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THE UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

TERPENES OF MARINE INVERTEBRATES

STEREOCHEMISTRY OF THE WITTIG REARRANGEMENT

A DISSERTATION

SUBMITTED TO THE GRADUATE FACULTY

in partial fulfillment of the requirements for the

degree of

DOCTOR OF PHILOSOPHY

BY

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Norman, Oklahoma

1962

TERPENES OF MARINE INVERTEBRATES

STEREOCHEMISTRY OF THE WITTIG REARRANGEMENT

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PART I

TERPENES OF MARINE INVERTEBRATES

INTRODUCTION

Previous chemical work on gorgonians (class Anthozoa; subclass Alcyonaria: order Gorgonacea) has been directed particularly toward the halogenated amino acid content of their skeletal material (1). More recently, the sterols of several species have been investigated by the late Werner Bergmann of Yale University (2). The most recent report deals with the occurrence of taurobetaine and creatine in gorgonians (3). Prior to the work reported herein, there have been no reports of terpenes in gorgonians.

Since terpenes are normally obtained from plant material (4) and gorgonians have zooxanthellae associated with them, these algal cells may play a role in the formation of the terpene compounds. It has been shown that the isolated zooxanthallae from Plexaura crassa contain large amounts of the terpenes studied in this work. In this respect, it is of interest to note the isolation of a sesquiterpene fraction from the essential oil of a seaweed (5). The presence of a cadinene was indicated on the basis of dehydrogenation of the oil to 1,8-dimethylnaphthalene.

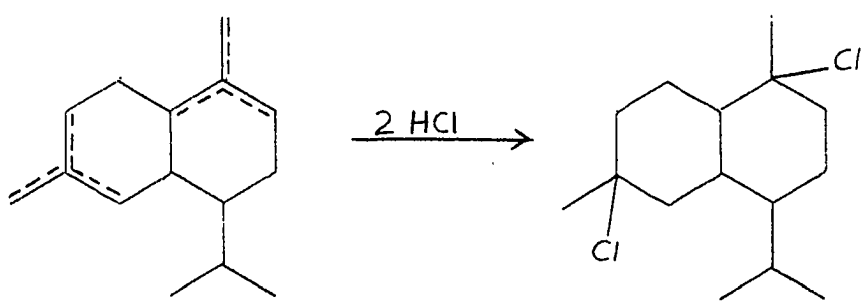
The present work is part of a systematic study of gorgonians. The lipid fraction from Plexaura crassa (Ellis and Solander) was investigated for content of nonlipid material, and an oil now recognized as a

sesquiterpene and a crystalline terpenoid compound were isolated.

This investigation also includes preliminary work on an oil from Pterogorgia americana (Gmelin) and a solid from Xiphigorgia anceps (Pallas).

DISCUSSION

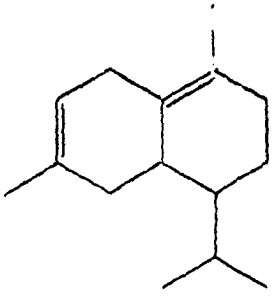
The cork-like outer layer, or cortex, was removed from the hard protein skeleton of several specimens of Plexaura crassa. Percolation of pentane over the crushed cortex afforded the lipid fraction from which a sesquiterpene oil and, incidentally, palmitic acid were isolated. Purity of the oil could not be established because of its unusual instability to heat and air oxidation. Chemical and spectroscopic evidence indicated that the principal component was a (+)-cadinene. A cadinene is defined as any one of nine possible dienes (formula I) convertible by addition of hydrogen chloride to cadinene dihydrochloride (II). The physical properties of the oil from Plexaura crassa do not agree with those of the five known cadinenes (6).



I II

Structure III, distinguished from other cadinenes by location of the double bonds, is tentatively proposed for the sesquiterpene on the basis of the available chemical and spectroscopic information.

Evidence leading to the proposed structure follows.



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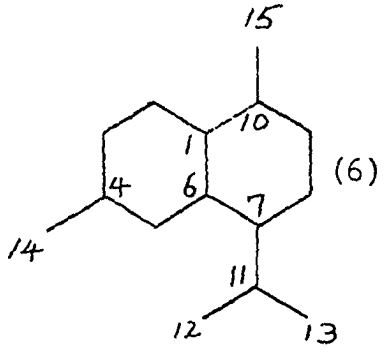

IV

Carbon and hydrogen analysis agreed with the formula $C_{15}H_{24}$, and peracid determination of unsaturation confirmed the presence of two olefinic bonds.

The infrared spectrum of the oil indicated the presence of a trisubstituted double bond and the absence of a terminal methylene group. An uncorrelated strong band at 11.46μ was probably due to absorption by the tetrasubstituted olefinic group. A doubly allylic methylene was indicated by the nuclear magnetic resonance spectrum of the oil, and formation of (+)-cadinene dihydrochloride showed that the double bonds were centered around the C_4 and C_{10} carbon atoms (formula IV).

Identity of the dihydrochloride was established by the fact that analysis of the compound agreed with the formula $C_{15}H_{26}Cl_2$, and its infrared spectrum (KBr) was identical with that of (-)-cadinene dihydrochloride obtained from cade oil. This assignment of structure was confirmed by the formation of optically inactive cadinene dihydrochloride from an equimolar mixture of the two enantiomers mentioned above. The racemic compound had the same melting point as that reported for ($\pm$)-cadinene dihydrochloride prepared from a racemic cadinene from natural sources (7).

Additional evidence for the skeleton of the sesquiterpene was obtained by dehydrogenation of the oil with selenium. The product obtained was cadalene (1,8-dimethyl-4-isopropylnaphthalene), which was identified by conversion to its picrate and its trinitrobenzene adduct.

As mentioned above, palmitic acid was also obtained from the lipid fraction of Plexaura crassa. The fatty acid was identified by the unique series of evenly spaced absorption bands in the 7.41-8.48μ region of the infrared spectrum (8), by neutral equivalent and by melting point and mixture melting point with an authentic specimen. The infrared spectrum (KBr) of the palmitic acid was identical in every respect with that of authentic material.

After removal of the lipid fraction from the cortex of Plexaura crassa, it was found that prolonged Soxhlet extraction of the residue with pentane afforded a crystalline solid for which the name crassin acetate is suggested. Information to date indicates that the compound possesses a terminal methylene and one other olefinic bond, two saponifiable groups, one of which is an acetate, and a hydroxyl group. Evidence for the presence of these functional groups is described below.

