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1962

THE UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

I. CONFIGURATIONS OF THE DIASTEREOMERIC 2,3-DIPHENYL-2-BUTANOLS

II. CERTAIN CHEMICAL TRANSFORMATIONS OF A DITERPENE LACTONE ISOLATED FROM THE GORGONIAN, EUNICEA MAMMOSA

A DISSERTATION

SUBMITTED TO THE GRADUATE FACULTY

In partial fulfillment of the requirements for the

degree of

DOCTOR OF PHILOSOPHY

BY

WILLIAM EDWARD MARSICO

Norman, Oklahoma

1962

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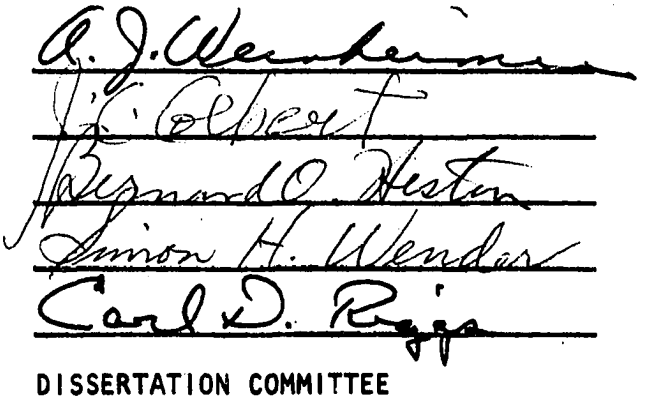

DISSERTATION COMMITTEE

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I am deeply grateful for the guidance and training which I received during my very pleasant association with Dr. Alfred J. Weinheimer.

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THE IDENTIFICATION OF THE

ERYTHRO- AND THREO-2,3-DIPHENYL-2-BUTANOLS

PART I

INTRODUCTION

The Wittig rearrangement (1) of bis-α-methylbenzyl ether produces two diastereomeric 2,3-diphenyl-2-butanols which melt at 65° and 85°. To study the steric course of this rearrangement, a knowledge of the configurations of these alcohols was necessary. The present work was undertaken to establish the erythro- and threo- configurations of these alcohols.

An interesting side reaction involving the abnormally facile deboronation of two diastereomeric benzyl boranes is described.

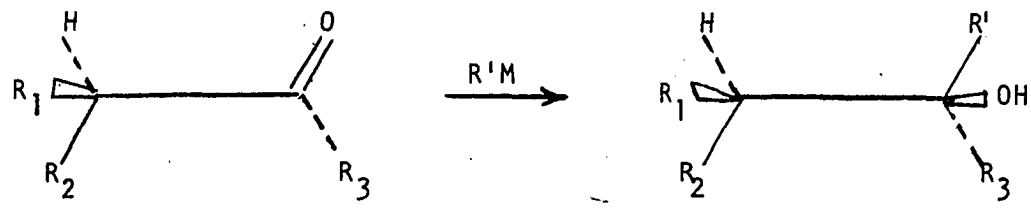
PART I

DISCUSSION

Configurations of the Diastereomeric 2,3-Diphenyl-2-Butanols

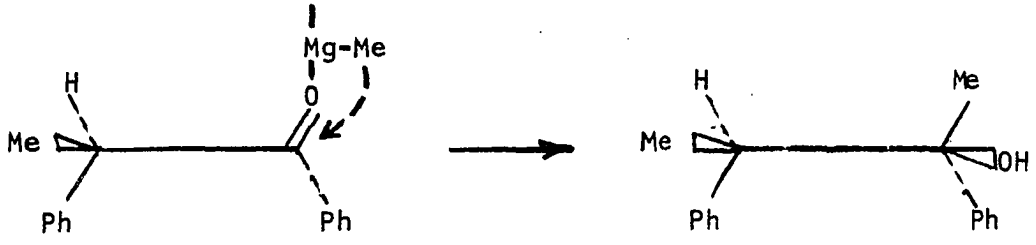
The erythro and threo configurations were assigned by means of three stereospecific syntheses. The asymmetric induction rule, as it applies to ketones, hydrogenolysis of oxiranes, and the method of hydroboration, followed by oxidation, were employed to give three independent structure proofs for each isomer.

The first assignment of configuration involves application of the "Rule of Asymmetric Induction." (2,3,4). Results of the work done by Cram and his coworkers (2), using addition reactions of organometallics to various ketones can be summarized by the following statement: "Reactions involving the addition of an organo-metallic to a carbonyl adjacent to an asymmetric center will form, predominantly, the diastereomer which results from approach of the incoming group from the least hindered side, when the ketone assumes the most stable conformation."



The system shown above, is drawn in its most stable conformation when the carbonyl, complexed with the organo-metallic, has the greatest steric requirement and R_1 is smaller than R_2. Thus, the incoming group attacks from the side occupied by the hydrogen. The configurations of thirty-six compounds were predicted and correlated through application of this method.

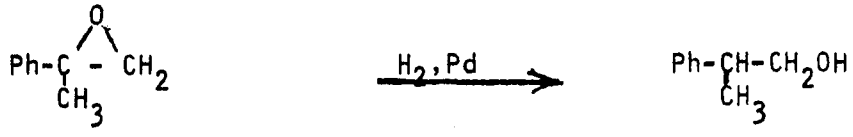
This treatment can be extended to the reaction of methyldeoxybenzoin and methyl-Grignard by depicting the most stable conformation of the ketone as that having the carbonyl flanked by methyl and hydrogen groups of the adjacent carbon. It is then possible to predict a predominance of <u>threo</u> alcohol through attack of the methyl group from the side occupied by hydrogen.

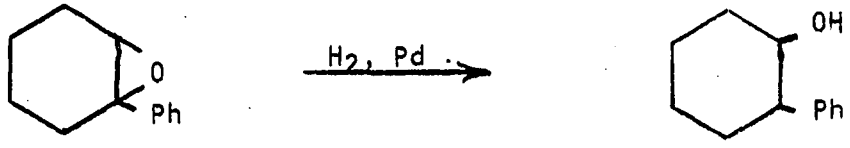


<u>threo</u>

When the reaction was carried out and the erythro- threo composition determined by chromatographic separation, the isomer melting at 65° was obtained in a threefold excess over the isomer melting at 85°. Thus, the induction rule indicates the lower melting isomer to be threo- and the higher melting isomer to be erythro-2,3-diphenyl-2-butanol.

The second synthetic approach to these alcohols utilized the stereo-specific hydrogenolysis of oxiranes. Unpublished results obtained in these laboratories, show that aryl-1,2-epoxides, when hydrogenated with palladium-charcoal catalyst at moderate hydrogen pressures, open with inversion of configuration at one of the carbon atoms to give β--phenylethanols as products. For example, hydrogenation of optically active 2-phenylpropylene oxide, with 20-30 pounds pressure, gave optically active 2-phenylpropanol in which the benzyl carbon had been inverted. Furthermore, 1-phenylcyclohexene oxide, under the same reaction conditions, gave cis-2-phenylcyclohexanol. The formation of the cis- structure could have occurred only by inversion of the benzyl carbon. These two conversions can be seen in the following illustrations.

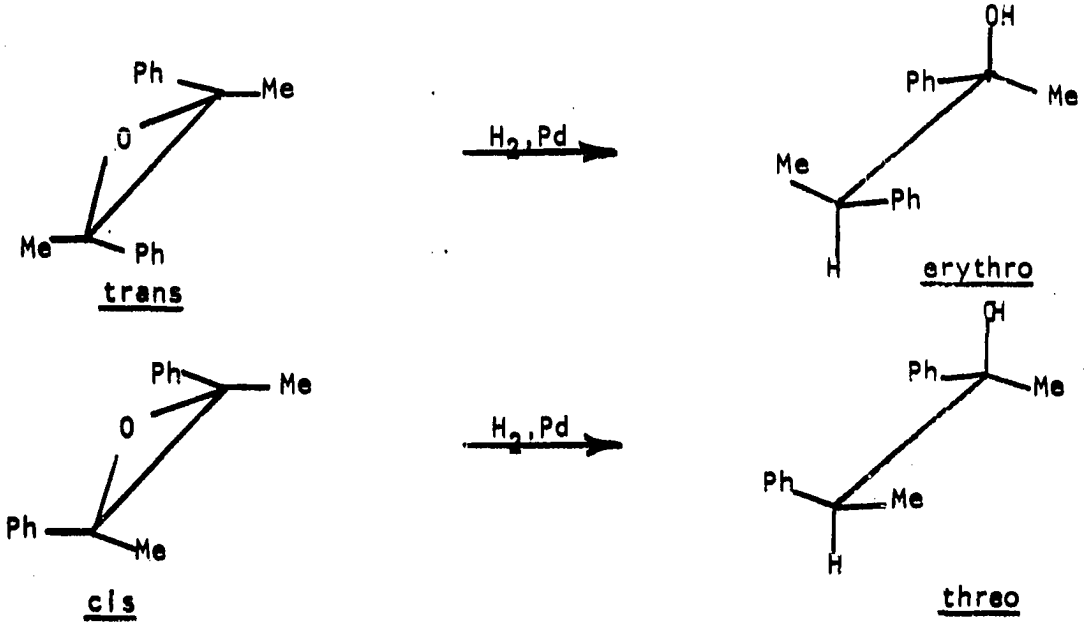




This information makes it possible to predict the configuration of the products from the hydrogenolysis of cis- and trans-α,α' -

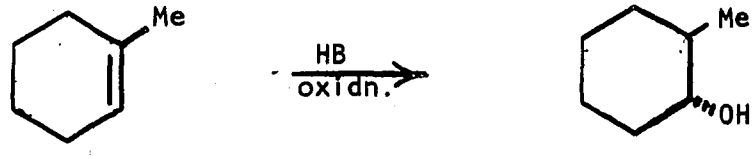
dimethylstilbene oxides. The identities of the cis- and trans- dimethylstilbenes are based on the isomerization of olefin melting at 65° to the one melting at 105° through treatment with sodium amide (5), which represents the isomerization of the cis to the more favored trans olefin. Further evidence for the olefin structures is given by the palladium charcoal hydrogenation of the trans olefin to dl-2,3-diphenylbutane, and cis olefin to meso-butane (6). This hydrogenation is known to occur with cis addition of hydrogen (7). Finally, having the more symmetrical trans as the higher melting isomer is consistent with the structural assignments.

The per-acid epoxidation of olefins occurs through cis addition of oxygen across the double bond (8,9,10), so that the perbenzoic epoxidation of the cis- and trans- butenes can be depended upon to give the corresponding cis- and trans- oxides. With the structure of starting compounds and the steric path of the reaction known, it is possible to predict that the trans-α,α'-dimethylstilbene oxide should give the erythro- and the cis-butene oxide the threo-2,3-diphenyl-2-butanol. These reaction courses may be illustrated in the following manner.

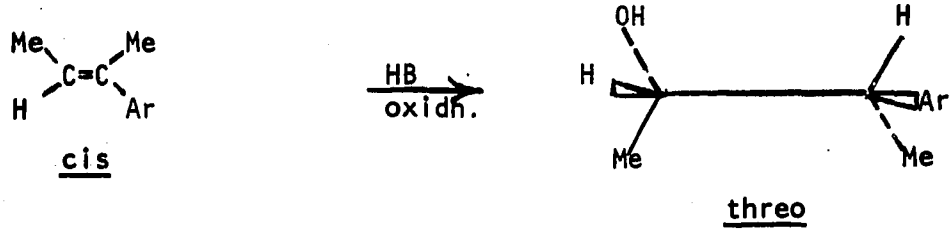


The trans-α,α'-dimethylstilbene oxide, upon hydrogenation on palladium charcoal in ethanol at 25 pounds pressure, gave a high yield of the alcohol melting at 85°, and the cis- oxide, under the same conditions, gave a high yield of the 65° isomer. Once more it is evident that the alcohol melting at 65° is the threo- and that melting at 85° is the erythro- butanol.

