Morpholino) 1-phenyl-2-propanol (II) with Sodium Hydride. -- To a slurry of 0.515 g. (0.0214 mole) of sodium hydride in 15 ml. of dry tetrahydrofuran was added 0.500 g. (0.00138 mole) of the methiodide. A very slow evolution of hydrogen was noted. The reaction flask was sealed under nitrogen with a mercury valve and the mixture was refluxed for 4 hours. The mixture was cooled, flooded with 35 ml. of hexane and filtered to remove the excess sodium hydride. The filtrate, which became milky presumably due to the precipitation of a small amount of unreacted methiodide was filtered again. The solvent was distilled from the clear

filtrate and 0.123 g. (67% yield) of cis-propenylbenzene oxide was left as a light yellow liquid. The infrared spectrum (chloroform) was identical with that of an authentic specimen of cis-propenylbenzene oxide (oxide band at 851 cm^{-1}) and was homogeneous by gas chromatography (5% SE-30 at 75°). Also, a gas chromatogram of the cis-oxide admixed with authentic trans-propenylbenzene oxide showed two partially separated peaks, the first of which corresponded to the authentic trans-oxide. The n.m.r. spectrum (carbon tetrachloride) of the cis-oxide prepared above displayed signals in the methyl region at 1.03 d (J = 5.3 c.p.s.). The benzyl proton was at 3.93 d (J = 4.0 c.p.s.) and the proton on the carbon bearing the methyl group was at 3.51 m. The aromatic protons appeared at 7.26 s. This spectrum was identical with the n.m.r. spectrum from an authentic specimen of cis-propenylbenzene oxide.

Preparation of cis-Propenylbenzene Oxide from cis-Propenylbenzene. -- The olefin (0.153 g., 0.00195 mole) dissolved in about 2 ml. of chloroform was treated with a solution of 0.283 g. (0.001425 mole) of m-chloroperbenzoic acid (85% purity) in 4 ml. of chloroform. The solution was kept at room temperature with stirring for 26 hours during which time a white precipitate of m-chlorobenzoic acid was observed. The

reaction mixture was then treated with 10% aqueous sodium sulfite until the mixture gave a negative test with starch-iodide paper. The reaction mixture was washed twice with 10% aqueous sodium carbonate, twice with water, once with brine and dried over sodium sulfate. Removal of solvent afforded 0.137 g. (79% yield) of the cis-oxide as a colorless liquid. The infrared spectrum (chloroform) of the oxide showed a band characteristic of cis-oxides at 852 cm^{-1} (15,16). The n.m.r. spectrum (carbon tetrachloride) was identical in all respects with that obtained in the preceding experiment.

Preparation of trans-Propenylbenzene Oxide from trans-Propenylbenzene. -- To 2.0 g. (0.0170 mole) of the olefin dissolved in 15 ml. of chloroform was added a solution of 3.66 g. (0.0181 mole) of m-chloroperbenzoic acid in 50 ml. of chloroform over 15 minutes with stirring. The solution was kept at room temperature with stirring for 4.5 hours during which time a white precipitate of m-chlorobenzoic acid was observed. The reaction mixture was then treated with 10% aqueous sodium sulfite until the mixture gave a negative test with starch-iodide paper. Approximately 20 ml. of 10% aqueous sodium carbonate was added and the white precipitate dissolved. The

layers were separated and the organic phase was washed once with 20 ml. of 10% aqueous sodium carbonate, once with 20 ml. of brine and dried over anhydrous sodium carbonate. Removal of solvent afforded 2.206 g. (97% yield) of the trans-oxide as a slightly yellow liquid. The infrared spectrum (chloroform) of the oxide showed a band characteristic of trans-oxides at 858 cm^{-1} (15,16). The n.m.r. spectrum (carbon tetrachloride) displayed signals in the methyl region at 1.36 d (J = 5.1 c.p.s.). The benzyl proton gave a signal at 3.44 d (J = 1 c.p.s.) and the aromatic protons at 7.25 s.

Hydroboration of 4-(1-Phenyl-1-propenyl) Morpholine (I) Followed by a Variety of Non-Oxidative Treatments. -- The apparatus and the hydroboration procedure used in these experiments were the same as those used for the hydroboration-alkaline hydrogen peroxide reactions of enamine (I). In each experiment the mole ratio of borine to enamine (I) was 2:1.

Following the various treatments shown in Table II, the usual procedure used for isolation of the olefin involved removal of most of the tetrahydrofuran by distillation. The aqueous residue was then extracted thoroughly with ether and the combined ether solution was washed with water until the washings

were neutral to pH paper. In experiment 2, Table II it was noted that the aqueous phase was strongly basic, presumably due to the presence of morpholine. After drying the combined ether extracts with sodium sulfate and removing the ether, propenylbenzene was afforded in the yields shown in Table II as a mobile, slightly yellow liquid. Identification of the crude product as cis-propenylbenzene was based largely on the n.m.r. spectrum which showed only traces of impurities. In all cases, the methyl group showed signals at 1.84 dd (J = 7.0 and 1.5 c.p.s.), the vinyl protons gave signals from 5.3 to 6.6 m and the aromatic protons gave a strong signal superimposed on a narrow multiplet at 7.23 m. Similar values have been reported for cis-propenylbenzene (14).

Isolation of the Aminoalkylboronic Acid (VIII). -- (a). After hydroboration of the enamine (I) (2.184 g., 0.01074 mole) by the usual procedure, 2 ml. of glacial acetic acid was added and the mixture was brought to reflux (see experiment 7, Table II). At the end of the reflux period, two clear, colorless layers were observed. The mixture was diluted with 30 ml. of water and treated with 5 ml. of 5 N sodium hydroxide to neutralize the acetic acid. After distilling most of the tetrahydrofuran, the residue

was extracted with four 10 ml. portions of ether. The combined ether extracts were washed with water until the washings were neutral to pH paper and dried over sodium sulfate. Removal of the ether afforded 1.038 g. (46%) of the aminoalkylboronic acid (VIII) as a semi-solid which solidified upon trituration with hexane. After air-drying the aminoalkylboronic acid (VIII) showed m.p. 95-97° (melted to a turbid liquid). The infrared spectrum had prominent bands at 3330 cm^{-1} (hydroxyl groups on boron) and 1118 cm^{-1} (ether linkage of morpholine moiety). This compound was noted to be soluble in both N hydrochloric acid and 5 N sodium hydroxide.