Carbon, hydrogen and oxygen analysis pointed to the formula $C_{21}H_{30}O_5$. Consumed peracid showed that the compound was doubly unsaturated. Presence of a terminal olefinic bond was indicated by characteristic infrared absorption and by ozonolysis to formaldehyde. The nature of the second double bond could not be ascertained from the infrared spectrum due to bands in both the di- and tri-substituted olefinic absorption regions.

Saponification equivalents of crassin acetate showed the presence

of two hydrolyzable groups. Presence of the acetate was confirmed by infrared absorption and by conversion of acetic acid, obtained by saponification, into its p-phenylazophenacyl derivative. Failure to obtain an alcohol upon extraction of an aqueous alkaline solution of crassin acetate and precipitation of an oily solid upon acidification indicated that the other saponifiable group was either a lactone or an ester of a low molecular weight alcohol.

Presence of a hydroxyl group was indicated by infrared absorption, and confirmed by active hydrogen determination. Lack of reaction of the compound to form characteristic alcohol derivatives indicated that the hydroxyl was probably tertiary.

Supporting evidence for the formula indicated above was that catalytic hydrogenation of the amorphous solid obtained by lithium aluminum hydride reduction of the compound indicated the presence of two reducible bonds. Calculations were based on the loss of the acetyl and conversion of a lactone into two hydroxyl groups.

Attempts to establish the carbon skeleton of the compound failed. Selenium dehydrogenation of both crassin acetate and its lithium aluminum hydride reduction product gave materials which in iso-octane solution exhibited an absorption maximum in the benzenoid region of the ultraviolet spectrum and did not form a picrate.

A crude oil obtained by vacuum distillation of the pentane extract of Pterogorgia americana was supplied by Dr. Leon S. Ciereszko. Recent mass spectral evidence by Ciereszko and Attaway (9) showed another sample of purified oil to be a sesquiterpene. The ultraviolet spectrum of the oil showed no selective absorption; and peracid determination of unsatura-

tion indicated the presence of 1.6 double bonds, which suggested that the oil was a mixture. Further investigation was not possible because of a lack of material.

A solid obtained from the pentane extract of Xiphigorgia anceps, and purified by chromatography over alkaline alumina in chloroform was furnished by Ciereszko. Carbon, hydrogen and oxygen analysis and other available data best fit the formula $C_{22}H_{32}O_4$.

A single saponification equivalent agreed well with that derived from the formula, and Ciereszko suggested the presence of a lactone group on the basis of obtaining an acid as the only isolable saponification product.

Hydrogenation of the compound with reduced platinum oxide in ethyl acetate indicated the presence of two olefinic bonds, and gave a mixture which was separated into two components by fractional crystallization from ethyl acetate. Carbon and hydrogen analysis of the higher melting reduction product agreed well with the formula $C_{22}H_{36}O_4$, but analysis of the lower melting product did not agree as closely as desirable for the tetrahydro compound.

Extracts of a mixture from attempted dehydrogenation of the lithium aluminum hydride reduction product of the solid showed ultraviolet absorption due only to sulfur (10).

EXPERIMENTAL

All melting points and boiling points are uncorrected. Pentane used for extractions was redistilled Phillips commercial grade. Alumina used for chromatography was Merck (Darmstadt) grade I.

Unless otherwise indicated, the following analyses were performed by Miss Nancy Meehan of this laboratory: saponification equivalents by the procedure in Methodes et Reactions de L'Analyse Organique (11), acetyl determinations by the procedure of Clark (12), and C-methyl determinations after the method of Barthel and LaForge (13). The molecular weight of the solid from Xiphigorgia anceps was determined by Mr. W. E. Marsico with a Mechrolab vapor pressure osmometer.

Isolation of Sesquiterpene Oil, Palmitic Acid and Crassin Acetate from Plexaura Crassa.--The freshly collected animals were dried by hanging in the shade during the sunny part of the day, followed by heating in an oven at about 60° for up to 24 hours. The cortex was stripped from the animals and crushed to a coarse powder with a meat grinder.

Slow percolation of five gallons of pentane over 10.5 kg. of the dried cortex, followed by concentration, gave 825 g. of dark, viscous residue. The sesquiterpene oil and palmitic acid were obtained by flash distillation of the extract with an Asco 2" Rota-Film molecular still. The more insoluble crassin acetate crystallized in the boiler upon prolonged Soxhlet extraction of the residual cortex material with pentane.

Properties of Plexaura Crassa Oil.--Flash distillation of the concentrated extract to 90° at 0.2 mm. afforded the more volatile fraction from which the sesquiterpene oil was obtained in a 0.33% yield based on dried cortex. Final purification was accomplished by chromatography over alkaline alumina in hexane followed by simple redistillation to give a material which boiled at 71° at 2.3 mm., had n_D^{27} 1.4948, $[\alpha]_D^{31}$ + 24.5° (c 6.0, chloroform), showed characteristic infrared absorptions at 6.07, 11.46 and 12.15 μ, and strong end absorption in the ultraviolet region (in ethanol). Refractive indices of the oil from other isolations were n_D^{24} 1.4958, n_D^{27} 1.4947, $n_D^{26.8}$ 1.4940, and n_D^{26} 1.4942.

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.52; H, 11.87.

The sesquiterpene polymerized to a viscous mass upon heating for several hours or upon exposure to air for a few days. Satisfactory storage was accomplished by sealing the material in ampoules under a carbon dioxide atmosphere.

Dr. Leon S. Ciereszko has recently obtained an oil from the acetone extract of the isolated zooxanthellae of Plexaura crassa (9). The oil shows characteristic infrared absorption bands corresponding to those of the sesquiterpene oil above.

The nuclear magnetic resonance spectrum of the sesquiterpene was obtained at Yale University, and interpreted by Professor C. E. Boozer of Emory University. The spectrometer was operated with an oscillator frequency of 60 Mc in a magnetic field of 5200 gauss with carbon tetrachloride as solvent and tetramethyl silane as internal standard.

The nuclear magnetic resonance peaks, in parts per 10 million from benzene, were assigned to formula I as follows: the region 60-62 to the isopropyl group methyls, 55-59 to the saturated aliphatic methylene and the tertiary aliphatic hydrogens, 53 to the allylic methyl groups with the allylic methylene at 52, 49 to the methylene group allyic to both double bonds, 47 to the bridge hydrogen, and 20 to the vinyl hydrogen. The sharpness of the 62 peak was not understood, and the peak at 13 was unassigned as were some of the other smaller peaks.