The third stereospecific synthetic route to the alcohols employed the hydroboration technique developed by Brown (11). The hydroboration reaction with subsequent oxidation, is known to produce an alcohol by the anti-Markownikoff, cis- hydration of an olefinic linkage. The stereochemistry is shown by converting 1-methylcyclopentene, and 1-methylcyclohexene, in high yields, to trans-2-methylcyclopentanol and trans-2-methylcyclohexanol, respectively (12).



Further illustration is given by the conversion of trans-2-p-anisyl-2-butene to erythro-3-p-anisyl-2-butanol, and of the cis- isomer to the threo- butanol (13).

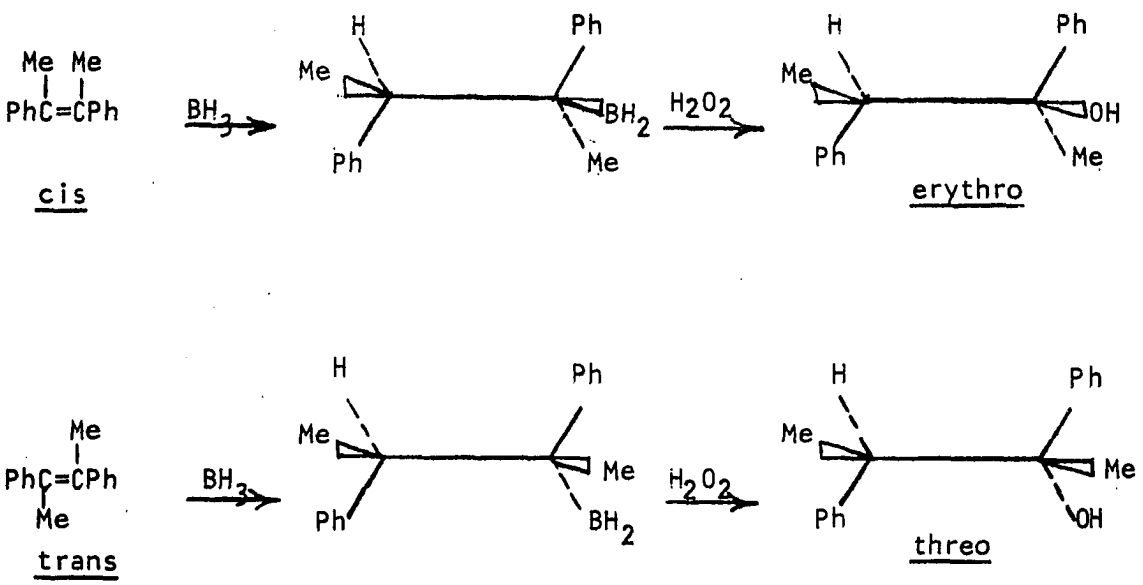


cis

threo

The reaction can be described as the cis- addition of borine (BH_3)[1] across the double bond to produce mono-, di-, or tri- alkylboranes, depending upon the hindrance of the olefin. Tetra substituted olefins have been shown to give monoalkylboranes (14,15). The borane is hydrolyzed in alkaline medium, then oxidized by hydrogen peroxide to the borate, which rapidly hydrolyzes to an alcohol and boric acid.

Turning again to the cis- and trans-α,α'-dimethylstilbenes, it is possible to predict the synthesis of threo-2,3-diphenyl-2-butanol from the trans-, and erythro- butanol from the cis- dimethylstilbene when the hydroboration procedure is applied to these olefins.



1. Borine does not exist undissociated. However, there is good evidence that it is effectively the attacking species in the hydroboration reaction (14,16).

The hydroborations, both *in situ* and *ex situ*, (14,17) were effected with several systems (18) of reagents and solvents. Using aluminum chloride, boron trifluoride etherate, in diethyl ether, with the *trans*- olefin, followed by alkaline hydrogen peroxide oxidation, a 65% yield of the isomer melting at 65° was obtained. However, the *cis*- olefin, under the same conditions, falied completely to give hydroxylic products, but instead, gave a saturated butane formed by the alkaline promoted dealkylation of the *cis*- adduct. This dealkylation will be discussed in detail later in this section. Attempts to oxidize the *erythro*- borane with hydrogen peroxide in alkaline solution at 0° and room temperature failed to give more than traces of the desired *erythro*- alcohol. Since hydrogen peroxide oxidizes organoboranes only in alkaline medium, the alternative of autoxidation (19,20,21,22) was examined. By passing a stream of dry air through a solution of the borane, at -80°, a 23% yield of the alcohol melting at 85° was obtained. Several attempts to produce this alcohol in higher yield through the use of air and oxygen at -80° and room temperature were not successful.

The 85° alcohol was synthesized by autoxidation only in the case cited above. Since the stereospecificity of the autoxidation reaction has not been established before now, this reaction sequence with the *erythro*- borane does not constitute a structure proof. However, in view of the fact that S_E reactions (23,24) are often stereospecific, it is not unusual that the 85° alcohol was produced with exclusion of the 65° isomer. The autoxidation of the *erythro*- borane to the *erythro*- alcohol does supplement the structural assignments of the alcohols from the hydroboration procedure.

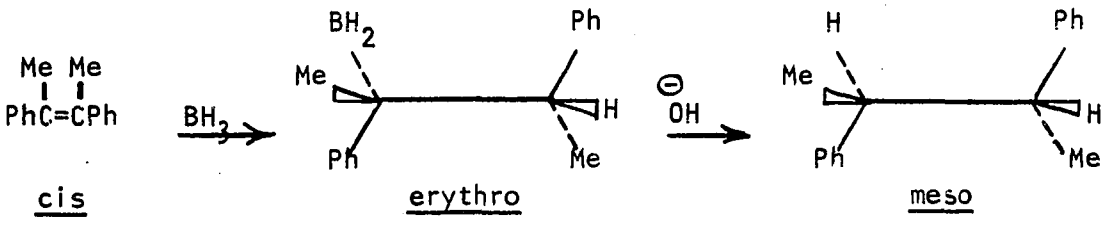
These three stereo-selective syntheses, any one of which would suffice in establishing the relative configurations, show conclusively that the threo- is the alcohol which melts at 65°, and the erythro is the alcohol which melts at 85°.

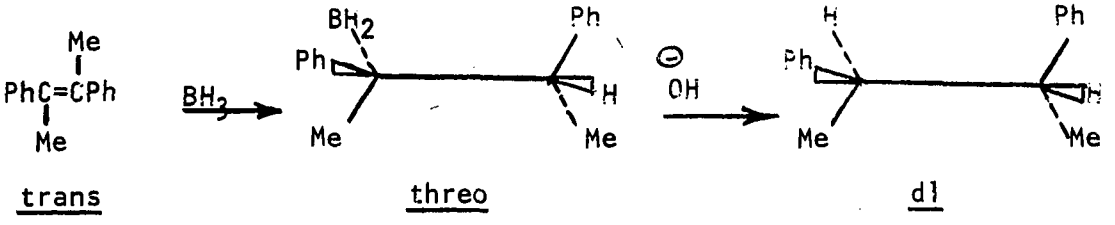
Dealkylation of Threo- and Erythro-2,3-Diphenyl-2-Butylboranes

In the discussion of the synthesis of 2,3-diphenyl-2-butanol by means of the hydroboration sequence, it was mentioned that a hydrocarbon was produced in place of the expected alcohol. The occurrence of this hydrocarbon stimulated an investigation which led to the disclosure of several interesting phenomena.

Identification of the hydrocarbon as meso-2,3-diphenylbutane, immediately showed that this product was the result of an overall cis-addition of hydrogen to the starting material, cis- dimethylstilbene. Production of this hydrocarbon was shown to be independent of hydrogen peroxide by effecting the reaction in substantial yield with dilute sodium hydroxide alone. Water or dilute acetic acid at room temperature would not cause this dealkylation. Since an organo-borane must have been produced under the conditions of the hydroboration reaction, evidenced by air oxidation of this borane to the butanol, the hydrocarbon must have been the product of the dealkylatior of this borane. Knowing that borine added cis to the double bond, then this dealkylation can be said to have occurred by either of two mechanisms; the frontside replacement of boron by hydrogen, or the less probable situation of hydrogen addition to an equilibrating intermediate which would produce the more stable of the two possible isomers. In order to show that the reaction was not occurring by this latter mechanism, threo-2,3-diphenyl-2-butylborane was dealkylated by stirring with dilute sodium hydroxide for

several hours at room temperature to give dl-2,3-diphenylbutane in 70% yield. Comparison of both hydrocarbons with the corresponding pure, authentic, hydrocarbons (6,25), showed the meso- butane to be produced with 100% stereoselectivity, and the dl- butane to be produced with greater than 95% stereoselectivity. The courses of these stereospecific dealkylations can be seen in the following illustration.





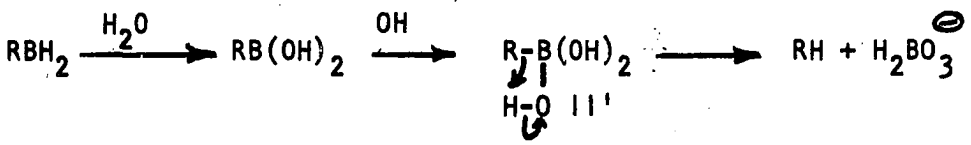
Another interesting facet of these dealkylations is the extreme reactivity of these boranes. That both boranes dealkylate readily at room temperature when reacted with dilute base, shows the boron-carbon linkage to be much more easily broken than those of most organo-boron systems. Some examples of the conditions necessary to effect this

reaction in various systems will appear shortly. Further, the erythro- isomer, as previously described, dealkylated so readily that oxidation was not possible. With the exception of one example, in which cyclopentadiene was found to give a 3 - 4% yield of cyclopentanol in addition to the expected homoallyl alcohol (26), there are no examples in the literature of dealkylation occurring during the oxidation step of the hydroboration route to an alcohol. In view of this fact, the dealkylation of the erythro- isomer is seen to be exceptionally facile.

Since the reactivity of these two boranes must depend upon the structure of the organic portion of the molecule, it would be desirable to know what effect structure can have on the rates of dealkylation in systems other than the benzyl system encountered here. First it is necessary to describe the intermediate which undergoes dealkylation in this system. It is reasonable to assume that the monobenzylboranes, derived from the cis- and trans- olefins, undergo the usual metal hydride hydrolysis with water to form 2,3-diphenylbutane boronic acids or derivatives of these acids. Attempts to isolate these acids by hydrolysis of the borane failed to give products which could be recognized as distinct chemical individuals. Since there are no examples in the literature of the hydrolysis of a monoalkylborane directly to a boronic acid, it is possible that such attempts lead to a polymeric boronic anhydride rather than the free acid. For purposes of convenience, however, these intermediates will be referred to as simple acids since substituents other than hydroxyl in no way change the interpretation of the reactivity of the boronic function. A series of boronic acid dealkylations can now be given in which the correlation of structure and reactivity is possible.