(b). Hydroboration of enamine (I) (4.060 g., 0.020 mole) was carried out as described earlier with the exception of the hydrolysis step in which 5 ml. of dry methanol was used instead of water. The reaction mixture was distilled to remove the tetrahydrofuran, methanol and methyl borate leaving the dimethylaminoalkylboronate as a heavy, turbid liquid. This material was treated with 20 ml. of distilled water containing 3.5 ml. (0.060 mole) of glacial acetic acid and kept at room temperature for one hour during which time the dimethylaminoalkylboronate dissolved leaving a slightly turbid solution. This solution was

neutralized with 5 N sodium hydroxide and the precipitated aminoalkylboronic acid (VIII) was collected on a funnel. After air-drying overnight the material weighed 3 g. (60%) and showed the same melting point and infrared spectrum as the material isolated in part (a) above. A small sample was recrystallized from acetone-hexane to afford an analytical sample, m.p. 97.2-102° (melted to a turbid liquid).

Anal. Calcd. for $C_{13}H_{20}BNO_3$: C, 62.67; H, 8.09; B, 4.34; N, 5.62. Found: C, 62.76; H, 7.97; B, 4.16; N, 5.78.

(c). The enamine (I) (5.37 g., 0.027 mole) was hydroborated in the usual fashion with the exception of the hydrolysis step in which 10 ml. of 1 N hydrochloric acid was added carefully instead of water. Then 25 ml. of 1 N hydrochloric acid was added all at once and the flask was kept at room temperature for 3 hours. The aqueous solution was then washed twice with ether to give the neutral fraction of the reaction. Sodium hydroxide (5 N) was added to the aqueous phase until the pH was slightly above 7. The precipitated aminoalkylboronic acid (VIII) was collected on a funnel, washed with water and allowed to air-dry overnight. This material weighed 4.5 g (66%) and showed the same infrared spectrum as the material in parts (a) and (b)

above. Removal of ether from the neutral fraction left 1.1 g. (14%) of the amine borane (X) as a heavy liquid. The infrared spectrum showed absorption at 2410 cm^{-1} characteristic of amine boranes.

cis-Propenylbenzene from the Aminoalkylboronic Acid (VIII). -- (a). A solution of 0.892 g. (0.00395 mole) of the aminoalkylboronic acid (VIII) in 20 ml. of 50% aqueous tetrahydrofuran was refluxed for 20 hours. The tetrahydrofuran was distilled and the residue was cooled and extracted three times with ether. The aqueous phase showed a pH of 9 (pH paper) due to the presence of morpholine. The combined ether extracts were washed with water until the washings were neutral to pH paper and dried over sodium sulfate. Removal of the ether afforded 0.296 g. (70%) of cis-propenylbenzene as a slightly yellow liquid. Without further purification the infrared and n.m.r. spectra were identical in all respects with other samples of cis-propenylbenzene isolated from experiments summarized in Table II.

(b). A short-path distillation apparatus was charged with 0.171 g. (0.00069 mole) of the aminoalkylboronic acid (VIII) and a vacuum of 35 mm. was applied. The material was warmed gently with a micro burner to its melting point and the distillate, 0.125 g., was

collected. The n.m.r. spectrum of the distillate indicated the presence of only cis-propenylbenzene and morpholine.

A Kinetic Study of the Aqueous Treatment of the Intermediate Aminoalkylborane (III). -- The enamine (I) (2.03 g., 0.010 mole) was hydroborated and the reaction mixture was hydrolyzed as described in earlier experiments. Then 15 ml. of water was added all at once and the reaction mixture was brought to reflux with stirring. After 0.5 hours a 5 ml. aliquot was removed, flooded with 25 ml. of water and extracted with three portions of ether. The combined ether extracts were washed twice with water, once with brine and dried over anhydrous sodium carbonate. The ether solution was diluted to 100 ml. in a volumetric flask and analyzed using the Barber-Colman gas chromatograph. This procedure was repeated at one hour intervals for a total of six hours. Equal volumes (0.8 μl.) of the ether solution containing product olefins were injected on the gas chromatographic column. The aliquot removed after 0.5 hours gave a gas chromatogram showing a mixture of isomeric propenylbenzenes containing 33% of the trans-isomer. The aliquot taken after 1 hour contained approximately 10% of the trans-isomer relative to the cis-isomer and subsequent aliquots taken

at 1 hour intervals showed progressively less of the trans-isomer. The reaction appeared to be complete after 3 hours (maximum peak height for the cis-isomer) and the gas chromatogram of aliquots after 3, 4, 5 and 6 hours showed an olefin composition of about 99% cis-isomer and 1% trans-isomer.

Preparation of the Hydrochloride of the Aminoalkylboronic Acid (VIII). -- Dry hydrogen chloride gas was bubbled through an ethereal solution of 1.435 g. (0.00576 mole) of the aminoalkylboronic acid (VIII) until precipitation ceased. The hydrochloride was collected on a funnel, washed with ether and allowed to air-dry briefly. The hydrochloride, 1.67 g. (100%) showed m.p. 131° (d) and was soluble in water. The infrared spectrum showed absorption in the region between 2500 and 2800 cm^{-1} characteristic of ammonium compounds. This salt was observed to decompose upon standing at room temperature for a few weeks giving off an odor of propenylbenzene.

cis-Propenylbenzene from the Hydrochloride of the Aminoalkylboronic Acid (VIII). -- A small sample of the hydrochloride of the aminoalkylboronic acid (VIII) was heated gently (microburner) in a test tube until a mobile liquid was observed to form. Then, about 3 ml. of hexane was added in order to prepare

a sample for gas chromatographic analysis. The hexane solution gave a peak corresponding to cis-propenylbenzene. No peak for the trans-isomer could be detected.