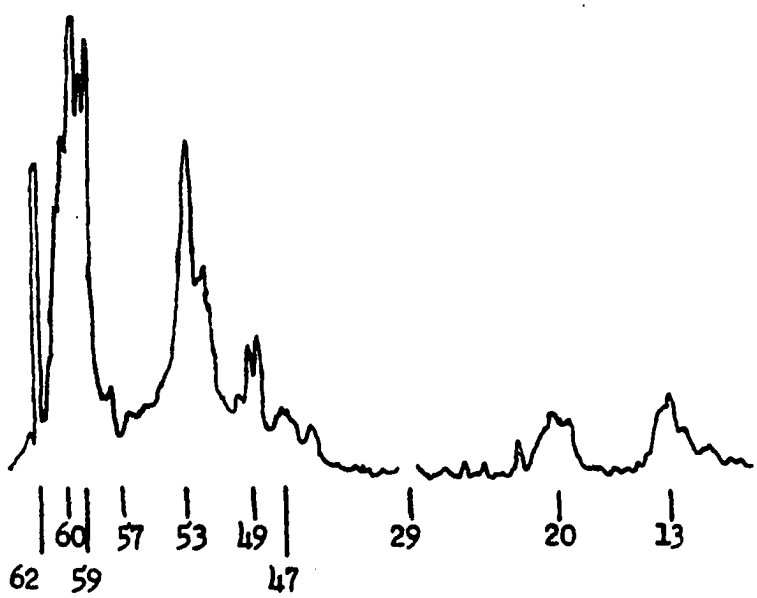

Figure 1. Nuclear magnetic resonance spectrum of sesquiterpenic oil in parts per 10 million from benzene.

Quantitative Peracid Determination of Unsaturation of Plexaura Crassa Oil.--A 0.741 N solution (25 ml.) of perbenzoic acid in chloroform, prepared by the method of Braun (14), was mixed with 467.2 mg. of Plexaura crassa oil in 50 ml. of cold chloroform and kept at 0-4° in a

refrigerator. Aliquots (2 ml.) were added to excess sodium iodide solution (2 g. sodium iodide, 50 ml. water, 5 ml. chloroform and 5 ml. acetic acid), and the liberated iodine was titrated with 0.107 N sodium thiosulfate solution. Determinations on a blank showed no appreciable decomposition of the peracid. The results of the experiment, tabulated below, indicated the presence of two olefinic bonds.

Time (hrs.)	0.2	1.0	4.3	25
$Na_2S_2O_3$ (ml.)	2.65	2.51	2.35	2.16
Moles of $Ph\text{-}CO_3H$ per mole of sesquiterpene	1.70	1.84	1.97	2.16

(+)-Cadinene Dihydrochloride from Plexaura Crassa Oil.--Hydrogen chloride was passed into 12 ml. of an ice-cold ether solution of the oil (0.607 g.) for one hour. Evaporation of the solvent afforded a mixture of liquid and crystalline material which was filtered. A few repetitions of hydrogen chloride treatment of successive filtrates gave 0.12 g. (14%) of crude (+)-cadinene dihydrochloride, which after several recrystallizations from pentane, melted at 117-118°, and showed $[\alpha]_D^{31}$ + 36° (c 0.75, chloroform). A second preparation led to a dihydrochloride with the same melting point and $[\alpha]_D^{26.5}$ + 44.6° (c 1.01, ethyl acetate). The infrared spectrum (KBr) of the (+)-cadinene derivative was identical with that of authentic (-)-cadinene dihydrochloride obtained from cade oil. The reported melting point for a (+)-cadinene dihydrochloride is 118-119° (7).

Anal. Calcd. for $C_{15}H_{26}Cl_2$: C, 64.97; H, 9.45; Cl, 25.58. Found: C, 64.85; H, 9.47; Cl, 25.75.

(-)-Cadinene Dihydrochloride from Cade Oil.--(-)-Cadinene dihydrochloride, obtained by the method of Campbell and Soffer (15), from the (-)-cadinene of cade oil melted at 118-119° and showed $[\alpha]_D^{34}$ -36.9° (c 0.298, chloroform) and $[\alpha]_D^{26.5}$ -39.2° (c 0.995, ethyl acetate). Reported values for the dihydrochloride are m.p. 117-118° and $[\alpha]_D^{20}$ -36.9° (c 3.10, chloroform) (16).

(±)-Cadinene Dihydrochloride.--A mixture of the dihydrochlorides of (+)-cadinene (20.2 mg.) from Plexaura crassa and (-)-cadinene (19.9 mg.) from cade oil in 4 ml. of ethyl acetate solution was cooled slowly in a dry ice bath. Removal of the mother liquor left 18.8 mg. (46.9%) of (±)-cadinene dihydrochloride which melted at 105.5-106.5° and was optically inactive ($[\alpha]_D^{26.5}$ 0.00 ± 0.02°). These properties were unchanged by recrystallization from ethyl acetate. The optically inactive dihydrochloride has been reported to melt at 105.5-106.5° (7).

Dehydrogenation of Plexaura Crassa Oil.--Cadinene (1.58 g.) mixed with 3 g. of powdered selenium under a nitrogen atmosphere was heated at 285° (bath temperature) for 20 hours. Chromatography of the reaction product over neutral alumina in hexane gave 0.64 g. of combined cadalene fractions which were distinguished by their infrared absorption spectra (17). Formation of crude cadalene picrate in 92% yield from part of the material represented a 38% yield of cadalene for the dehydrogenation reaction. After recrystallization from alcohol, the cadalene picrate melted at 114-115°. The reported melting point is 115° (18). The trinitrobenzene adduct of the arene melted at 110.5-111°. The recorded melting point is 112-113° (19). The melting points of the derivatives were not depressed by admixture of authentic specimens prepared from

cadalene from cade oil.

Identification of Palmitic Acid.--After removal of the sesquiterpene fraction, a second Rota-Film flash distillation to 113° at 0.25-0.35 mm. of the cold pentane extract of Plexaura crassa afforded 41.13 g. of yellow waxy solid. The crude distillate had a neutral equivalent of 495 (435.8 mg. required 2.81 ml. of 0.3134 N alcoholic sodium hydroxide). Repeated recrystallization from hexane gave an acid which showed a neutral equivalent of 254 (252 mg. required 3.17 ml. of 0.3134 N sodium hydroxide). The calculated value for $CH_3(CH_2)_{14}COOH$ is 256.4. The infrared spectrum of the purified compound showed characteristic bands at 7.87, 8.01, 8.15, 8.30 and 8.43 μ (8); and was identical in every respect with that of palmitic acid. Its melting point and mixture melting point with authentic palmitic acid (Eastman) was 63-64°. The reported melting point is 63° (8).