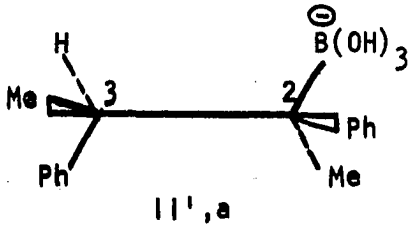
Dibutylacetyleneboronate was shown to give acetylene on brief treatment with dilute sodium bicarbonate (27), and α-toluene, and 2-thiopheneboronic acids were found to produce toluene and thiophene, respectively, with hot aqueous sodium hydroxide (28). In contrast, 1-butane- (29), and benzene- (30) boronic acids gave only traces of the corresponding hydrocarbons after potassium hydroxide fusion. This series of reactions indicates a correlation of dealkylation ease with the ability of the organic residue to sustain a negative charge. Thus, the ethynyl, benzyl, and 2-thenyl derivatives, with structures which allow stabilization of an anion, undergo facile deboronations, while the phenyl and butyl derivatives, with no stabilization ability, deboronate with difficulty. The boronic acids studied in this work are seen to have reactivities comparable with acetylene boronate and the toluene boronic acid.

A third phenomenon observed in the dealkylation of these isomeric boranes is the difference in reaction rate of the erythro- and threo- isomers. The production of the hydrocarbon from the erythro-borane under the same conditions which gave alcohol from the threo-borane illustrates that the erythro- dealkylated much faster than the threo- isomer. Since the carbon bearing the boron function has identical substitution in both isomers, this difference in reaction rates is most reasonably explained in terms of conformational effects exerted in the transition state of the boron - carbon fission. The mechanism for this fission can be described as the attack of hydroxide on the electron deficient boron atom, followed by a 1,3- shift (31) of the 2,3-diphenyl-2-butyl group from boron to hydrogen.

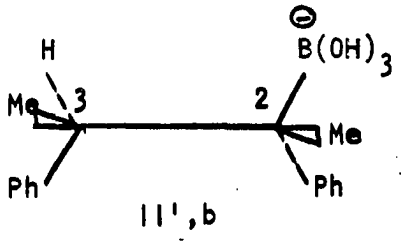


R = PhCH-CPh (Me Me) a) threo b) erythro

It is in the alkyl - hydrogen shift shown in II' that the anion stability will affect the rate of reaction. The manner in which the conformation of the transition states and this anion stabilization are related is described as follows. The boron moiety, when complexed by solvent, or existing as a substituted boronic acid, for instance, an anhydride of the type R - O - B(OH) - O - B -, will have a greater steric requirement than phenyl or methyl groups and, therefore, force the boronic acid into the following conformation by occupying the position between hydrogen and the methyl group.



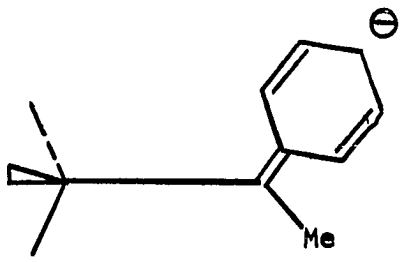
II',a



II',b

Carbon - boron bond breakage, with carbanion development at C_2 will force planarity of the C_2 phenyl and methyl groups if the charge is stabilized

through resonance. This planarity must be approached before quinoid type contributions from the phenyl group can operate in this stabilization.



Thus, the C_2 phenyl must approach a C_3 methyl in II' a, as compared to the energetically much more favorable situation of its approach to a C_3 hydrogen in II' b. Hence, there will be less anion stabilization, or higher activation energy in the threo- isomer and, therefore, slower reaction.

PART I

SUMMARY

The identification of the erythro- and threo-2,3-diphenyl-2-butanols was accomplished by means of three stereoselective synthetic pathways. The use of the "Rule of Asymmetric Induction" to predict a predominance of one of the two possible isomeric alcohols from the reaction of a Grignard reagent with a ketone; the use of the stereospecific hydrogenolysis of epoxides; and the stereospecific hydration of olefins by means of hydroboration, indicate that the erythro- isomer is identified by the melting point of 85°, and the threo- isomer is identified by the melting point of 65°.

The study of the dealkylations observed in the erythro- and threo- 2,3-diphenyl-2-butylborane system can be summarized as follows. These reactions represent the first example of a stereospecific dealkylation of an organo-borane. The hydrocarbon product is the result of a cis- addition of hydrogen to the double bond of the olefin. Furthermore, these reactions represent the first illustration of dealkylation seriously competing with oxidation in the hydroboration procedure for alcohol synthesis. Finally, the significantly faster dealkylation of the erythro- borane compared to the threo- borane, is interpreted as a conformational effect exerted, in the transition state of the dealkyla-

tion, to stabilize the incipient anion which results form the carbon - boron bond fission.

PART I

EXPERIMENTAL

α-Methyldeoxybenzoin. — Crystalline deoxybenzoin (32) (13.1 g., .0668 mole) m.p. 56-57, was added to sodium amide , prepared (33) from 1.53 g. (.0675 g. atom) sodium, in 250 ml. of liquid ammonia. After stirring five minutes, 9.47 g. (.0666 mole) of methyl iodide in 10 ml. of ether was rapidly added to the green solution. An additional 100 ml. of ether was added to dissolve precipitated solids, and the resulting solution was stirred thirty minutes. The ammonia was evaporated on a steam bath while ether was added to maintain a volume of 150 ml. The mixture was cooled to 0°, then 100 ml. of water was added and the solution filtered. After separation, the aqueous phase was extracted with ether, the combined ether portions washed with water, dried, and evaporated to give 12.0 g. of residue which solidified when cooled. Recrystallization from methanol gave 4.7 g. of α-methyldeoxybenzoin, m.p. 51-52, reported, 52 (34). Successive crops afforded 6.2 g. of less pure material.

2,3-Diphenyl-2-butanols from Methyl Magnesium Iodide and α-Methyldeoxybenzoin. α-Methyldeoxybenzoin, m.p. 51-52, (3.94 g., 0.0187 mole) in 50 ml. of dry ether was added to a magnetically stirred solution of methyl magnesium iodide made from 3.20 g. (0.0225 mole) of methyl iodide and 0.57 g. (0.0234 g. atom) of magnesium turnings. After two hours

stirring in a nitrogen atmosphere, the mixture was cooled to 0° and 45 ml. of 10% ammonium chloride solution was added. When all the solids had dissolved, the phases were separated and the ether layer was washed with three 25 ml. portions of water, dried over sodium sulfate and evaporated to give 4.33 g. of oil. The theoretical yield is 4.23 g.

This oil was chromatographed on an alumina column (Alcoa F-20, 77 by 2.5 cm.) with ether in hexane as solvent. The results of the chromatography can be seen in the following table.

FRACTION	SOLVENT	YIELD	MELTING RANGE
1 - 16	10% Ether Hexane 50 ml. Fractions	Trace	Oil
17 - 20	"	0.47 g.	72 - 83°
21 - 25	"	0.60 g.	Oil
26 - 31	"	0.61 g.	52 - 62°
32 - 34	25% Ether Hexane 300 ml. Fractions	2.57 g.	60 - 65°

The quantity of alcohol melting at 85° was adjusted to 0.96 g. by approximating the amount of this alcohol in the remaining fractions from melting point - composition data (36). Fractions 21 - 25 were discarded and the erythro- threo- alcohol ratio was calculated from the total solid material obtained from the chromatography; 3.76 g., 88.7%. This gives 25.5% and 74.5% for the percent erythro- and threo- butanols, respectively. Fractions 17, 18, and 19, were recrystallized from hexane

to give alcohol melting at 85.0 - 85.5, while sublimation of material obtained in fraction 33, gave alcohol which melted at 66 - 67°.

Cis- and Trans-α,α'-Dimethylstilbene. -α-Methylbenzyl chloride (60 g., 0.423 mole), prepared from the reaction of α-methylbenzyl alcohol with thionyl chloride (35), in 70 ml. ether was added to a well stirred suspension of sodium amide (11.9 g., 0.51 g. atom sodium) in 500 ml. of liquid ammonia over a thirty minute period. After stirring thirty minutes, sufficient ammonium chloride was added to dispel the red color. The ammonia was then evaporated, while wet ether was added at a rate such that 250 ml. of solution remained in the flask. To this solution was added 200 ml. of water and the resulting phases filtered through filter aid; the ether layer was washed twice with water, dried over sodium sulfate and evaporated. The residual oil was dissolved in 200 ml. of hot methanol and refrigerated one day to deposit 8.3 g. oily crystals, m.p. 91 - 100. Recrystallization from methanol gave 6.2 g. of the trans- olefin, m.p. 104 - 105; reported m.p. 105 - 106 (5). After obtaining a second crop of 9.0 g. with further cooling, the methanol was removed and the remaining 23, g. was distilled. The first two fractions, boiling at 120 - 136° at 2 mm., were repeatedly recrystallized from methanol to give 4.7 g. of the cis- olefin, m.p. 65.5 - 67; reported m.p. 65 - 66 (5). An oil having the characteristic odor of dl-2,3-diphenylbutane, coprecipitated with the cis- olefin, making its purification most difficult.

Trans-α,α'-Dimethylstilbene oxide. — To 28 ml. of cold chloroform, containing 0.00104 mole of perbenzoic acid per ml., was added 5 g. (0.024 mole) of trans-α,α'-dimethylstilbene. The reaction was followed

over a three day period by adding 5 ml. portions of the peracid solution until an excess of peracid persisted as indicated by a positive potassium iodide test. The solution was then washed with three 20 ml. portions of 10% sodium hydroxide solution, followed by four 25 ml. portions of water, dried over sodium sulfate, and evaporated to give 7.0 g. of solid. Three crystallizations from ethanol gave 3.7 g. (69%) of trans- oxide m.p. 108.5-110; reported m.p., 107 (37).

Cis-α,α'-Dimethylstilbene oxide. — The cis- olefin (5.0 g. .024 mole) was treated in the manner described above to give 6.2 g. of crude material. This was recrystallized several times from methanol and, finally, hexane, to give 0.53 g. of pure cis- oxide m.p. 51 - 52; reported m.p., 52 - 53 (37). Subsequent crops gave approximately one gram of less pure oxide.

Hydrogenation of trans-α,α'-Dimethylstilbene oxide. — The trans- oxide, m.p. 108.5 - 110, (0.50 g. .0022 mole) was hydrogenated in 30 ml. ethanol with 0.5 g. of 5% palladium charcoal at 30 pounds pressure for 5 hours. Filtration of the solution through filter aid and distillation of solvent gave 0.58 g. of solid m.p. 75 - 78. This material was chromatographed on alumina with 10% ether in hexane to give a total of 0.46 g. (92%) of erythro-2,3-diphenyl-2-butanol melting in a 79 - 83° range. A center fraction, m.p. 82 - 83, had an infrared spectrum identical with 2,3-diphenyl-2-butanol, m.p. 84 - 85, prepared from the reaction of methylmagnesium iodide with methyldeoxybenzoin and did not depress the melting point of this alcohol.

Attempts to hydrogenate the oxide at 40 pounds pressure for forty-eight hours and at 30 pounds for twenty four hours with palladium

charcoal in ethanol failed to give satisfactory yields of the alcohol. Extended hydrogenation periods, or high pressures evidently isomerized or dehydroxylated the alcohol since the yields of alcohol were progressively improved as the reaction times and pressure were decreased.

Hydrogenation of cis-α,α'-Dimethylstilbene Oxide. — The same procedure described above for hydrogenation of the trans- oxide, was applied to 0.53 g. (0.0024 mole) of the cis- oxide, m.p. 51 - 52°, to give a quantitative yield of material melting, 62 - 63°. This material was shown by mixed melting point and infra-red spectrum to be identical with the corresponding 2,3-diphenyl-2-butanol prepared from the reaction of methyl magnesium iodide with methyldeoxybenzoin.