Preparation of the Amine Borane (X) from the Hydrochloride of the Aminoalkylboronic Acid (VIII). -- This procedure is modeled after that reported (24) for the preparation of pyridine borane. To 1.634 g. (0.00572 mole) of the hydrochloride of the aminoalkylboronic acid (VIII) dissolved in 25 ml. of chloroform was added 0.435 g. (0.0114 mole) of sodium borohydride ground to a fine powder. Rapid evolution of hydrogen was observed upon addition. The reaction flask was kept at room temperature with stirring for 10.5 hours after which time the reaction mixture was flooded with ether and filtered. The funnel contained a significant quantity of a white solid which turned to a tan paste on standing. No further work was done with this material. The solvent was removed from the filtrate leaving 0.098 g. of the crude amine borane (X) as a tan, gummy material. The infrared spectrum showed a very broad band with maximum absorption at 2450 cm^{-1} which is characteristic for amine boranes.

cis- and trans-Propenylbenzene from the Crude Amine Borane (X). -- The gummy material whose isolation

is described in the previous experiment was refluxed in benzene for 12 hours. A gas chromatogram of the benzene solution after this time showed two peaks corresponding to 36% trans- and 64% cis-propenylbenzene. This estimate is based on the peak areas as determined by the product of peak heights and peak widths at half-height.

SUMMARY

The *ex situ* hydroboration of 4-(1-phenyl-1-propenyl) morpholine (I) followed by alkaline hydrogen peroxide treatment affords the normal product, 1-(4-morpholino) 1-phenyl-2-propanol (II) and an unexpected product, *trans*-propenylbenzene. Various conditions for the oxidative treatment have been examined. The stereochemistry of the intermediate aminoalkylborane (III) has been determined and leads to the conclusion that *trans*-propenylbenzene results from a *cis*-elimination.

Treatment of the intermediate aminoalkylborane (III) with water, sodium hydroxide, acetic acid or sodium acetate affords good yields of *cis*-propenylbenzene. The aminoalkylboronic acid (VIII), formed by hydrolysis of (III), has been isolated and characterized. Pyrolysis or aqueous treatment of (VIII) affords *cis*-propenylbenzene. A *trans*-elimination mechanism is discussed to account for the formation of this olefin.

The formation of a nominal amount of *trans*-propenylbenzene during the various non-oxidative treatments of the intermediate aminoalkylborane (III) has been observed. Evidence has been provided which implicates an intermediate amine borane (X) in the formation of *trans*-propenylbenzene. A *cis*-elimination mechanism has been proposed to rationalize the formation of *trans*-propenylbenzene.

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PART III

ISOLATION OF CHLORINE-CONTAINING COMPOUNDS FROM THE GORGONIAN, *BRIAREUM ASBESTINUM* PALLAS

INTRODUCTION AND DISCUSSION

This laboratory has been concerned with the isolation and structure elucidation of compounds from certain marine invertebrates such as *Eunicea mammosa*, *Pseudoplexaura porosa*, and *Eunicea palmeri*. Each of these species is fairly rich in terpenoid materials whose structure elucidation has been the subject of many interesting and fruitful investigations. The present work was undertaken with the aim of isolating related materials from the marine invertebrate *Briareum asbestinum*.

The other species referred to above have been found to contain sesquiterpene hydrocarbons and solid diterpene lactones. The former are isolated from cold pentane washings of the ground animal; the latter

from a lengthy extraction with hot hexane employing a Soxhlet-type apparatus. With Briareum asbestinum the above extraction scheme gave a dark, heavy oil from the cold pentane washings and some red solid material from the hexane extraction. Inspection of the oil from the pentane washings by thin layer chromatography gave no indication that the sesquiterpene hydrocarbons were present. Also, chromatography of the red solid from the hexane extraction on a Florisil column using benzene as the eluant (conditions used to isolate the diterpene lactone from Eunicea mammosa) gave no distinct, isolable compound.

The red solid was chromatographed on a Florisil column this time using 50% ethyl acetate in benzene as the eluant. Under these conditions, the red pigment was not held on the column but some green pigment remained at the top of the column throughout the chromatography. From 4.685 g. of the solid, 3.391 g. of red pigmented material was collected from the column. Trituration of this material with ether dissolved most of the red pigment leaving a small amount of tan solid behind. Thin layer chromatography of this ether-insoluble tan solid showed the presence of two compounds; a major spot followed closely by a minor spot. Several recrystallizations (benzene-hexane) gave a white,

crystalline solid m.p. 204.5-205° (d) but this material was still a mixture of two compounds. Initially, the compound corresponding to the leading spot in the thin layer of this mixture was designated as asbestinin A; the latter asbestinin B. However, these names are now reserved for another pair of compounds isolated from this species (see below) which, though showing closely similar chromatographic and solubility properties, have been shown by x-ray crystallographic studies to be unlike the pair just described. Due to limited quantities of material, no further work was done with the pair of compounds isolated by continuous hexane extraction.

Subsequent work actually led to the isolation of a second pair of compounds in greater quantity. Continuous ether extraction of ground Briareum asbestinum afforded 2.072 g. of another light tan solid whose thin layer chromatogram (ether) again showed a pair of closely spaced spots. The lead spot is designated as asbestinin A; the latter asbestinin B. However, there remained the problem of the efficient separation of the two asbestinins present in the crude mixture. Since recrystallization techniques failed, it was decided to examine preparative column chromatography techniques in an effort to resolve these two compounds.