Properties of Crassin Acetate.--Crassin acetate was obtained in 0.65% yield by prolonged Soxhlet extraction of the residual cortex material with hot pentane. Darker batches of the compound were decolorized with activated charcoal in ethanol. Recrystallization from ethanol-water gave needles which melted at 142-144°, gave a single peak on gas phase chromatography, had an optical rotation of $[\alpha]_D^{25}$ +70.7° (c 4.0, ethanol), showed only end absorption in the ultraviolet region (ethanol), and exhibited infrared absorption peaks ($CHCl_3$) at 2.78, 3.32, 3.40, 5.77, 6.15, 6.80, 7.24, 7.35 w, 7.65 w, 8.01, 8.46, 8.99, 9.13, 9.72, 10.23 w, 10.48, 11.25, 11.72, 12.04 and 12.30 μ. Attempts to form the acetate, phenylurethane and tosylate derivatives failed.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34; O, 22.07. Found: C, 69.91; H, 8.44; O, 21.71.

Other samples purified by Dr. Leon S. Ciereszko (9) in various ways showed respective carbon and hydrogen contents as follows: sublimed, 69.73, 8.33; recrystallized from ether, 70.11, 8.31; and recrystallized from carbon tetrachloride-hexane, 70.45, 8.66.

Additional analytical data on crassin acetate is summarized in Table I.

From 20 g. of the acetone extract of zooxanthellae isolated from Plexaura crassa, Ciereszko (9) has recently obtained 4 + g. of crassin acetate which was identified by its infrared spectrum and by melting point and mixed melting point with a sample of the material described above.

Quantitative Peracid Determination of Unsaturation of Crassin Acetate.--A solution of crassin acetate (328.3 mg.) in 75 ml. of 0.2445 N perbenzoic acid in chloroform was prepared and treated by the procedure described above for the Plexaura crassa oil. Liberated iodine was titrated with 0.107 N sodium thiosulfate solution. Results indicated the presence of two olefinic bonds as tabulated below.

Time (hrs.)	0.3	1.0	5.1	24
$Na_2S_2O_3$ (ml.)	3.98	3.87	3.72	3.66
Moles of $Ph\text{-}CO_3H$ per mole of crassin acetate	1.30	1.55	1.88	2.02

Formaldehyde from Ozonolysis of Crassin Acetate.--Crassin acetate (0.435 g.) in glacial acetic acid (25 ml.) was treated with a stream of

TABLE I

ANALYTICAL DATA ON CRASSIN ACETATE

	Saponification Equivalent	Volatile Acid As % Acetyl	C-Methyl %	Active Hydrogen	Molecular Weight	Methoxyl
Found	186*	10.69**	13.06*	0.43**	343***	0.00**
	188*	11.14*	13.33*		339**	
	189*	11.37*	13.74**			
	191*	11.76*				
		12.82*				
Required for $C_{21}H_{30}O_5$	181	11.88		0.276	362	

*Analyses by Miss Nancy Meehan of this laboratory.

**Analyses by A. Bernhart, Microanalytical Laboratories, Mulheim (Ruhr) Germany. The molecular weight determination by the Rast method.

***Molecular weight determination, cryoscopic in benzene, by Professor A. J. Weinheimer.

ozone (8%) in oxygen at a rate of flow of 105 cc. per minute for 36 minutes. The solution was diluted with 50 ml. of water, 2 g. zinc dust added, and the mixture was allowed to stand 22 hours. Steam distillation into an aqueous dimedon solution followed by adjustment of the pH to 5-6 (20) afforded the dimedon derivative of formaldehyde (0.145 g., 41.6%). The derivative alone and mixed with an authentic specimen melted at 190.5-191°. The reported melting point is 191-191.5°(21).

Acetic Acid from Saponified Crassin Acetate.--Crassin acetate (2.00 g.) was refluxed 1 1/2 hours with an aqueous methanolic solution of potassium hydroxide prepared from 0.96 g. of potassium hydroxide, 20 ml. of methanol and 6 ml. of water. After standing overnight, methanol was removed by concentrating the mixture on a steam bath. Addition of 3 ml. of water followed by acidification with sulfuric acid gave a tacky solid. The aqueous solution was decanted, and the solid was washed with three 5 ml. portions of water. Steam distillation of the combined water solutions, followed by neutralization of the distillate with dilute potassium hydroxide and concentration on a hot plate, gave a salt which was converted into crude p-phenylazophenacyl acetate (1.43 g.) in 91% yield. The derivative, recrystallized from alcohol, melted at 125-127° as reported (22), and the melting point was not depressed when the compound was mixed with an authentic specimen. Paper chromatography by the procedure of Kepner and co-workers (22) showed only p-phenylazophenacyl acetate to be present.

Duclaux values (found: 6.8, 7.1, 7.2; reported: 6.8, 7.1, 7.4) (23) of the steam distillate of another sample of crassin acetate indicated the presence of acetic acid.

Lithium Aluminum Hydride Reduction of Crassin Acetate.--A solution of 3.00 g. of crassin acetate in 175 ml. of dry ether was added to a stirred suspension of 2.5 g. of lithium aluminum hydride in 60 ml. of ether. The mixture was stirred two hours and let stand overnight. Decomposition of excess lithium aluminum hydride with methanol followed by an excess of water gave a white sludge which remained in the water layer. The mixture was decanted and the aqueous portion was extracted with ether. After drying over sodium sulfate, the combined ether solutions afforded 2.46 g. of white amorphous solid. This weight of product corresponded to 91.8% yield based on a molecular weight of 324 obtained from the formula $C_{19}H_{32}O_4$ which would result from a loss of an acetyl group and conversion of a lactone into two hydroxyl groups.

Catalytic Hydrogenation of the Lithium Aluminum Hydride Reduction Product of Crassin Acetate.--The amorphous solid (208.1 mg.) in glacial acetic acid was reduced with hydrogen at atmospheric pressure in the presence of 0.2 g. of Adams catalyst. Absorption of 32 ml. of hydrogen (25°, 740 mm.) in 1 1/4 hours indicated the presence of 1.98 reducible bonds per mole.

Dehydrogenation of Crassin Acetate and the Lithium Aluminum Hydride Product of Crassin Acetate.--Crassin acetate (0.5 g.) mixed with 2 g. of powdered selenium in a sealed tube was heated at 263° for 12 hours. The iso-octane extract showed an absorption maximum at 256 mμ in the ultraviolet region.