2,3-Diphenyl-2-butanol from Hydration of trans-α,α'-Dimethylstilbene. — Several systems of reagents were used in attempts to hydroborate the trans- olefin. Sodium borohydride - boron trifluoride etherate in diglyme, (dimethyl diethylene glycol), sodium borohydride - aluminum chloride in diglyme, and boron trifluoride etherate - lithium aluminum hydride in diethyl ether were used to generate diborane with the olefin in situ to give yields of alcohol which varied from traces to 60%.

The following describes the conversion of the olefin to the butanol through use of the in situ method. To 3.00 g. (.0144 mole) of trans-α,α'-dimethylstilbene and 1.50 g. (.0288 mole) of aluminum chloride in 30 ml. of dry diglyme (11), was added 1.09 g. (.0288 mole) of sodium borohydride, in 30 ml. diglyme, over a thirty minute period. The resulting solution was magnetically stirred for six hours in a nitrogen atmosphere. The solution was cooled to 0° and 10 ml. of water was cautiously added. After stirring forty-five minutes, 1.577 ml. of 28%

hydrogen peroxide was added, the solution adjusted to pH 9-10 with 3N sodium hydroxide, and stirred an additional hour. The solution was mixed with 500 ml. of water and extracted with several portions of ether. After removing the diglyme from the ether extracts by repeated water washings, the ether was dried and distilled to give 3.01 g. of oil which solidified when seeded with threo- alcohol. This oil was placed on an alumina column and washed with hexane until the eluate was free from an oily forerun. The alcohol was then eluted with 50% ether, hexane to give 0.95 g., m.p. 53 - 58°, in fraction 6, 1.47 g., m.p., 63 - 64°, in fractions 7 and 8, combined; and 0.11 g., m.p. 58 - 62°, in fraction 9. The total yield of alcohol was 2.53 g., or 78%. Fraction 8, m.p. 63 - 64°, did not depress the melting point of the corresponding alcohol obtained from the reaction of methyl magnesium iodide and methyldeoxybenzoin.

2,3-Diphenyl-2-butanol from Hydration of cis-α,α'-Dimethylstilbene. — A solution of 3.0 ml. of boron trifluoride etherate in 20 ml. of diglyme was added to the cis- olefin (2.00 g., 0.00962 mole) and sodium borohydride (0.33 g., 0.00862 mole) in 50 ml. of diglyme over a thirty minute period. After stirring seventeen hours at room temperature, the mixture was cooled to -80° and a stream of air, which had passed from successive magnesium perchlorate and ascarite columns, was bubbled for eight hours through this solution. Then, 30 ml. of 3N sodium hydroxide solution was added, the solution stirred an hour, diluted with water and worked up in the manner previously described to give 2.0 g. of oil. This oil was dissolved in ethanol and reduced with palladium charcoal at 24 pounds hydrogen pressure for four hours. The solution was then filtered,

stripped of solvent and chromatographed on alumina with hexane and hexane-ether solvent, as before. The total isolable alcohol, 0.45 g., (23%) m.p. 80 - 83, did not depress the melting point of erythro- 2,3-diphenyl-2-butanol which had been prepared from the Grignard reaction with methyldeoxybenzoin.

dl-2,3-Diphenylbutane from hydroboration - dealkylation of trans-α,α'-dimethylstilbene. — To a magnetically stirred solution of 3.00 g. (.0144 mole) of the trans- olefin and 0.62 g., (.0164 moles, 50% excess calculated on RBH_2) sodium borohydride in 50 ml. diglyme at 0°, was added 4.0 ml. of boron trifluoride etherate in 10 ml. of diglyme over a forty-five minute period. The resulting solution was stirred for four hours at 0° under an atmosphere of nitrogen. The cold solution was then treated with 20 ml. of 3N sodium hydroxide solution, the ice bath removed, and the solution stirred for eleven hours. The usual work up gave 3.7 gm. oil which was chromatographed on alumina with hexane. The hydrocarbon fraction yielded 2.1 g. (71%) of oil, n_D^{25} 1.5538, m.p. 11 - 15, and n_D^{25} 1.5523, m.p. 10, after flash distillation, reported (25) n_D^{25} 1.5530, m.p. 12 - 13. This material was compared with authentic dl-2,3-diphenylbutane and found to contain less than 5% meso - butane from the peak intensity at 9.60 (25) in the infra-red spectrum.

Meso-2,3-Diphenylbutane from hydroboration - dealkylation of cis-α,α'-dimethylstilbene. — Boron trifluoride - etherate (3.0 ml.) in 20 ml. of diglyme was added to 2.00 g. (0.00963 mole) of cis-α,α'-dimethylstilbene and 0.408 g. (0.0108 mole 50% excess calculated on RBH_2) sodium borohydride in 50 ml. diglyme at 0° in the manner described above. The cold solution was made alkaline to pH 9 - 10 with 3N sodium hydroxide and

stirred one hour while the flask was allowed to warm to room temperature. The workup gave 1.83 g. of solid m.p. 108 - 128. Chromatography on alumina gave 1.39 g. (69%) of solid, m.p. 125 - 127. The mixed melting point with authentic meso-2,3-diphenylbutane (25) was 127 - 127.5.

PART I

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CERTAIN CHEMICAL TRANSFORMATIONS OF A DITERPENE LACTONE ISOLATED FROM THE GORGONIAN, EUNICEA MAMMOSA

PART II

INTRODUCTION

Terpenes have been encountered only recently in gorgonians (1). The properties and sources of a few terpenoid compounds, isolated from the hydrocarbon extracts of certain gorgonians have been reported (2,3,4), but little is known of the structures of these compounds. In continuation of the work on chemical compounds isolated from marine invertebrates, the structure of mammosin, which is the major solid isolated from the pentane extracts of Eunicea Mammosa, has now been studied.

The purpose of this thesis is to discuss chemical reactions of mammosin which have been performed in order to determine certain structural features of the molecule. Structural interpretations which arise from these transformations are included when possible. In many instances these interpretations are based on inconclusive data, but are hopefully justified because they may serve as foundations from which further work on this compound might develop.

Because of the instability of mammosin to alkali, many of the reactions were effected with a more stable compound, dihydromammosin, the product of the hydrogenation of mammosin at atmospheric pressure. Assuming that the addition of a mole of hydrogen does not cause drastic

skeletal rearrangements, it is reasonable to identify certain structural features of the hydrogenated product with the parent molecule.

PART II

DISCUSSION

Mammosin can be classified as a diterpenoid compound which has the formula $C_{20}H_{30}O_4$. The infra-red spectrum of this compound shows absorption maxima at 3450 and 1760 cm^{-1}., indicating the presence of a hydroxyl and lactone group (5). A determination of the number of active hydrogens in the molecule, indicates only one hydroxyl group to be present. Because of the inertness of the remaining oxygen, it is tentatively placed in an ether linkage.

The Ether Function

With the exception of methoxyl- and ethoxyl- groups, non-cyclic ethers occur so infrequently in terpenoid systems that the possibility of this ether existing as such will not be considered. Since mammosin gave a negative methoxyl group determination, the unknown oxygen can most logically be placed in a cyclic ether structure. Cyclic ethers most commonly occurring in terpene systems are those composed of 3-, 5-, and 6- membered oxygen containing rings. These may be epoxide, furan, pyran, or their di-, or tetrahydro- derivatives. The existence of the epoxide, furan, pyran, and dihydrofuran or pyran can be precluded because of thelack of reactivity of mammosin in solvolytic media. Thus, it was not possible to solvolyze the ether or otherwise

alter mammosin with aqueous acetic acid, or perchloric acid and aqueous acetic acid at room temperature. Concentrated hydrochloric acid in ethanol also failed to react with mammosin at room temperature. Still more vigorous conditions were applied by treating mammosin with absolute ethanol saturated with anhydrous hydrogen chloride. This produced the compound, $C_{20}H_{31}O_4Cl$. Similar treatment of mammosin with hydrogen bromide gave the analogous compound, $C_{20}H_{31}O_4Br$. The disappearance of the infra-red peak at 1660 $cm.^{-1}$, assumed to be an indication of a double bond in mammosin (5,6,7), and the absence of additional carbonyl absorption suggest that both compounds are addition rather than ether fission products. Fission of a vinyl ether would be expected to produce a new carbonyl, and fission of an epoxide should give a halohydrin or glycol. The possibility that a halohydrin was formed cannot be excluded from chemical evidence but seems improbable because products resulting from known addition reactions such as peracid epoxidation, and bromination also have this 1660 $cm.^{-1}$ peak missing from their spectra. The maximum at 185 mμ observed in the ultra-violet spectrum of mammosin is further evidence against the presence of a vinyl ether because these are known to absorb at wavelengths longer than 190 mμ. (8,9,10).

A tetrahydrofuran or pyran remains as the possible choice for the ether function in mammosin. An infra- peak at 1100 $cm.^{-1}$ is consistent with this assignment (5). It is possible that fission of this function occurred during the acetylation of mammosin. This reaction was effected by the use of a potent acetylating system composed of acetic anhydride and perchloric acid in ethyl acetate (11). Titration of the unconsumed acetic anhydride as acetic acid after completion of the

reaction permits quantitative evaluation of the number of acetyl groups which entered the molecule. Mammosin was found to react with three equivalents of acetyl when treated with the acetylating reagent for several hours. Results which will be given later will show that one equivalent of acetyl reacted with the hydroxyl group and the remaining two equivalents reacted with two other functional groups. It is possible that one of these equivalents reacted with a double bond since olefins are known to interfere with the determination (11). If this is so then the remaining equivalent possibly reacted with the ether. Absorption maxima at 1768, 1727, 1708, and 1230 $cm.^{-1}$, and absence of hydroxyl absorption in the infra-red spectrum of the product, indicate the presence of the lactone, an acetate, and probably a ketone, respectively. The possibility that the ketone is present in a methyl ketone cannot be excluded. If only one equivalent of acetyl reacts with the ether function during the proposed fission, then an additional double bond should be created from E_1 elimination of the necessary carbonium ion. However, this elimination did not occur because the triacetylated material reacted with only one mole of hydrogen when hydrogenated with palladium at atmospheric pressure. Unfortunately, the triacetylated material could not be sufficiently purified to allow further characterization.

The Hydroxyl Group

The hydroxyl group in mammosin is shown to be in a tertiary position by the following evidence. Mammosin fails to give derivatives with phenylisocyanate, p-phenyazophenylisocyanate, p-toluenesulfonyl chloride, or acetic anhydride in pyridine; reagents expected to react with

primary or unhindered secondary hydroxyl groups. Dihydromammosin, presumably having the same hydroxyl function as mammosin, reacts reluctantly with the perchloric acid, acetic anhydride reagent (11) to give a product which is apparently the monoacetate. Unfortunately, impurities in the analytical specimen caused the percent compositions of the elemental analysis to vary from the calculated value by a margin greater than the desired 0.4%. These values, however, correspond more closely to calculated percent composition of the monoacetate than any of the other products which would be reasonably predicted. A dehydration occurs when dihydromammosin is treated with hot formic acid or hot ethanolic hydrobromic acid. The product, anhydrodihydromammosin, $C_{20}H_{30}O_3$, has peaks at 220, and 280 mμ. in the ultra-violet spectrum. Finally dihydromammosin is recovered unaltered from chromium trioxide in pyridine, a system which has been shown to oxidize secondary alcohols to ketones under the same conditions employed in this attempt (12).