Since ether proved to be an efficient solvent for the thin layer separation of asbestinin A from asbestinin B, it seemed reasonable to employ this solvent on a preparative scale using column chromatography (silicic acid). Although this technique afforded some pure asbestinin A, the use of ether was rejected on the basis that the low ether solubility of the two compounds caused extensive precipitation of material on the column. The residual mixture of asbestinin A and B was recovered by washing the column with ethyl acetate. Silicic acid chromatography of the recovered mixture, this time using 20% ethyl acetate in benzene as the eluting solvent, afforded pure asbestinin A in much higher yield. The total quantity (1.661 g.) of pure asbestinin A isolated from the ground Briareum asbestinum corresponds to 0.092% yield based on the dry weight of the ground animal. The remainder of the material recovered from the silicic acid column consisted of a mixture containing asbestinin A and B now greatly enriched in B. Pure (by thin layer) asbestinin B was obtained by a second silicic acid column chromatography (30% ethyl acetate in benzene). The early cuts afforded 0.234 g. of a mixture of the asbestinins; the latter cuts provided 0.251 g. of chromatographically

pure asbestinin B which was recrystallized from ethanol-water giving 0.197 g. of crystalline material.

Pure asbestinin A, recrystallized from 1:1 benzene-hexane, showed m.p. 226-227° (d) and $[\alpha]_D^{25}$ -93.6°. This compound was presumed to correspond to the diterpene lactones isolated from other marine invertebrates. Surprisingly, an attempt to obtain a mass spectral cracking pattern revealed the presence of chlorine in the compound, as evidenced by a characteristic pair of peaks for hydrogen chloride at 35 and 37 in the ratio of 3:1. Asbestinin A failed to give a normal mass spectral pattern (no parent ion detectable) apparently due to the very low volatility of this compound. The appearance of hydrogen chloride was apparently the result of thermal decomposition during the attempt to obtain the mass spectrum. The chlorine content of asbestinin A was confirmed by its elemental analysis for carbon, hydrogen, oxygen, and chlorine which indicated an empirical formula of $C_{30}H_{41}O_{12}Cl$.

Asbestinin B, the minor component in the crude mixture of asbestinin A and B, showed m.p. 223-224.5° (d). Like asbestinin A, asbestinin B also contains chlorine as confirmed by its elemental analysis for carbon, hydrogen, oxygen and chlorine which indicated an empirical formula of $C_{32}H_{41}O_{14}Cl$. When the sample

of asbestinin B was forwarded to the x-ray laboratory for examination, it was discovered by Dr. Hossain that this material was a mixture of two crystalline forms (plates and needles). After Dr. Hossain had mechanically separated these two forms, an elemental analysis of the needles indicated an empirical formula of $C_{32}H_{47}O_{15}Cl$. Unfortunately, only a carbon-hydrogen determination could be obtained on the plate form because only a minute quantity of this material was available. However, the analysis revealed a significant difference between the two forms with respect to percentages of carbon and hydrogen.

The infrared spectrum (KBr) of asbestinin A (Figure 1) and asbestinin B(needles)(Figure 2) are quite similar. Small differences in the fingerprint region of these two spectra are apparent. Both spectra exhibit a rather large broad band in the hydroxyl region. However, the infrared spectrum of each compound in chloroform solution showed the complete absence of hydroxyl absorption. Apparently, the potassium bromide used to obtain the spectra shown in Figures 1 and 2 contained sufficient water to display the broad absorption in the hydroxyl region. No sinal due to hydroxyl hydrogen was present in the n.m.r. spectrum in dimethyl sulfoxide of asbestinin A. The absence of hydroxyl in asbestinin A

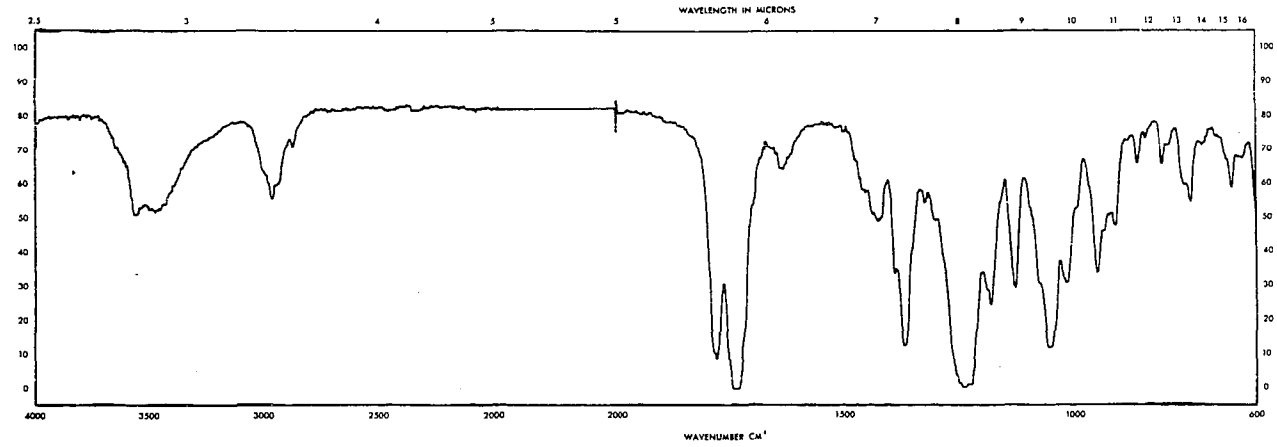

Figure 1. -- Infrared Spectrum of Asbestinin A.

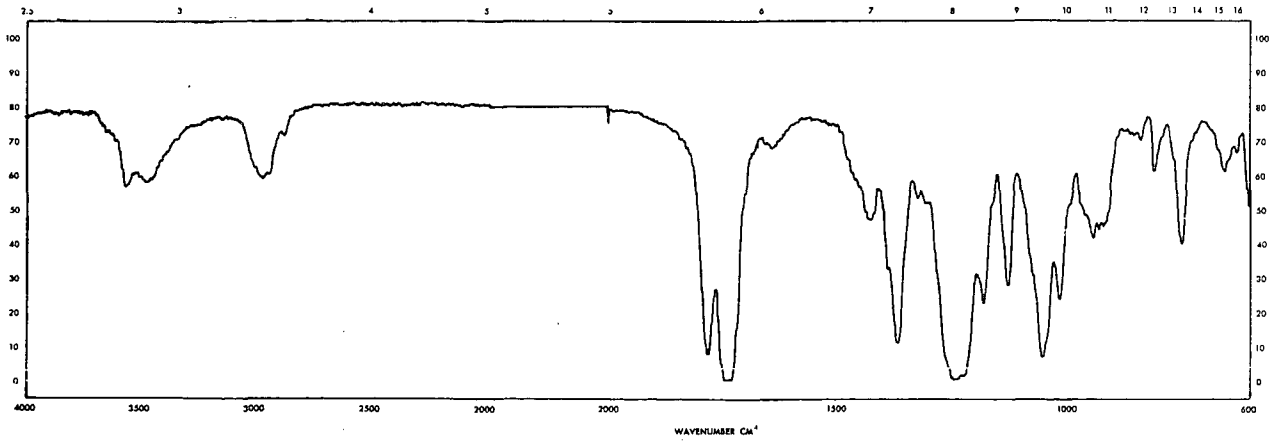

Figure 2. -- Infrared Spectrum of Asbestinin B.