The lithium aluminum hydride reduction product of crassin acetate (0.5 g.) and 2 g. of selenium heated at 280° for 24 hours gave 0.30 g. of oil which partially solidified upon addition of hexane. Chromatog-

raphy of the reaction product over Magnesol (Westvaco Chlor-Alkali Division of the Food Machinery and Chemical Corporation) in hexane afforded 0.06 g. of liquid which showed an ultraviolet absorption maximum at 258 mμ in iso-octane, and failed to form a picrate. Elution with benzene gave a brown viscous oil (0.16 g.) which showed a doublet in the carbonyl region of the infrared spectrum.

Oil from Pterogorgia Americana.--An oil obtained by vacuum distillation of the pentane extract of Pterogorgia americana by Dr. Leon S. Ciereszko showed only end absorption in the ultraviolet region in ethanol.

Quantitative Peracid Determination of Unsaturation of the Oil from Pterogorgia Americana.--A solution of the oil (386.4 mg.) in 75 ml. of 0.1980 N perbenzoic acid in chloroform was prepared and treated by the procedure described above for the Plexaura crassa oil. Liberated iodine was titrated with 0.0997 N sodium thiosulfate solution. Results indicated the presence of 1.6 double bonds as tabulated below. Calculations were based on the oil being a dicyclic diolefinic sesquiterpene which was recently suggested by Ciereszko and Attaway (9) on the basis of obtaining a molecular weight of 204 by mass spectral analysis of a purified sample of the oil.

Time (hrs.)	1.0	11.0	35	79
$Na_2S_2O_3$ (ml.)	3.06	2.68	2.46	2.34
Moles of $Ph\text{-}CO_3H$ per mole of sesquiterpene oil	0.90	1.28	1.49	1.61

Properties of the Solid from Xiphigorgia Anceps.--A crystalline solid was obtained by continuous pentane extraction of the cortex of

Xiphigorgia anceps and purified by chromatography over alumina in chloroform by Dr. Leon S. Ciereszko. The solid melted at 93-94°, had $[\alpha]_D^{28}$ + 13.2° (c 2.8, chloroform), showed only end absorption in the ultraviolet region (in alcohol) and characteristic infrared absorption bands ($CHCl_3$) at 3.45, 3.53, 5.72, 6.07 w, 6.88, 7.29 w, 7.57, 8.35, 8.97, 9.26, 9.75, 10.54 w, 11.25 w, and 11.65 μ.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; O, 17.75; SE, 180; MW, 360. Found: C, 73.04, 73.28; H, 9.60, 9.43; O, 17.45; SE, 177; MW, 367; C-Me, 2.

Another sample obtained by Ciereszko showed carbon and hydrogen contents of 73.13 and 9.20 respectively.

Saponification of the Solid from Xiphigorgia Anceps (9).--From 70 mg. of the solid Ciereszko obtained 60 mg. of an acid which melted at 125-127° as the only isolable product upon saponification.

Anal. Calcd. for $C_{22}H_{36}O_6$: C, 66.64; H, 9.15. Found: C, 66.53; H, 9.63.

Catalytic Hydrogenation of the Solid from Xiphigorgia Anceps.--The solid (349.9 mg.) in 32 ml. of ethyl acetate was reduced with hydrogen at atmospheric pressure in the presence of 0.3 g. of Adams catalyst. Absorption of 54.8 ml. of hydrogen (27°, 737 mm.) indicated the presence of 1.8 reducible bonds. Although the reaction appeared to be complete in 4 minutes, hydrogenation conditions were maintained 2 1/4 hours.

Filtration gave a large amount of the more insoluble reduction product mixed with catalyst. Extraction of the residue with hot ethyl

acetate afforded 97.9 mg. of material which melted at 138-139°. The melting point was unchanged after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.55; H, 10.07.

Concentration of the filtrate on a steam bath gave 139.8 mg. of solid which melted at 107-110°. After several recrystallizations from ethyl acetate, a constant melting point of 113-114° was obtained.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96; O, 17.56. Found: C, 71.81; H, 10.05; O, 18.19.

Lithium Aluminum Hydride Reduction of the Solid from Xiphigorgia Anceps.--The solid (0.34 g.) was reduced with 0.5 g. of lithium aluminum hydride by the procedure described above for crassin acetate. Recovered reduction product amounted to 0.30 g. of light brown oil.

Attempted Dehydrogenation of the Lithium Aluminum Hydride Reduction Product of the Solid from Xiphigorgia Anceps.--The lithium aluminum hydride reduction product of the solid from Xiphigorgia anceps (0.2 g.) was heated with 0.5 g. of sulfur at 185° for 9 hours in a sealed tube. Only ultraviolet absorption due to sulfur (10) was observed for the chloroform and methanol extracts of the reaction mixture.

SUMMARY

A sesquiterpene oil containing a (+)-cadinene as the principal component, palmitic acid and a C_{21} terpenoid lactone have been isolated from the lipid material of the gorgonian Plexaura crassa.

Preliminary chemical characterization of an oil from Pterogorgia americana and a solid from Xiphigorgia anceps has been initiated.

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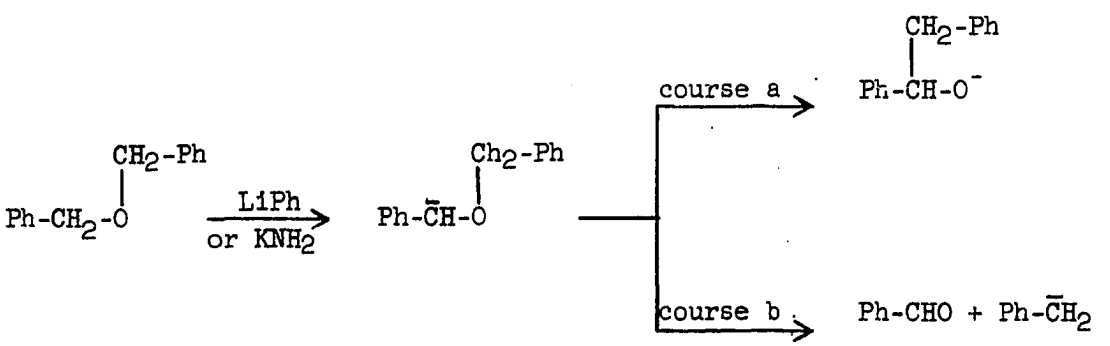
PART II