The Lactone Group

Although mammosin is not acidic, it was dissolved in hot aqueous ethanolic sodium bicarbonated solution. The solution was extracted with ether and then acidified to give unaltered mammosin as the only product. Reduction of the ether gave a small amount of material which was probably unhydrolyzed mammosin. This demonstrates the presence of the lactone group. It is significant that hydrolysis with the stronger base sodium hydroxide produced a mixture of lactones upon acidification. This phenomenon is most reasonably explained by proposing the epimerization of a hydrogen α to the lactone carbonyl. It was not possible, however, to

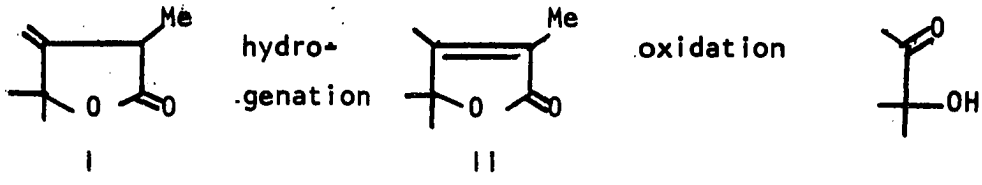
isolate a pure compound after treatment of mammosin with potassium carbonate in boiling tetralin. This system was demonstrated to cause epimerization of lactones having active α-hydrogens (13).

The ultra-violet spectrum of mammosin shows a maximum at 185 mμ., while the dihydro- derivative shows a strong absorption peak at 220 mμ. This maximum indicates the possibility of a conjugated carbonyl system. Since migrations of double bonds, which are resistant to hydrogenation both before and after migrations, have been shown to occur in certain terpene systems during palladium catalyzed hydrogenations (14,15), it is probable that a similar type of migration occurred during the hydrogenation of mammosin to form an α,β- unsaturated lactone in dihydromammosin. Lactones having this structure are known to absorb in the 215 - 230 mμ. region (16). That mammosin gives a positive test and dihydromammosin a negative test with tetranitromethane is also consistent with this conclusion, since this reagent will generally detect isolated double bonds, but not those conjugated with a carbonyl group (17).

Extensive double bond migrations have not been observed in other terpene systems, and those observed are usually allylic type rearrangements. The mammosin system might, therefore, be expected to be conducive to a 1,2- shift of a double bond. Minimum migration would be realized in this system if an isolated β,γ- double bond shifted into the conjugated α,β- position in the lactone. This new lactone system, because of added electronic stability, and also because of hindrance, might be expected to show decreased reactivity when compared with the original system. Regarding this proposed decrease in reactivity as another indication that an α,β- unsaturated lactone is present, dihydro-

mammosin was found to be unaffected by dilute sodium hydroxide at room temperature, whereas, mammosin was readily hydrolyzed under the same conditions. It was necessary to reflux the dihydro derivative several hours with aqueous sodium hydroxide in ethanol in order to hydrolyze the lactone. The hydrolysis product, an intractable solid, failed to relactonize when acidified. It was not possible to isolate a pure compound from this residue after esterification with diazomethane and attempted separation by chromatography. When the acid was heated past the melting point an evolution of gas was observed. A sample of this acid was, therefore, heated at 185°, until gas ceased to be evolved, in an attempt to isolate a decarboxylated or otherwise degraded product. However, no pure compounds could be isolated from the reaction mixture. Further evidence for the α,β- unsaturated lactone was obtained by oxidizing the compound with potassium permanganate to give a neutral fragment with the formula $C_{17}H_{30}O_4$. Isolation of this neutral compound, having infra-red absorption peaks at 3520 and 1724 $cm.^{-1}$, shows that a hydroxy ketone was produced and the lactone group was destroyed. The loss of the three carbon fragment can be interpreted as the cleavage of an α-methyl-α,β-unsaturated lactone. Enhanced absorption of the hydroxyl without concomitant enhancement of the carbonyl group absorption in the infra-red spectrum of this molecule, suggest the possibility of a dihydroxy ketone, one hydroxyl group being the original tertiary alcohol, the other remaining from the lactone. For this reason the terminus of the lactone is presumed to have a tertiary oxygen since a secondary oxygen would be expected to yield a ketone under the conditions of the reaction. An attempt to prepare an α- benzylidene derivative was not successful as

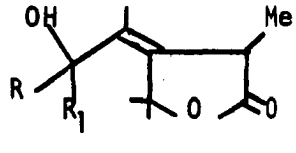
evidenced by recovery of starting dihydromammosin. This result is consistent with the proposed α- methyl substitution and α,β- unsaturation in the lactone. As a summary, the following partial structures can be drawn for the lactone function in mammosin (I), and dihydromammosin (II).



I II

It is also possible that the lactone exists as a 6- membered ring, although these occur less frequently in terpene systems than the 5- membered counterpart.

The peaks at 220 and 280 mμ. observed in the ultra-violet spectrum of anhydrodihydromammosin can now be rationalized in terms of the proposed structures for mammosin and dihydromammosin. Assuming no double bond isomerizations or skeletal rearrangements occur during the dehydration step, (an assumption which could easily be incorrect since acid catalyzed rearrangements are common in several terpenoid systems, (18,19,20)), then the hydroxyl group must occupy a position four carbons from the lactone carbonyl to give the extensive conjugation observed upon elimination of this group. Partial structure (IV) illustrates this proposed relationship in mammosin.



IV

A 1, 2- shift during hydrogenation, followed by a dehydration would give the conjugated system expected (7) from the ultra-violet spectrum of the dihydro derivative.

Reduction of the lactone group in dihydromammosin was achieved by treatment of the compound with lithium aluminum hydride in tetrahydrofuran. The product, $C_{20}H_{36}O_4$, was shown to have three hydroxyl groups by the Zerewitinov method. Mammosin, when treated in the same manner produced an intractable solid which consumed four equivalents of acetate when treated with the perchloric acid, acetic anhydride reagent (11). Since three hydroxyl groups must be present in the product, only one equivalent of acetate reacted with an unknown functional group. The reduction of the lactone group thus had eliminated one of the reactive functional groups present in mammosin.

The Double Bond System

Addition Reactions

The double bond migration which occurs during hydrogenation of mammosin has been described. Two, or the equivalent of two double bonds must be present in mammosin if this unsaturated linkage still exists in the dihydro derivative after the consumption of one mole of hydrogen. One of these double bonds undergoes the usual olefin reactions while the other is inert as evidenced by the reaction of mammosin with one mole of reagents known to add to olefinic linkages. Thus, mammosin is seen to decolorize one mole of bromine, add one mole of hydrogen chloride or hydrogen bromide, and react with one mole of perbenzoic acid to give mammosin oxide $C_{20}H_{30}O_5$, all having an infra-red spectrum

in which the characteristic double bond peak at 1660 $cm.^{-1}$ no longer exists, or is greatly diminshed.

The double bond in dihydromammosin, however, is unreactive to any of these reagents. Thus, it is apparent that during the reduction of mammosin, one of two possibilities exists; the reactive bond is hydrogenated while the other bond which is probably hindered, is shifted to the α,β- position in the lactone where it is again unreactive because of steric and electronic effects; or the reactive bond is shifted to the α,β- - position while the other bond is reduced. Since the bond most susceptible to addition reactions should also be most susceptible to hydrogenation, it follows that the nonreactive bond should be the bond that migrates.

Hydrogenation of Mammosin

Mammosin was smoothly reduced by one mole of hydrogen at atmospheric pressure with palladium to give dihydromammosin, $C_{20}H_{32}O_4$, melting 182 - 183, in 90% yield. Hydrogenation of mammosin at pressures higher than atmospheric gave a variety of products which probably resulted from isomerization of one or more of the double bonds. Thus, hydrogenation at 30 - 40 pounds pressure with palladium-charcoal in ethanol gave only trace amounts of dihydromammosin; the remaining material was an oil from which no other pure compound could be isolated. When mammosin was hydrogenated with platinum on charcoal in acetic acid at 40 pounds, a small quantity of a new derivative, isodihydromammosin, was isolated. This material, melting 193 - 194, has infra-red and ultra-violet spectra identical with those of dihydromammosin, which melts at 182 - 183. Ele-

mental analysis of this material gave the formula, $C_{20}H_{32}O_4$, and the melting point of a mixture of this material with the dihydro derivative was not significantly depressed. A specific rotation of 86.5° for this material, which compares with 22.2° for dihydromammosin, shows it to be another dihydro derivative of mammosin. Isodihydro- and dihydromammosin were also obtained in trace amounts from hydrogenation of mammosin with platinum in acetic acid at 1300 pounds; the major portion of the material was again recovered as an intractable oil. Hydrogenation of mammosin at similar pressures with palladium in ethanol, gave a small quantity of dihydromammosin as the only isolable product.

Because of the identical ultra-violet and infra-red spectra of these two isomers, it is reasonable to assume that the isodihydro derivative is the result of hydrogen addition to the side of the double bond opposite to that which gives dihydromammosin.

In an attempt to determine if hydrogenolysis of the lactone function in mammosin had occurred with hydrogenation at high pressure, the crude product was treated with a hot, ethanolic sodium bicarbonate solution. Acidification of this solution gave a small quantity of material, melting at 108 - 109.5, which had lactone carbonyl absorption in the infra-red spectrum. Other attempts to obtain this material gave mixtures of compounds which had melting points in this range; but these could not be separated by crystallization.

Ozonolysis

In many instances ozonolysis of mammosin produced acidic and neutral fragments which were water soluble or volatile enough to be swept from the reaction vessel by the oxygen stream. The acidic products,

after oxidation of the ozonide, could not be obtained from the aqueous phase in significant quantity by simple ether extraction. The small quantities of material which were obtained from the ether extractions could not be identified even though several attempts were made to prepare and chromatograph the p-bromo phenacyl esters. The volatility of the neutral fragments was made apparent both by loss of the ozonide upon distillation of the methylene chloride reaction medium, and the formation, during ozonization, of small amounts of material in the potassium iodide trap into which the exit oxygen stream was passed. Complete degradation to these fragments indicates the presence of a large unsaturated ring or chain, since a fused ring system, having only two double bonds could not give such extensive cleavage products.

Mammosin was ozonized at room temperature to give a substantial yield of formaldehyde upon steam distillation of the ozonide. This immediately suggests the presence of a terminal methylene group. However, lack of a sufficiently intense peak in the 885 - 895 $cm.^{-1}$ region of the infra-red spectra makes the presence of this group improbable. A nuclear magnetic resonance signal at 8.3τ and an infra-red peak at 995 $cm.^{-1}$ are, however, both in accordance with a methyl substituted vinyl group. This structure has been shown to give formaldehyde and a ketone upon oxidation with ozone or potassium permanganate (19), so that it is not unreasonable to propose such a grouping in mammosin to account for the formaldehyde production. The fact that ozonolysis at -80° produces no formaldehyde indicates that the shift of the bond to the terminal position is not favored at this temperature.

Dihydromammosin, upon ozonolysis, gives a compound $C_{16}H_{28}O_4$. The shift of the carbonyl absorption maximum to 1724 $cm.^{-1}$ and a peak at 3480 $cm.^{-1}$ show this compound to be a hydroxy ketone. Since three carbon atoms were presumably lost with ozonolysis of the lactone in dihydromammosin, several unsuccessful attempts were made to isolate formaldehyde as a fission product which would account for loss of the remaining carbon atom. The fact that the major ozonolysis product of dihydromammosin is a high molecular weight ketone, rather than the smaller fragments obtained from ozonolysis of mammosin, is again consistent with the proposed shift of a double bond from the endo to exo position in a large ring during the hydrogenation of a double bond.