was further substantiated by its failure to undergo acetylation under conditions which readily esterify even tertiary alcohols. Although the unchanged asbestinin A was not actually recovered after the acetylation attempt, thin layer chromatograms of aliquots of the reaction mixture indicated that asbestinin A remained unchanged.

Both asbestinin A and asbestinin B (needles) have the following significant infrared bands in common: broad carbonyl at 1740 cm^{-1}, 1240 cm^{-1} (acetate), 1780 cm^{-1} (saturated γ-lactone) and 1370 cm^{-1} (methyl). When the spectra of asbestinin A and asbestinin B are obtained using chloroform solutions a small, sharp band appears at 3560 cm^{-1}. This band is assigned as an overtone band of the lactone carbonyl.

The n.m.r. spectrum of asbestinin A (Figure 3) can be interpreted only in broad terms pending further structural evidence. An unsymmetrical triplet appears at 0.95 p.p.m. (J = 8.0 c.p.s.) which may reasonably be assigned to the methyl of an ethyl group. Three other signals appear in the methyl region at 1.28, 1.42 and 1.55 p.p.m. These signals are assumed to be due to methyl groups on carbon bearing oxygen (e.g., acetate) although the last signal is also reasonable

for a vinyl methyl group. Two closely spaced sharp signals appear at 1.97 and 2.00 p.p.m. The former signal may be attributed to two similar acetate methyls and the latter signal is probably due to a third acetate methyl. A signal at 2.22 p.p.m. is assigned as a fourth acetate methyl. Although a chemical shift of 2.22 p.p.m. is more reasonable for a methyl ketone, it is assigned to an acetate group for the following reasons. First, no attenuation of this signal was observed when asbestinin A was treated with sodium deuteroxide in deuterium oxide in the n.m.r. sample tube. The signal would be expected to disappear under these conditions if the signal was due to a methyl ketone. Secondly, a microanalytical acetyl determination on asbestinin A indicated 4.26 acetyl groups. The amount in excess over 4.0 is probably due to the partial release of hydrochloric acid during the acetyl determination.

A singlet (1 H) appearing at 3.10 p.p.m. rapidly disappears when asbestinin A is treated with sodium deuteroxide in deuterium oxide in the n.m.r. sample tube. The persistence of this signal when asbestinin A is treated with deuterium oxide alone precludes the possibility that this signal is due to a hydroxyl hydrogen. A reasonable interpretation of these facts

is that the signal at 3.10 p.p.m. is due to a lone proton alpha to a ketone carbonyl. Although normal ketone absorption (1710 cm^{-1}) is absent in the infrared spectrum the possibility of a strained ketone is not precluded since it would be masked by the strong acetate absorption. A chemical shift of 3.10 p.p.m. is somewhat high for a methine proton alpha to a ketone unless it is flanked by another electronegative functionality (e.g., γ-lactone carbonyl). A reasonable conclusion, then, is that this readily exchangeable methine proton is of the acetoacetic ester type.

After the signal at 3.10 p.p.m. discussed above has been removed by deuterium exchange, there remains a small quartet (1 H) at 3.12 p.p.m. (J = 8.0 c.p.s.). This methine proton signal is tentatively assigned to a hydrogen attached to carbon bearing an ether oxygen but probably is not coupled with a secondary methyl group since no corresponding doublet signal appears in the methyl region.

A singlet (1 H) at 3.83 p.p.m. is considered to be due to a proton on the carbon bearing the chlorine atom.

Finally, the region from 4.7 to 6.3 p.p.m. (7 H) shows a complex pattern including a doublet at 4.87 p.p.m. (J = 3.8 c.p.s.) which is tentatively assigned to a

proton on carbon bearing the lactone oxygen. The balance of the pattern can be assigned to protons under the acetate groups in addition to vinyl protons.

The n.m.r. spectrum of asbestinin B (needles) is quite similar to that of asbestinin A (Figure 4). Each spectrum has the methyl triplet mentioned earlier at 0.95 p.p.m. (J = 8.0 c.p.s.). In contrast to asbestinin A, asbestinin B (needles) has four instead of three other signals in the methyl region at 1.30, 1.42, 1.48 and 1.55 p.p.m. Three acetate methyls appear at 1.92, 1.98 and 2.00 p.p.m. A signal at 2.26 p.p.m. is tentatively assigned to a fourth acetate methyl. A microanalytical acetyl determination on asbestinin B (needles) indicated 4.716 acetyl groups. The excess over 4.0 is again considered to be due to the release of hydrochloric acid during the acetyl determination.

A singlet appears at 3.02 p.p.m. superimposed on what appears to be a quartet. This same pattern is found in the n.m.r. spectrum of asbestinin A and is tentatively assigned in a similar way, although the exchangeable nature of the proton responsible for the 3.02 p.p.m. signal was not demonstrated.