STEREOCHEMISTRY OF THE WITTIG REARRANGEMENT

INTRODUCTION

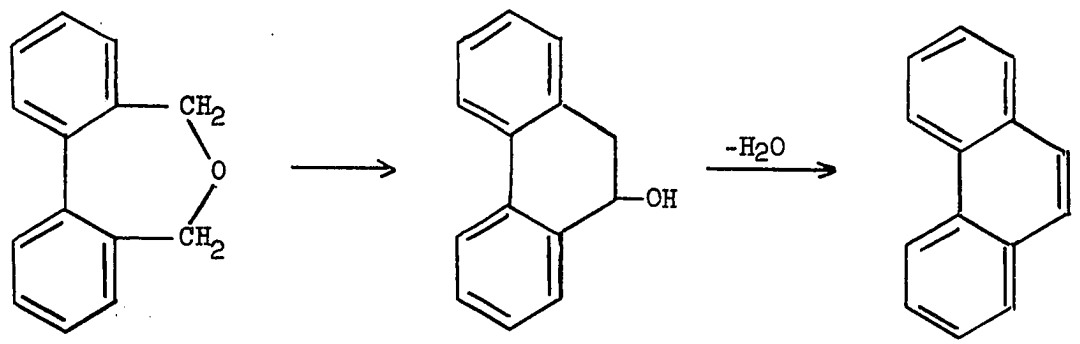
Many benzyl ethers, and ethers which have similarly activated hydrogen atoms may be rearranged to alcohols by strong bases such as phenyllithium (1) or potassium amide (2). Dibenzyl ether has been converted to 1,2-diphenylethanol by each of these strong bases as shown in course a.



This Wittig rearrangement presumably involves removal of an α-hydrogen of a benzyl group giving a carbanion which rearranges to the the alcoholate ion.

Benzyl ethers that have been rearranged include allyl (2), s-butyl (2,3) and methyl (1). Ethers with groups such as α-cyanobenzyl (4), α-methylbenzyl (5), benzhydryl (3,6,7,8) fluorenyl (4,9), desyl (10), and α- and γ-pyridyl (11,12) have also been studied.

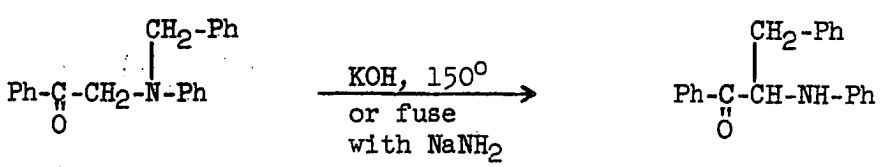
The reaction has been applied to the synthesis of phenanthrene (13,14) by rearrangement of diphenan to 9,10-dihydro-9-phenanthrol followed by dehydration.



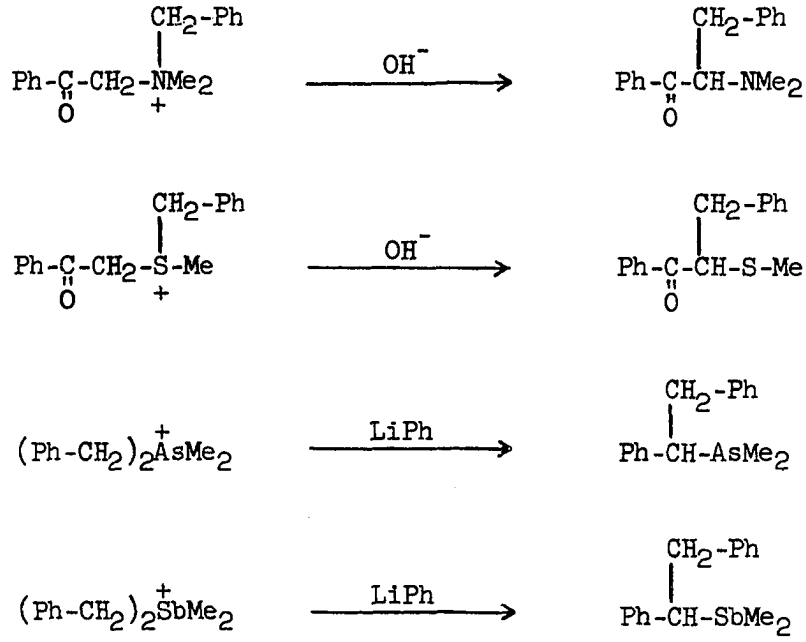
The rearrangement is often accompanied and occasionally superseded by an independent elimination reaction leading to cleavage of the ether as shown in course b. This cleavage has been examined by Cram, Kingsbury, and Langemann (15).

The conversion of benzyl ethyl ether to benzyl alcohol and ethylene by propylsodium (7) and potassium amide (2) is an example of still another type of β-elimination occasionally encountered in attempted rearrangements of some ethers.

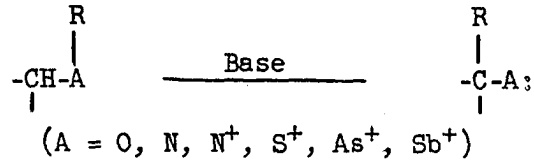
The rearrangement has recently been effected with certain tertiary amines (16,17) as well as with ethers. This is illustrated in the equation below by the rearrangement of N-benzyl-N-phenacylaniline to α-anilinophenethyl phenyl ketone by potassium hydroxide at 150° and by fusion with sodium amide.



The closely related Stevens rearrangement of quaternary ammonium and sulfonium salts has been extended to include the corresponding arsonium and stibonium compounds (18). Typical examples are given in the following equations.



Each of these cases of base catalyzed 1,2-shifts results in the replacement of an active hydrogen in the benzyl (or similar) group by the group (R) which migrates from the hetero atom.

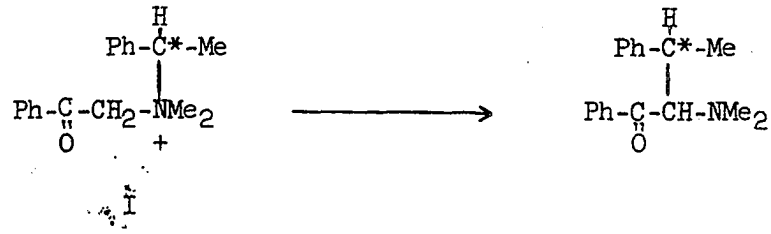


(A = O, N, N^+, S^+, As^+, Sb^+)

The 1,2-shifts of quaternary ammonium salts have been studied more thoroughly with respect to mechanism than those of other types of compounds. Rearrangements of a mixture of quaternary ammonium salts

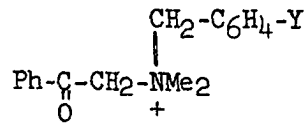
first established the intramolecular nature of the reaction (19). The individual salts rearranged at comparable rates. In the mixture, each was found to rearrange independently without interchange of migrating groups.