Dehydrogenation Attempts

Many attempts were made to dehydrogenate mammosin and dihydromammosin to obtain an aromatic nucleus which would establish the carbon frame of the system. These dehydrogenation attempts consisted of heating these compounds in sealed tubes under vacuum, or in an atmosphere of nitrogen or air, with selenium or palladium charcoal. Temperatures ranging from 250 - 400° were employed. At temperatures in the 350 - 450° range no more than traces of oily, non aromatic products could be obtained from the palladium-charcoal, or selenium melt even after extractions for extended periods with boiling ether, hexane, acetone, or benzene. Attempts to dehydrogenate these compounds at lower temperatures gave unaltered or, slightly modified starting material.

Dihydromammosin, when treated with palladium charcoal for several hours at 250°, was not affected. When the temperature was raised to 350°, the only isolable material was its dehydration product,

anhydrodihydromammosin. Mammosin, when treated with selenium at 250°, produced a compound having a melting point and infra-red spectrum which was suggestive of the dihydro derivative. Treatment of mammosin or dihydromammosin with either dehydrogenating agent at 350 - 400°, produced a few milligrams of oil which possessed no aromatic character in the ultra-violet spectrum before or after purification by chromatography.

Preliminary investigations of two other degradative approaches were unfruitful. Thus, potassium hydroxide fusion of the dihydro derivative at 250° gave an inseparable mixture of acidic products having an infra-red spectrum similar to the acid obtained on hydrolysis of dihydromammosin. Distillation of the dihydro derivative from powdered zinc gave no isolable products.

The failure of the mammosin system to produce aromatic residues and the consistent loss of material, presumably as volatile fission products, under the dehydrogenation conditions again suggests the presence of a large ring or straight chain. Either would be expected to fragment before cyclizing and dehydrogenating.

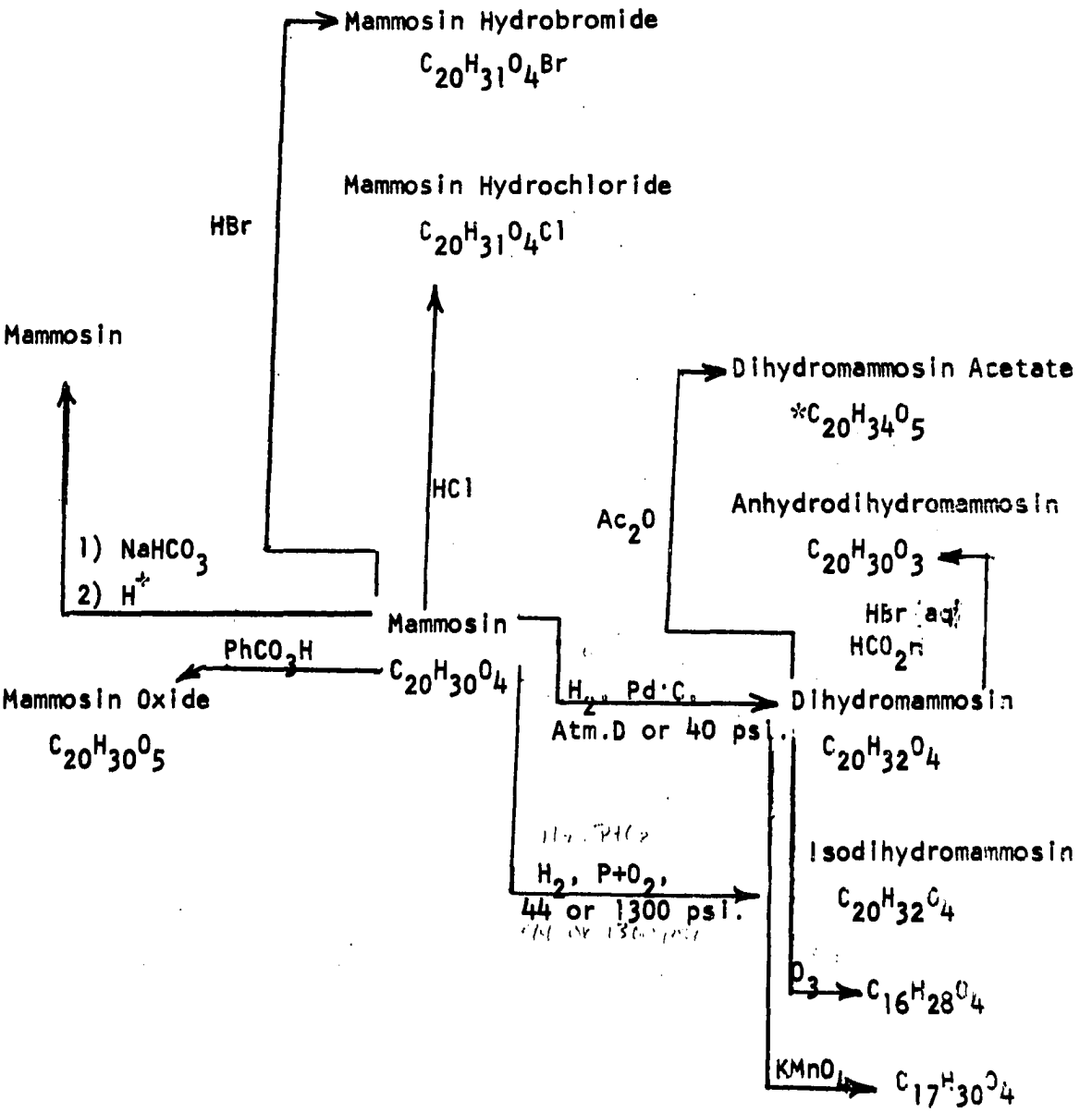
Concerning the Carbon Nucleus of Mammosin

For the purpose of determining the number of possible rings in mammosin it is convenient to consider the molecule as a saturated straight chain hydrocarbon, $C_{20}H_{42}$. Removal of the two hydrogens for each of the proposed two double bonds and four hydrogens for the lactone indicates that two rings, carbocyclic or oxygen bearing, must exist to account for the missing four hydrogens. For reasons stated in the discussion of the ether function, one of the rings may reasonably

be assigned a 5-, or 6- membered cyclic ether structure. Since mammosin is found to give at least three carbon-methyl groups on analysis, and since at least three of the carbon atoms which compose the lactone group must be external to another ring or chain system in order to give a C_{17} ketone on oxidation, then the remaining nine or ten atoms must compose or be associated with the remaining ring. In view of the difficulties encountered in the dehydrogenation attempts and the evidence for cleavage of mammosin to much smaller fragments with ozonalysis, the proposal of such a macro ring does not seem unreasonable. Furthermore, rings of this type have been shown to exist in terpene systems (20,21,22), although they are much less frequently encountered than hydronapthalene or hydroazulene skeletons.

The various reactions which have been performed with mammosin and dihydromammosin are summarized in the following diagram.

DIAGRAM I



* Unsatisfactory Analysis

PART II

SUMMARY

The following observations can be made about mammosin and dihydromammosin from information gained in the various chemical transformations described in this work. Mammosin is a diterpene γ-lactone having one of three possible methyl groups α to the lactone carbonyl group. Reduction of one active double bond at atmospheric pressure gives dihydromammosin in which a remaining double bond is conjugated with the lactone carbonyl group. A tertiary hydroxyl group can be eliminated from the dihydro derivative by hot acid treatment to give an anhydrodihydro derivative which shows the presence of extensive conjugation in the ultra-violet region. Because of this conjugation upon elimination, the hydroxyl group can be tentatively placed four carbons from the lactone carbonyl. A fourth oxygen, because of its inertness, is placed in an ether linkage which is reasonably a 5- or 6- membered cyclic structure such as a tetrahydrofuran, or pyran. Inability to obtain aromatic residues and extensive fragmentation during dehydrogenation, along with formation of smaller fragments during ozonolysis of mammosin indicate a large ring or straight chain to be the nucleus of the system. This ring or chain is seen to be necessary when a molecule $C_{20}H_{30}O_4$, having only three ring systems

possible, is considered to have a acrome and a [illegible] present.

possible, is considered to have a lactone and a cyclic ether structure present.

PART II

EXPERIMENTAL

All melting points are uncorrected. The alumina used in chromatography was Merck (Darmstadt), active neutral. Carbon-methyl, active hydrogen, and elemental analyses were performed by the Alfred Bernhardt Laboratories, Mulheim, Germany. The infra-red spectra were obtained by scanning chloroform solutions of the materials using the Perkin Elmer Model 21, spectrophotometer; the ultra-violet spectra, unless otherwise stated, were obtained by use of cyclohexane solutions in 0.1 cm. cells with the Beckman, DK-1. The nuclear magnetic resonance spectra were kindly obtained by Dr. C. Boozer, Emory University, on a Varian 40 megacycle instrument. Crude mammosin was most generously provided by Dr. Leon Ciereszko, University of Oklahoma.

Purification of Mammosin. — Crude mammosin, obtained from the pentane extracts of Eunicea Mammosa cortex, is most conveniently separated from pigmented contaminants by chromatography.

A solution of 24.4 g. of the dark orange solid in 300 ml. of benzene was placed on a 15 by 1 1/2" Florisil column and eluted with benzene. Distillation of the solvent and trituration of the resulting solid gave 17.3 g. of white dense powder, m.p. 153-155. Mammosin in this state of purity was used in the reactions reported. An analytical

specimen, m.p. 154-155.5, $[\alpha]_D^{27.3}$ -89.4° (0.75, $CHCl_3$), was obtained after several recrystallizations from 3:1 hexane, benzene solution.

Anal. Calculated m.w. for $C_{20}H_{30}O_4$: 334. Found by the Rast method (Bernhardt): 344; and with a Mechrolab, "Osmometer": 341. Calculated for one active hydrogen: 0.30%. Found: 0.28%. Calculated for two C-methyl: 8.80%. Found: 9.63 and 9.93%. Calculated for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04; O, 19.14. Found: C, 71.69, 71.60; H, 9.02, 9.10: O, 19.26. The infra-red spectrum showed maxima at 3450, 1760, 1660, 1450, 1380, 1300, 1100, 919, 895, 866 and 837 $cm.^{-1}$. The ultra-violet spectrum gave a maximum at 185 $m\mu, \epsilon 4.6 \times 10^4$. NMR signals at: 8.92, 8.26, 8.06, 7.82, 7.17, 6.86, 6.65, 5.44, 5.20, 4.98, 4.80, 4.65, 4.10, 3.50 τ.

Attempted Hydroxyl Derivatives. — Mammosin failed to give derivatives when treated with phenylisocyanate or acetic acid in pyridine at room temperature or 100°. No precipitate could be obtained from treatment of mammosin with p-phenylazophenylisocyanate in hot benzene. Mammosin was recovered after briefly heating and standing 3 days with p-toluenesulfonyl chloride in 1:1 pyridine, benzene solution, m.p. 146-153.

Acetylation of Mammosin. — To 0.400 g. (1.50 m moles) of mammosin was added 2.00 ml. of an acetylating reagent composed of 2.0 ml. of 70% perchloric acid, 25 ml. of acetic anhydride, and 75 ml. of ethyl acetate (5.17 N in hydrogen ion after hydrolysis) made according to the directions of Fritz and Schenk (11). After standing 1 hour, the

solution was hydrolyzed with 10 ml. of 3:1 pyridine, water solution and titrated with 0.485 N methanolic sodium hydroxide, using 1:1 cresol-red, thymol-blue as the indicator. The solution required 16.23 ml. indicating that 2.02 eq. of acetyl per mole of mammosin were consumed. Mammosin, treated for 7 hours in this manner consumed 2.74 eq. of acetyl per mole.