In contrast to the n.m.r. spectrum of asbestinin A the spectrum of asbestinin B (needles) has a small

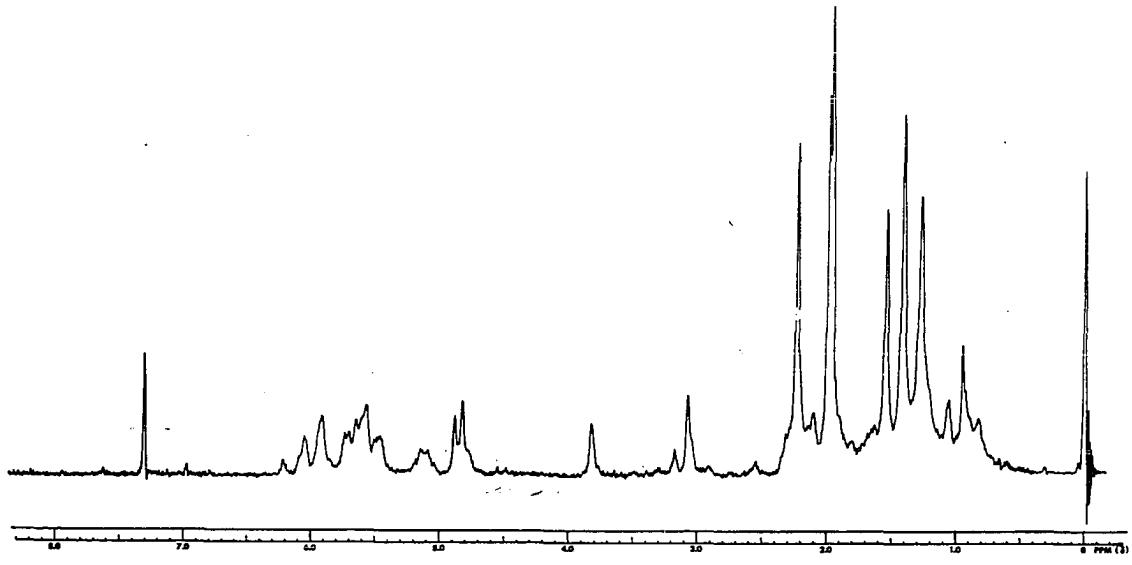

Figure 3. -- N.m.r. Spectrum of Asbestinin A.

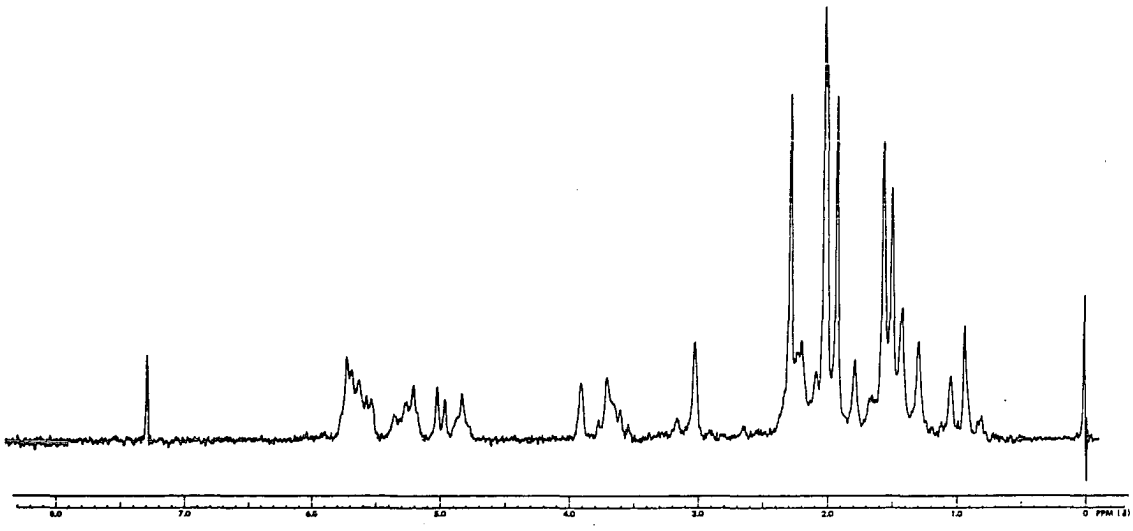

Figure 4. -- N.m.r. Spectrum of Asbestinin B (needles).

but complex pattern at 3.70 p.p.m. which will remain unassigned in the present work. A singlet (1 H) at 3.90 p.p.m. is considered to be due to a proton on carbon bearing the chlorine atom. The remaining pattern from 4.75 to 5.83 p.p.m. (7 H) is assigned to protons on carbon bearing acetate groups and the lactone oxygen. Unlike asbestinin A asbestinin B shows no signals above 5.83 p.p.m. Therefore, the possibility of the presence of vinyl protons is reduced.

The isolation of asbestinin A and B provides a novel addition to the growing list of natural products isolated from marine sources. Naturally occurring compounds containing halogen are extremely rare. The only other halogen-containing natural product of marine origin was reported recently by T. Irie, M. Suzuki and T. Masamune (1). They isolated the bromine-containing compound, laurencin, from the marine organism Laurencici glandulifera. Laurencin has the elemental composition $C_{17}H_{23}O_3Br$. Structural assignment of this compound was based largely on n.m.r. decoupling experiments.

EXPERIMENTAL

All melting points are uncorrected.

All solvents used for chromatography were redistilled prior to use.

Optical rotations were obtained with a Gaertner L-320 Polarimeter.

Thin layer chromatograms were obtained on 5 x 20 cm. glass plates coated with a 0.25 mm. layer of Silica Gel H (E. Merck AG. Darmstadt). Iodide vapor was used for visualization of the spots.

Column chromatography was performed utilizing either 100 mesh silicic acid (Mallinckrodt analytical reagent grade) or 100-200 mesh Florisil (Floridin Company).

Elemental analyses are by A. Bernhardt, Microanalytical Laboratories, Mulheim (Ruhr), Germany.

N.m.r. spectra were obtained with a Varian A-60 instrument using deuteriochloroform as solvent and tetramethylsilane as internal standard. Chemical shifts are reported in δ-values (p.p.m. from TMS)

and are followed by the multiplicity of the signals and corresponding coupling constants. The multiplicity is denoted by the symbols: s, singlet; d, doublet and t, triplet. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer.

The Briareum asbestinum, collected in Jamaica, at South Cay, March 29, 1965 and ground in a Waring blendor was kindly supplied by Dr. Leon S. Ciereszko.