This intramolecular interpretation was supported (20) by the rearrangement of optically active α-methylbenzylphenacyldimethylammonium bromide (I) with almost complete retention of optical activity in the asymmetric center (C*).



I

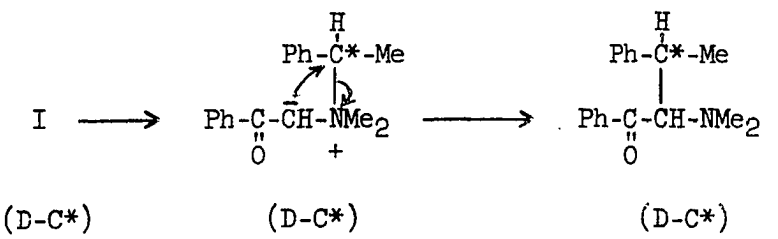
An internal nucleophilic displacement mechanism was suggested by kinetic studies of the rearrangement. Thus, Thomson and Stevens (21) found the rearrangement to be a unimolecular reaction which exhibited a limit to increase of rate by base. The relative rates of isomerization of a series of ammonium salts substituted in the para position of the migrating benzyl group decreased in the order NO_2 > halogen > Me, H > OMe.



The order is consistent with that observed in the S_N2 nucleophilic displacements on the corresponding benzyl halides by basic ions (22). If the groups had migrated as carbonium ions (S_N1), the reverse order of rates would have been expected on the basis of the relative

unimolecular rates of hydrolysis of the corresponding benzyl halides, insofar as they have been determined (23). Moreover, migration of an optically active group as a carbonium ion would be expected to lead to some racemization.

In the rearrangement of the optically active quaternary ammonium salt discussed above, no attempt had been made to relate the spatial configuration of the optical center of the product with that of the starting material. This reaction was re-examined (24) and was shown to proceed not only without racemization, but also with retention of configuration of the optical center.



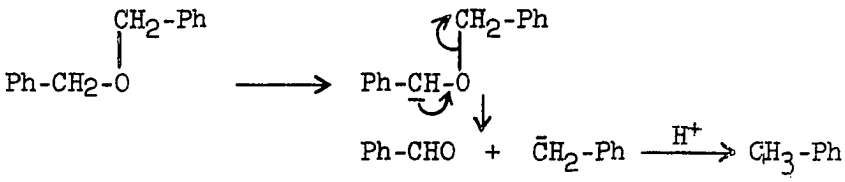
This retention of configuration of the migrating group completed the evidence required to demonstrate that the reaction proceeded by an intramolecular nucleophilic displacement (S_Ni) mechanism as proposed (2).

Available evidence does not permit establishment of a definite mechanism for the 1,2-shift in the ether-carbinol rearrangement as was the case in the rearrangement of quaternary ammonium salts.

It has been suggested (2) that the rearrangement probably proceeds by an internal displacement (S_Ni) of the migrating group by the carbanion as in the Stevens rearrangement. Hauser and Kantor found that the relative ease of rearrangement of a series of ethers decreased in the order benzyl, allyl $>$ s-butyl $\gg$ neopentyl, phenyl. This order is related

directly to the relative ease of bimolecular displacement of the corresponding halides (S_N2) by basic anions (22), but also to their solvolytic, or S_N1, reactivity.

Stability of rearrangement products to reaction conditions has demonstrated that cleavage of the ethers, mentioned earlier, is a side reaction competing with the rearrangement. This was shown by submitting the rearrangement product of dibenzyl ether to the conditions of the rearrangement (potassium amide in refluxing ether) (2); the alcohol was recovered unchanged and none of the cleavage products were isolated. The cleavage fragments probably arose from the initially formed ether carbanion in an elimination reaction competing with the rearrangement.



This stability of isomerization product was also demonstrated in studies of the rearrangement of s-butyl benzyl ether (25).

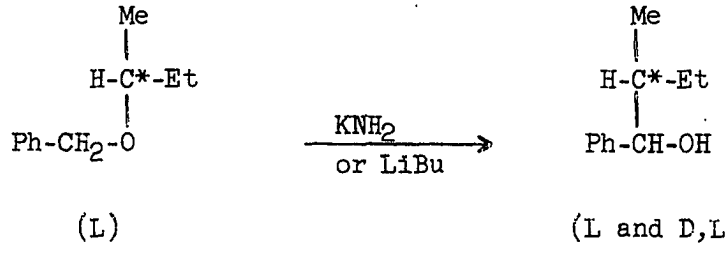
An alternate mechanism considered (1,2) for the rearrangement was the possible recombination of these cleavage fragments to give the isomerization products.



This possibility was rejected because the use of phenyllithium and butyllithium as basic catalysts did not lead to formation of isolable amounts of the benzaldehyde addition products. If benzaldehyde had been

an intermediate, benzhydrol and butylphenyl carbinol, respectively, should have been formed by reaction with the catalysts. However, Schöllkopf (3) has recently proposed this fragmentation and recombination mechanism (discussed below) on the basis of extensive racemization observed in rearrangements of ethers in which the migrating group is optically active s-butyl. The mechanism is compatible with the absence of formation of benzaldehyde addition products when the cleavage-recombination is considered to proceed entirely within a solvent envelope.

Rearrangement of two ethers containing the optically active s-butyl group has shown that the process does not occur by a purely S_Ni type mechanism. Hauser and Kantor (25) rearranged optically pure s-butyl benzyl ether by refluxing with potassium amide in ether for one week. The product, s-butylphenyl carbinol, was 75% racemized; however, the optical form in excess was the same as that in the starting ether, which indicated migration with considerable retention of configuration. This is in the range of 13 to 33% retention of activity observed by Schöllkopf (3) upon rearrangement of the same ether with butyllithium in several solvents.



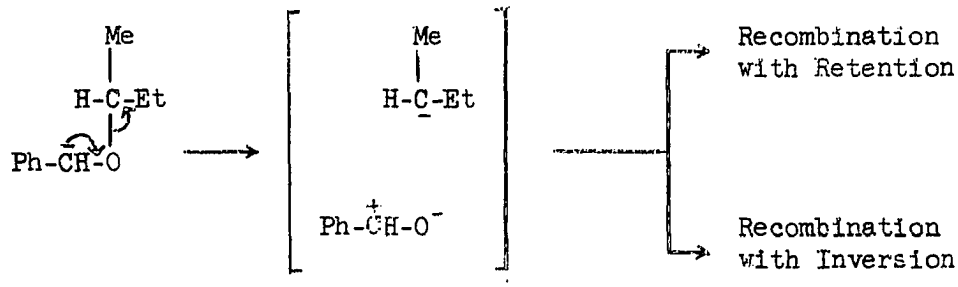
(L) (L and D,L)

Racemization was shown (3) not to occur before rearrangement by recovery of optically active starting material after partial reaction.