Acetylation of Dihydromammosin. — Dihydromammosin (0.300 g., 0.875 m mole) with 3.00 ml. of the acetylating solution for 1 1/2 hours, consumed 0.27 eq. of acetyl. The pyridine, water solution deposited 0.12 g. of yellow solid after standing 18 days. This was recrystallized several times from aqueous ethanol to give 50 mg. of dihydromammosin acetate, m.p. 191-192.5.

Anal. Calculated for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05; O, 21.41. Found: C, 69.03; H, 8.91; O, 21.31.

Attempted Reaction of Dihydromammosin with Chromium Trioxide. — Dihydromammosin, m.p. 177-179°, was allowed to stand for 24 hours at room temperature with 1.0 g. of chromium trioxide in 15 ml. of pyridine. The mixture was then poured into water and extracted with ether; the ether was washed with dilute hydrochloric acid, then water, and dried. Evaporation of the solvent gave 0.18 g. of solid, m.p. 175-178°. This material had an infra-red spectrum identical with that of dihydromammosin and a mixed melting point with the dihydro derivative was not depressed; m.m.p. 177°.

Hydrolysis of Mammosin with Sodium Bicarbonate. — Mammosin,

0.10 g., was heated for 6 hours in 30 ml. of 5% sodium bicarbonate solution containing enough ethanol to make the solution homogeneous. After cooling, the clear solution was extracted with ether and the ether distilled to give 0.03 g. of oil. Acidification of the alkaline solution with conc. hydrochloric acid gave 0.05 g. of solid, m.p. 142-148. The melting point with mammosin, m.p. 152-154, was 149-154.

Hydrolysis of Mammosin with Sodium Hydroxide. — (1) Mammosin, 0.09 g. was dissolved in 10 ml. of 1.2 N ethanolic sodium hydroxide and the resulting yellow solution allowed to stand 1 hour at room temperature. Acidification of the solution with hydrochloric acid gave an intractable solid. The infra-red spectra of solids obtained from similar treatment of mammosin are identical with that of mammosin.

(2) To 50 ml. of 1.2 N methanolic sodium hydroxide was added 1.00 g. of mammosin and the resulting solution refluxed for 6 hours. Slow addition of hydrochloric acid to a phenolphthalein endpoint, followed by ether extraction gave 0.32 g. of frothy solid, sintering at 60°, the remaining material was recovered upon further acidification. Chromatography of the combined material on a Florisil column in benzene gave 0.53 g. of material m.p. 106-141, in the second fraction. The infra-red spectrum of this material is identical to mammosin. The remaining material was recovered as an intractable oil.

Attempted Hydrolysis of Dihydromammosin with Sodium Hydroxide. — Dihydromammosin, 0.21 g., was dissolved in 16 ml. of 0.25 N. methanolic sodium hydroxide. After refluxing 1 1/2 hours, water was added and 0.10 g. of solid was filtered. This was identified as dihydromammosin by melting point, m.p. 181-182.

Attempted Hydrolysis of Dihydromammosin with Sodium Carbonate. — Dihydromammosin was recovered, unaltered, after treatment with aqueous sodium carbonate in boiling ethanol or boiling diglyme (b.p. 160°) for 20 hours.

Hydrolysis of Dihydromammosin with Sodium Hydroxide. — To 13 ml. of 0.77 N methanolic sodium hydroxide was added 0.20 g. of dihydromammosin and the resulting solution refluxed 5 hours. Water was added and the clear solution was acidified to pH 2 with hydrochloric acid, then extracted with ether. Distillation of ether gave 0.22 g. of frothy solid which readily dissolves in dilute bicarbonate solution. This solid (0.622 m mole) was esterified with diazomethane (11.9 m moles) made from the reaction of N, N'-dinitroso-N,N'-dimethylterephthalamide (DuPont, EXR-101) with sodium hydroxide (23). After decomposition of the excess diazomethane, the methyl ester was extracted with ether, washed, and isolated to give 0.20 g. of oil, having an ester carbonyl maximum at 1718 $cm.^{-1}$. Chromatography of this oil on a 13 1/2 by 3/4" Florisil column failed to give a pure substance.

Treatment of Mammosin with Potassium Carbonate. — Mammosin, 0.20 g. was refluxed with 0.25 g. of freshly fused potassium carbonate in 15 ml. of dry tetralin for 5 hours. The mixture was filtered and most of the solvent distilled. Chromatography of the residue on alumina gave a small quantity of material which could not be purified by recrystallization from acetone, water.

Reduction of Dihydromammosin with Lithium Aluminum Hydride. — To 1.5 g. (39 m moles) of lithium aluminum hydride in 40 ml. of

tetrahydrofuran, was added 0.50 g. (1.48 m moles) of dihydromammosin in 10 ml. of tetrahydrofuran. After refluxing 4 1/2 hours, the mixture was cooled and methanol was added until vigorous reaction subsided. Approximately 25 ml. of water was added, then 2 g. of filter aid was stirred into the slurry to facilitate filtration. After filtration, washing the filter cake with ether, and extraction of the aqueous layer, the combined ether portions were reduced to give 0.48 g. of solid m.p. 167-187. This material was recrystallized three times from aqueous ethanol to give a few milligrams of dihydromammosin triol, m.p. 205-206.5.

Anal. Calculated for $C_{20}H_{36}O_4$: C, 70.54; H, 10.66; O, 18.80. Found: C, 70.39; H, 10.85; O, 18.82. Calculated for three active hydrogens: 0.88%. Found: 0.97%.

Quantitative Acetylation of the Mammosin-Lithium Aluminum Hydride Product. — Mammosin, 0.50 g. was treated with excess lithium aluminum hydride (approx. 1 g.) in the manner described above.

A portion of the crude product (0.210 g., 0.617 m mole based on the triol $C_{20}H_{34}O_4$) was treated for 2 hours with 2.00 ml. of 5.19 N acetylating reagent (11), as described earlier. Titration of sample and blank with 0.519 N methanolic sodium hydroxide indicated a difference of 4.35 ml. of base, or 2.26 meq. of acetyl consumed, or 3.64 eq. of acetyl per mole of reduction product.

Treatment of Mammosin with Hydrogen Bromide. — Mammosin (0.70 g., 2.08 m moles) was dissolved in 25 ml. of absolute ethanol which was saturated with hydrogen bromide. After standing at 0° for 2 hours,

this solution was poured into 250 ml. of ice water to give 0.22 g. of material. The aqueous solution deposited an additional 0.42 g. after standing all night. The combined material was recrystallized twice from benzene, hexane solution at a temperature less than 50°, to give 90 mg. of material with m.p. 186-186.5.

Anal. Calculated for $C_{20}H_{31}O_4Br$: C, 57.80; H, 7.52; O, 15.41; Br, 19.25. Found: C, 57.70; H, 7.33; O, 15.62; Br, 19.69. Infra-red maxima: 3470, 1781.

Treatment of Mammosin with Hydrogen Chloride. — Mammosin, 0.35 g., was treated for 6 hours with 20 ml. of ethanol, saturated with hydrogen chloride. Dilution with water and filtration afforded 0.11 g. of mammosin hydrochloride, m.p. 208-209.5, after four recrystallizations from aqueous ethanol.

Anal. Calculated for $C_{20}H_{31}O_4Cl$: C, 64.77; H, 8.42; O, 17.25. Found: C, 64.48; H, 8.36; O, 17.05. Infra-red maxima: 3580, 1775 $cm.^{-1}$ (KBr). Slight peak at 1645 $cm.^{-1}$.

Treatment of Mammosin with Aqueous Acetic Acid. — To 0.30 g. of mammosin was added 10 ml. of 80% acetic acid and the resulting solution was heated briefly at 100° and allowed to stand 19 hours at room temperature. The solution was then diluted with 100 ml. of water and extracted with ether. After washing with dilute bicarbonate and water, the ether was distilled to give 0.28 g. of solid m.p. 142-147. Admixture of this material with mammosin did not depress its melting point.

This material was treated with 10 ml. of 80% acetic acid containing 5 drops of 70% perchloric acid for 5 hours at room temperature to give 0.24 g. of material, m.p. 142-146. A mixture of this material with mammosin did not depress the melting point.

Treatment of Mammosin with Ethanolic Hydrochloric Acid. — Ethanol (15 ml.), containing 6 drops of concentrated hydrochloric acid, was added to 0.24 g. of mammosin and the resultant solution was allowed to stand 10 hours. This solution was heated for 2 minutes, then poured into cold water which caused the precipitation of 0.13 g. of material m.p. 147-150. This material did not depress the melting point of mammosin.

Treatment of Mammosin with Formic Acid. — Mammosin, 0.13 g., was heated with 4 ml. of 99% formic acid at 100° for 30 minutes, then allowed to stand, while cooling, an additional 4 hours. Dilution with water and extraction with ether gave an oil which failed to crystallize from aqueous ethanol or hexane. This oil had an infra-red spectrum characteristic of mammosin except for an additional carbonyl absorption at 1712 $cm.^{-1}$, and the absence of the 1660 $cm.^{-1}$ peak.

Treatment of Dihydromammosin with Hydrogen Chloride. — A solution of 20 ml. of 95% ethanol, which had been saturated with hydrogen chloride, and 0.20 g. of dihydromammosin was allowed to stand 1 hour at toom temperature. Dilution with water gave 0.15 g. of needles, m.p. 176-178, which did not depress the melting point of dihydromammosin.

This material was dissolved in 20 ml. of absolute ethanol, which had been saturated with hydrogen chloride, and refluxed 2 hours.

Addition of water to the hot solution and cooling gave 0.13 g. of solid m.p. 178-180, identified as dihydromammosin by the melting point.

Treatment of Dihydromammosin with Formic Acid. — Dihydromammosin 0.45 g., was treated with 10 ml. of 99% formic acid at 100° for 4 hours. Water was added and the cooled solution extracted with ether. The ether was washed with bicarbonate solution, dried, and distilled to a dark oil. After trituration with hexane and four recrystallizations from aqueous ethanol, there was obtained 50 mg. of beige solid, m.p. 147-150.

Anal. Calculated for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50; O, 15.02. Found: C, 75.49; H, 9.41; O, 15.30. Infra-red maxima, 1749, 1658, and 1595 $cm.^{-1}$.

This compound, anhydrodihydromammosin, was obtained in similar yield by treatment of dihydromammosin with ethanolic 48% hydrobromic acid at 100° for 2 hours.

Quantitative Epoxidation of Mammosin, Mammosin Oxide. — To 50 ml. of cold chloroform containing 15 meq. of perbenzoic acid (24), was added 0.200 g. of mammosin. The reaction course was followed by adding 2 ml. aliquots of this sample and a blank to 25 ml. portions of water, each containing 2 g. potassium iodide, 5 ml. of chloroform and 5 ml. of acetic acid, then titrating the liberated iodine with 0.99 N sodium thiosulfate solution. The difference in volume of thiosulfate solution required by sample and blank indicated the consumption of peracid per mole of mammosin to the following: 15 min.-0.75 mole of peracid per mole mammosin; 60 min.-0.96 mole; 135 min.-0.91 mole;

1005 min.-1.1 mole.