Material from the Hot Hexane Extraction of Briareum asbestinum. -- The finely ground Briareum asbestinum (1216 g.) was covered with about one liter of pentane and allowed to stand for one hour at room temperature. The pentane, heavily colored with dark green pigmented material, was allowed to drain from the bottom of the container. This process was repeated two more times with fresh pentane. The ground animal was then extracted with hot hexane in a Soxhlet-type apparatus for 48 hours. During the extraction period some red solid had deposited on the bottom of the flask. The hexane was distilled until the flask contained approximately one-half of the original volume of hexane (about 350 ml.). Filtration of the residual hexane afforded 4.6853 g. of a red-orange solid.

All of the red-orange solid was chromatographed on 300 g. of Florisil. The 44 x 365 mm. column was eluted first with benzene collecting 250 ml. cuts. No detectable amount of material was eluted from 2 liters of benzene eluate (6 cuts). The eluting solvent was changed to ethyl acetate in benzene (1:1) causing a red pigmented band to move down the column and leaving some green pigmented material at the top. Fraction 7 afforded 3.391 g. of dark red material most of which dissolved when triturated with 20 ml. of ether leaving a light tan solid. The solid (0.4654 g.) was collected on a funnel, washed with fresh ether and allowed to air dry. A thin layer chromatogram (1:1 ethyl acetate in benzene) of the solid showed a dark spot at R_f = 0.57 followed closely by a less intense spot. Recrystallization of this solid from benzene-hexane afforded 0.420 g. of a white crystalline solid which showed m.p. 204.5-205° (d). The infrared spectrum (KBr) of the recrystallized material had a sharp spike at 3520 cm^{-1}, a broad band at 1785 cm^{-1} (saturated γ-lactone), strong bands at 1740 and 1230 cm^{-1} (acetate) and a moderately strong band at 1370 cm^{-1} (methyl). A second recrystallization from benzene-hexane afforded a crop of tiny needles (0.085 g.) which showed m.p. 210-211° (d). A thin layer chromatogram (1:1 ethyl

acetate in benzene) showed 2 spots as before thus indicating that successive recrystallization is unsuitable for resolution of the mixture.

Anal. Found: C, 55.89; H, 6.58.

Isolation of Crude Asbestinin A and B. -- The finely ground Briareum asbestinum (1811 g.) was covered with hexane and allowed to stand for one hour. The hexane was allowed to drain from the bottom of the container. This process was repeated three times with fresh hexane until the washings were only faintly green in color. The hexane-extracted Briareum asbestinum was spread out and allowed to air dry after which it was extracted with ether in a large Soxhlet-type apparatus for about 12 hours. Removal of the ether left 33 g. of black, semi-solid material which contains both asbestinin A and B and a very large amount of heavily pigmented material.

Separation of the Crude Asbestinin A and B from the Pigment Material. -- The tarry ether extract from ground Briareum asbestinum (33 g.) was chromatographed on a 6.5 x 57 cm. column containing one kg. of Florisil. The column was eluted with 20% ethyl acetate in benzene and 150 ml. cuts were collected. As the pigmented material moved down the column, a yellow band separated at the front followed by an

elongated orange band. A dark green band remained at the top of the column throughout the chromato graphy. Thin layer chromatography (ether) of cuts 13 through 30 gave a slightly elongated dark spot (R_f = 0.3) imposed upon a long streak (R_f 0 to 1) of pigmented material for cuts 13 through 30. The material in these fractions is predominantly the orange pigment. The solvent was removed from the combined fractions, and the black residue was triturated with 50 ml. of ether and after 1/2 hour, the residue, a light yellow solid weighing 2.072 g., was filtered. The thin layer chromatogram (ether) of this material showed a major spot slightly ahead of a minor spot located at about R_f = 0.3. The major spot in this mixture is designated as asbestinin A; the minor, asbestinin B.

Chromatographic Separation of Asbestinin A from Asbestinin B, Ethyl Ether Eluant. -- A mixture of asbestinin A and B (1.99 g.) which was obtained from the Florisil chromatography of the crude ether extract from ground Briareum asbestinum was chromatographed on 100 g. of silicic acid. The 32 x 250 mm. column was eluted with ether and 50 ml. cuts were collected. Thin layer chromatograms (ether) of each of fractions 6 through 22 showed a single spot (asbestinin A uncontaminated with asbestinin B).

Fractions 6 through 22 were combined and removal of the solvent left 0.398 g. of asbestinin A as a slightly yellow solid. The solid was treated with Norite and crystallized from 1:1 benzene-hexane from which was obtained 0.134 g. of flat, elongated needles showing m.p. 226-227° (d) and $[\alpha]_D^{25}$ - 93.6° (α_D^{25} - 1.25°, 1 dm., c = 2.67, $CHCl_3$).

Anal. Calcd. for $C_{30}H_{41}O_{12}Cl$: C, 57.27; H, 6.57; Cl, 5.64. Found: C, 57.48; H, 6.38; Cl, 5.62.

The infrared spectrum (KBr) of this material had significant bands at 1740 cm^{-1}, 1240 cm^{-1} (acetate), 1780 cm^{-1} (saturated γ-lactone) and 1370 cm^{-1} (methyl). The n.m.r. spectrum showed methyl signals at 0.95 t (J = 8.0 c.p.s.), 1.28 s, 1.42 s and 1.55 s. Acetate methyls appear at 1.97 s, 2.00 s and 2.22 s. A methine proton alpha to a ketone carbonyl appeared at 3.10 s and a methine proton attached to carbon bearing the chlorine appeared at 3.83 s. A proton on carbon bearing the lactone oxygen appeared at 4.87 d (J = 3.8 c.p.s.) and a complex pattern due to protons on carbon bearing acetate and vinyl protons appeared from 4.7 to 6.3.

As a result of the low solubility of asbestinin A and B in ether, some material was observed to have precipitated at the top of the column. The column was

eluted with ethyl acetate until the eluate no longer showed the presence of asbestinin A and B by thin layer chromatography. The ethyl acetate was distilled leaving 1.490 g. of a mixture of asbestinin A and B as a solid.

Chromatographic Separation of Asbestinin A from Asbestinin B, 20% Ethyl Acetate in Benzene Eluant. -- A mixture of asbestinin A and B (2.040 g.) was chromatographed on 100 g. of silicic acid. The 32 x 250 mm. column was eluted with 20% ethyl acetate in benzene and 50 ml. cuts were collected. As shown by thin layer chromatography (ether), fractions 12 through 26 inclusive contained asbestinin A uncontaminated with asbestinin B.

Fractions 12 through 15, 17, 18 and 20 through 24 were dissolved in chloroform, the volume of the solution was reduced to about 7 ml. and this solution was flooded with hexane. The precipitated asbestinin A (0.8508 g.) was collected on a funnel. Recrystallization from chloroform-hexane afforded 0.4838 g. of a first crop of asbestinin A as long needles, m.p. 222-223° (d). The infrared spectrum (KBr) (Figure 1) was identical with that of the sample of asbestinin A which is described in the previous section. A microanalytical acetyl determination of asbestinin A (sample from chloroform-hexane) showed 4.26 acetyl groups.

Anal. Calcd. for four acetyl groups, 27.37. Found: acetyl groups, 29.14.

The n.m.r. spectrum of fraction 19 (not recrystallized) is shown in Figure 3 and is identical with the spectrum of the sample of asbestinin A which is described in the previous section. The total quantity of asbestinin A isolated from 1811 g. of the dry, ground Briareum asbestinum was 1.661 g. which corresponds to a yield of 0.092%. Fractions 27 through 55, inclusive, contained a mixture of the two asbestinins (determined by thin layer) and the total weight of material in these fractions was 0.511 g. The column was washed clean with neat ethyl acetate affording 0.169 g. of material. The material recovered from fractions 27 through 55, inclusive, together with that from the ethyl acetate wash was chromatographed on 50 g. silicic acid in order to isolate asbestinin B. The column was eluted with 30% ethyl acetate in benzene collecting 25 ml. cuts. As before, each cut was evaluated with respect to purity by thin layer chromatography. Fractions 5 through 8, inclusive, gave 0.234 g. of solid which was shown to be a mixture of asbestinin A and B with the latter in excess. Fractions 9 through 24, inclusive, contained 0.251 g. of pure asbestinin B as a solid. The material (0.197 g.) from fractions 9

and 10 was recrystallized from ethanol-water giving 0.104 g. of crystalline material which showed m.p. 223-224.5° (d).

Anal. Calcd. for $C_{32}H_{41}O_{14}Cl$: C, 56.10; H, 6.03; O, 32.70; Cl, 5.17. Found: C, 56.07; H, 6.04; O, 32.55; Cl, 5.14.

The asbestinin B from ethanol-water crystallized into two forms (plates and needles) which were mechanically separated by Dr. Hossain of the x-ray laboratory.

Asbestinin B (needles)

Anal. Calcd. for $C_{32}H_{47}O_{15}Cl$: C, 54.37; H, 6.72; O, 33.95; Four acetyl groups, 24.36. Found: C, 54.87; H, 6.53; O, 33.61; acetyl groups, 28.72.

Asbestinin B (plates)

Anal. Found: C, 56.56; H, 6.41.

Bromination of Asbestinin A. -- A solution of 0.146 g. (0.239 mmole) of asbestinin A in 8 ml. of glacial acetic acid was combined with a solution of 0.091 g. (0.242 mmole) of phenyltrimethylammonium bromide perbromide in 8 ml. of glacial acetic acid. The whole was allowed to stand at room temperature for one hour after which it was warmed briefly on the steam bath. The light green reaction mixture was then poured into 20 ml. water and the whole was extracted with the three 10 ml. portions of chloroform.

The combined chloroform solution was washed once with 10% aqueous sodium bicarbonate, once with water and dried over anhydrous sodium sulfate. Removal of the solvent left 0.149 g. of the crude reaction product as a slightly yellow semi-solid.

The crude bromination product was chromatographed on 10 g. of Florisil (20% ethyl acetate in benzene) collecting 5 ml. cuts. Fractions 5 through 7, inclusive, left a total of 0.111 g. of the purified bromination product as a colorless semi-solid after removal of solvent. Thin layer chromatography of this material showed a single spot which appeared slightly ahead of the spot for authentic asbestinin A. The bromination product was precipitated as a white, non-crystalline solid by flooding a benzene solution with hexane. The solid bromination product showed m.p. 250-255° (d) and the n.m.r. spectrum was essentially identical with that of the unchromatographed material.

Interestingly, the signal at 3.10 p.p.m. appearing in the n.m.r. spectrum of asbestinin A which was assigned as an exchangeable proton alpha to a ketone carbonyl was absent in the n.m.r. spectrum of the bromination product of asbestinin A. The infrared spectrum

had bands at 1230 and 1740 cm^{-1} characteristic of the acetate carbonyl group and 1795 cm^{-1} (γ-lactone).

Anal. Calcd. for $C_{30}H_{40}O_{12}ClBr$: C, 50.89; H, 5.69; Found: C, 50.85; H, 5.61.

SUMMARY

The gorgonian Briareum asbestinum has been examined with the aim of isolating compounds corresponding to the diterpenes obtained in this laboratory from other gorgonians. Two new solid chlorine-containing compounds, designated as asbestinin A and asbestinin B, were isolated from this species. Based on elemental analysis asbestinin A has the empirical formula $C_{30}H_{41}O_{12}Cl$ and asbestinin B has the empirical formula $C_{32}H_{41}O_{14}Cl$. Infrared and n.m.r. spectral data indicate that each of the asbestinins contains acetate groups, a γ-lactone and a sufficient number of methyl groups to permit their tentative classification as terpenoids.

Bromination of asbestinin A readily afforded a monobromo derivative, $C_{30}H_{40}O_{12}BrCl$.

BIBLIOGRAPHY

1. T. Irie, M. Suzuki and T. Masamune, Tetrahedron Letters, 1091 (1965).