To prepare mammosin oxide, 6 ml. of 2.1 N perbenzoic acid solution was added to the 0.50 g. (1.47 m moles) of mammosin in 20 ml. of cold chloroform, and the resulting solution was allowed to stand at 0° for 17 hours. The solution was then washed with cold 5% sodium hydroxide solution until the washings gave a negative peracid test with potassium iodide. After drying, the chloroform was distilled to give 0.88 g. of tacky residue. This was triturated with hot hexane to give a solid, m.p. 151-155. Repeated crystallizations from 3:4 hexane, benzene solutions gave a few milligrams of pure mammosin oxide, m. p. 188-189, which no longer had the 1660 $cm.^{-1}$ peak in the infra-red spectrum.

Anal. Calculated for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63; O, 22.83. Found: C, 68.43; H, 8.45; O, 22.58.

Bromination of Mammosin. — To 0.50 g. (1.47 m moles) of mammosin in 10 ml. of chloroform was added 0.18 g. (1.47 m moles) of bromine in 2 ml. of chloroform. The bromine was quickly consumed after addition of each drop. The addition of a few excess drops of bromine solution gave a persistent color. The solution was then washed with water, dried, and chloroform distilled to give 0.88 g. of yellow frothy solid which darkened when heated, and when exposed to light. Attempts to recrystallize this solid from aqueous ethanol were not successful.

Hydrogenation of Mammosin

Palladium-charcoal, Atmospheric Pressure. — Mammosin, 5.00 g., in 50 ml. of ethanol was hydrogenated at atmospheric pressure with 0.75 g. of 5% palladium-charcoal until the uptake of hydrogen ceased. A total of 398 cc. (ambient) of hydrogen were consumed. The theoretical uptake for one double bond in mammosin was 351 cc. Filtration and evaporation of solvent gave 5.17 g. of white solid, m.p. 175-178. This was recrystallized from aqueous ethanol to give 4.54 g. of dihydromammosin, m.p. 178-180. A second crop afforded 0.42 g. of material m.p. 166-171. Subsequent recrystallization of a portion of the main crop gave material, m.p. 182-183.

Anal. Calculated for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.42; H, 9.43; O, 19.17. The infra-red spectrum showed maxima at 3047, 1760, 1690, 1385, 1092, and 1038 $cm.^{-1}$. The ultraviolet spectrum showed a maximum at 220 $m\mu$, ϵ 2 x 10^4.

Palladium-charcoal, 35 pounds. Mammosin, 2.85 g., was hydrogenated with 0.3 g. of 5% palladium-charcoal at 35 pounds pressure. Filtration and evaporation of the solvent gave 2.85 g. of tacky solid which was chromatographed on a 16 by 3/4" alumina column with 50% benzene, ether solvent. Fraction 17, 250 ml., gave 0.25 g. m.p. 183-184, identified by melting point as dihydromammosin. Fraction 18, 250 ml. gave 0.28 g., m.p. 182-183, identified by melting point as the dihydro derivative, also. The melting points of the subsequent fractions decreased to 168°, in fraction 21, after which no other solid was obtained.

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Platinum-charcoal, 44 pounds. — Mammosin, 0.50 g., in 30 ml. of acetic acid was hydrogenated at 44 pounds for 25 hours with 0.5 g. of 5% platinum-charcoal to give 0.47 g. of material, m.p. 146-158 after the usual work up. Recrystallization of this material from aqueous ethanol gave 0.12 g. of solid, m.p. 181-184, which does not depress the melting point of dihydromammosin. Hydrogenation of this material with platinum-charcoal in acetic acid, for 13 hours at 30 pounds gave 0.09 g. of solid, m.p. 186-189, after one recrystallization from aqueous ethanol. Another similar recrystallization gave a few milligrams of isodihydromammosin, m.p. 191-192.

Platinum-charcoal, 1000 pounds. — Mammosin, 0.50 g., in 25 ml. of acetic acid was hydrogenated with 0.4 g. of 5% platinum-charcoal for 7 hours at 1000 pounds. After separation from the catalyst and solvent; the product was chromatographed on a 16 x 3/4" alumina column with benzene. Fraction 7, 1:1, gave 0.11 g. of material which was recrystallized twice from hexane to give 50 mg. of needles, m.p. 193-194.

Anal. Calculated for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.36, 71.47; H, 9.43, 9.50; O, 18.96. $[\alpha]_D^{32}$ 86.5 (0.406, $CHCl_3$). The infra-red spectrum is identical with dihydromammosin, m.p. 182-183.

Palladium-charcoal, 1000 pounds. — Mammosin, 0.30 g., was hydrogenated at 1100 pounds for 23 hours with 0.3 g. of 5% palladium-charcoal in 30 ml. of ethanol. Filtration and distillation of solvent gave 0.31 g. of frothy solid which was dissolved in 25 ml. of 5% sodium carbonate and sufficient ethanol to make the solution homogeneous. After

heating 20 minutes, the solution was extracted with ether to give 0.26 g. of solid upon evaporation. Two recrystallizations from aqueous ethanol gave a few milligrams of material, m.p. 166-174. Acidification of the bicarbonate solution gave a small quantity of material, m.p. 119-120. The infra-red spectrum of material obtained in a similar fashion, m.p. 108-109.5, shows maxima, 3430 and 1738 $cm.^{-1}$.

Hydrogenation of Dihydromammosin

Platinum-charcoal, 40 pounds. — Dihydromammosin, 0.25 g., in 25 ml. of acetic acid was hydrogenated with 0.2 g. of 5% platinum-charcoal at 40 pounds for 9 hours. Filtration and evaporation of the solution gave material which was identified as dihydromammosin by melting point 179-181.

Platinum-charcoal, 1300 pounds. — Dihydromammosin, 0.20 g., was hydrogenated in 20 ml. of acetic acid with 0.2 g. of 5% platinum-charcoal at 1300 pounds for 20 hours. Filtration and distillation of the solvent gave 0.20 g. of material, m.p. 160-170. Recrystallization of this material from aqueous ethanol gave 0.15 g. of material identified by its melting point as dihydromammosin, m.p. 175-179.

Attempted Dehydrogenations

Dihydromammosin, palladium-charcoal. — Dihydromammosin, 0.30 g., was thoroughly mixed with 0.6 g. of 10% palladium-charcoal and sealed in a 10 x 3/4" glass tube. This was heated 12 hours at 210-220; the residue was then removed and leached several times with ether to give material which sintered at 175°. This was recrystallized from

aqueous ethanol to give 0.2 g. of material, m.p. 180-182. This did not depress the melting point of dihydromammosin.

Mammosin, Selenium. — Mammosin, 0.75 g. was mixed with 1.50 g. of powdered selenium and heated in a sealed tube at 250-260° for 22 hours. The melt was triturated with benzene to give 0.75 g. of dark oil which was chromatographed on a 7 x 3/4" alumina column with benzene. Fraction 1, 250 ml., gave 0.23 g. of oil which had ultra-violet maxima at 295 and 220 mμ, and an infra-red spectrum similar to that of anhydrodihydromammosin. Fraction 6, 500 ml, gave 80 mg. of material, m.p. 152-170, which could not be further purified.

Dihydromammosin, palladium-charcoal. — Dihydromammosin 0.25 g., was mixed with 1.0 g. of 10% palladium-charcoal and heated at 300-350° at 25 mm. pressure for 4 hours. The residue was extracted with benzene in a Bailey-Walker apparatus for 2 hours to give 10 mg. of oil which showed broad peaks at 330 and 240 (end absorption) mμ in the ultra-violet spectrum (Beckman DU, in ethanol). Infra-red spectra of similarly obtained material has maxima at 1702, 1463, and 1380 $cm.^{-1}$.

Dihydromammosin, Selenium. — Dihydromammosin, 0.20 g., was mixed with 2.0 g. of powdered selenium and heated at 360° for 17 hours in a tube sealed under vacuum. The tube and contents were cooled, crushed, and extracted continuously for 3 hours with benzene to give 80 mg. of dark oil. This oil was combined with 0.17 g. of oil obtained from the reaction of 0.30 g. of dihydromammosin with 0.3 g. selenium at 275-285° for 13 hours, and chromatographed on alumina with benzene. Fractions 3, 4, 5, and 6, each 600 ml., were combined to give 0.17 g. of oil

which had peaks at 300 and 220 mμ in the ultra-violet spectrum (Beckman DU, in ethanol). Infra-red maxima at 1750, 1660, and 1600 cm.$^{-1}$. No precipitate was obtained when this oil was treated with 3 ml. of ethanol saturated with trinitrobenzene.

Ozonolysis

Ozonolysis of Mammosin. — A stream of oxygen, containing 8% ozone by weight, was passed at 50 cc. per minute for 1 1/2 hours through a solution of 1.00 g. (2.99 m moles) of mammosin in 35 ml. of chloroform. The solution was cooled with tap water throughout the ozonization. The chloroform was distilled under vacuum so that the temperature remained less than 50°. When nearly all the solvent had been removed, 50 ml. of water was added and the resulting mixture distilled into an ethanolic solution of dinitrophenylhydrazine. The precipate which was collected was recrystallized from ethanol to give material, m.p. 155-160. When this material was mixed with formaldehyde-dinitrophenylhydrazone, m.p. 168-169, a melting point of 167-168 was observed. Its infra-red spectrum was identical with that of formaldehyde DNP.

The residual aqueous phase was extracted with ether and the ether distilled to give 0.47 g. of gel having infra-red maxima at 1760 and 1718 cm.$^{-1}$. Several attempts to recrystallize the gel from hexane and ethanol were not successful.

Ozonolysis of Mammosin at -80°. — Mammosin (0.50 g., 1.49 m moles) in 50 ml. of methylene chloride was ozonized for 3 1/2 hours at -80°. The solution was reduced nearly to dryness, then 25 ml. of 25% potassium iodide was added and the resulting solution allowed to

stand 1 hour. Enough 10% sodium thiosulfate was added to reduce the iodine. Then the solution was extracted with ether, the ether washed with several portions of water, dried and stripped to give a negligible amount of oil. The combined aqueous layers were steam distilled into an ethanolic solution of dimedon without observable formation of a precipitate.

Ozonolysis of Dihydromammosin. — Dihydromammosin, (0.35 g., 1.04 m moles) was ozonized in 50 ml. of methylene chloride at -80° for 2 1/2 hours and treated in the manner described above to give 0.15 g. of oil. This oil crystallized after standing several days in aqueous ethanol. Several crystallizations from aqueous ethanol gave a few milligrams of material, m.p. 130-132.

Anal. Calculated for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93; O, 22.49. Found: C, 67.56; H, 10.05; O, 22.69. Infra-red maxima at 3580 and 1724 $cm.^{-1}$.

Steam distillation of the aqueous phase failed to give a precipitate when the distillate was treated with ethanolic dinitrophenylhydrazine. The pot residue gave an immediate precipitate when treated with this reagent. However, no pure compounds could be isolated by crystallization of this precipitate.

Oxidation of Dihydromammosin with Potassium Permanganate. — A solution of 1 g. potassium permanganate in 10 ml. of water and 50 ml. of acetone was added dropwise to 0.25 g. of dihydromammosin in 100 ml. of acetone. The solution was stirred 3 hours at room temperature; then 50 ml. of ethanol was added. After standing all night, the suspension

was filtered and the resulting solution made basic to pH 9 with dilute sodium hydroxide. Two ether extractions of the alkaline solutions gave 0.17 g. of semisolid material. Acidification of the alkaline solution and ether extraction gave 0.10 g. of oily products.

The semisolid was leached with hot hexane and the resulting solid recrystallized from aqueous ethanol to give a few milligrams of needles, m.p. 128-130.

Anal. Calculated for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13; O, 21.45. Found: C, 68.03; H, 10.39; O, 21.88. Infra-red maxima at 3410 and 1712 $cm.^{-1}$.

PART II

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