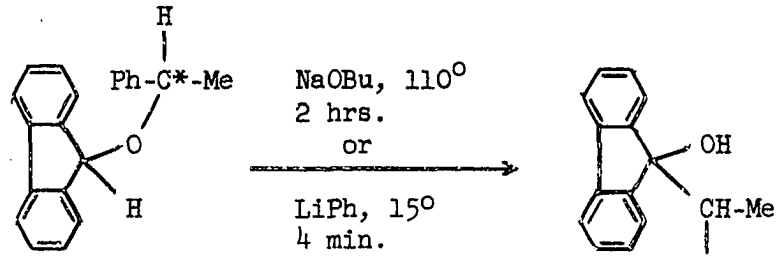
Also, subjecting samples of optically active product to both reaction and workup conditions showed that racemization did not occur after the rearrangement.

In another instance, the butyllithium catalyzed rearrangement of optically active s-butyl benzhydryl ether gave the expected alcohol with only 5% retention of optical activity (3).

On the basis of this low degree of retention of optical activity, Schöllkopf has proposed a mechanism of cleavage of the carbanion to an ion-pair intermediate followed by recombination of the fragments with both retention and inversion of configuration of the s-butyl group. Because of the inability of the carbanion to hold configuration, this route would be expected to lead to extensive racemization.



The mechanism would appear to be supported by the rearrangement (4) of (-)-9-fluorenyl-α-methylbenzyl ether to completely racemic 9-α-methylbenzylfluoren-9-ol. The optically active ether was rearranged by heating with sodium n-butoxide in n-butanol at 110° for two hours and by reaction with phenyllithium at 15° for four minutes. In both instances, the product showed no rotation in alcohol or in chloroform.

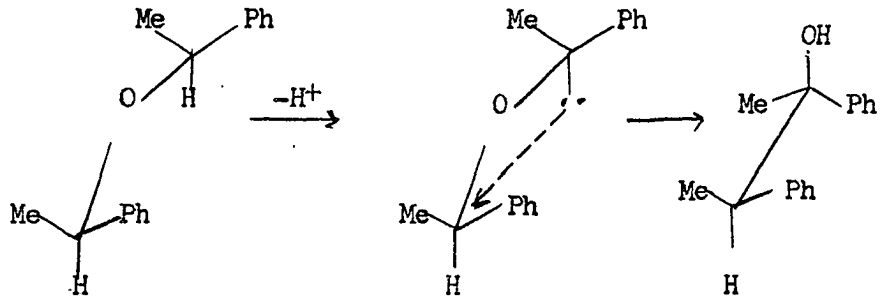


(-) (±)

The mechanism proposed by Schöllkopf does not appear to represent the predominant route in the rearrangement of meso and d,l bis (α-methylbenzyl) ethers. The individual ethers have been shown to rearrange without formation of an equilibrium mixture which would be expected if the reaction involves cleavage of the anion to an ion-pair intermediate. Thus, Weinheimer (5) showed that rearrangement of meso bis (α-methylbenzyl) ether gave erythro 2,3-diphenyl-2-butanol as the most readily isolable product, and that the d,l ether led to the threo alcohol. The individual ethers may not have been pure because the similarity of their physical properties hindered complete separation of the synthetic diastereomeric mixture. Nevertheless, there was a predominance of stereospecificity in the rearrangement of each of the ethers.

In addition to evidence indicating stereospecificity, Weinheimer found an inversion of configuration in the rearrangements of meso and d,l bis (α-methylbenzyl) ethers. The inversion could have occurred in either the migrating group or the ionized carbon atom. The latter interpretation was preferred on the basis of observed retention of configuration of the migrating group in the Stevens rearrangement, and the partial retention in the isomerization of s-butyl benzyl ether discussed above.

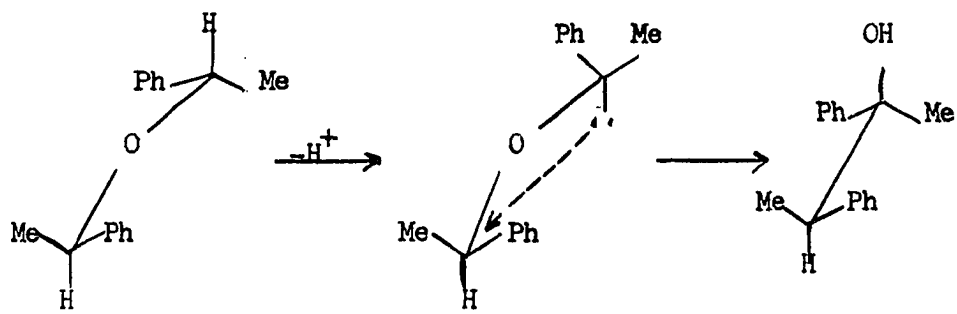
If there had been no inversion, the meso ether would be expected to give a threo 2,3-diphenyl-2-butanol as shown in the equation below. By the same course, the d,l ether should give the erythro alcohol.



meso threo

(In these figures, the bonds from the carbon at the top are directed away from the reader, while those from the lower carbon are directed toward the reader.)

Upon rearrangement, the meso ether actually gave erythro 2,3-diphenyl-2butanol and the racemic ether gave the threo alcohol. An inversion must have occurred during the rearrangement.



meso D-L' erythro

The mechanism proposed (5) to account for the observed predominance of stereospecificity and inversion of configuration was a con-

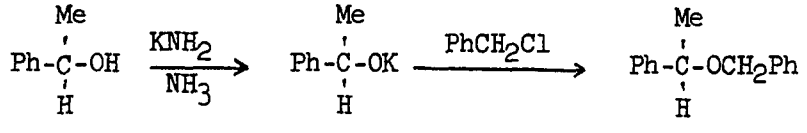
certed process of inversion of the carbanion and rearrangement to the alcoholate ion.

The present work was undertaken to test this proposal by a study of the rearrangement of two optically active ethers, benzyl-α-methylbenzyl ether and bis (α-methylbenzyl) ether.

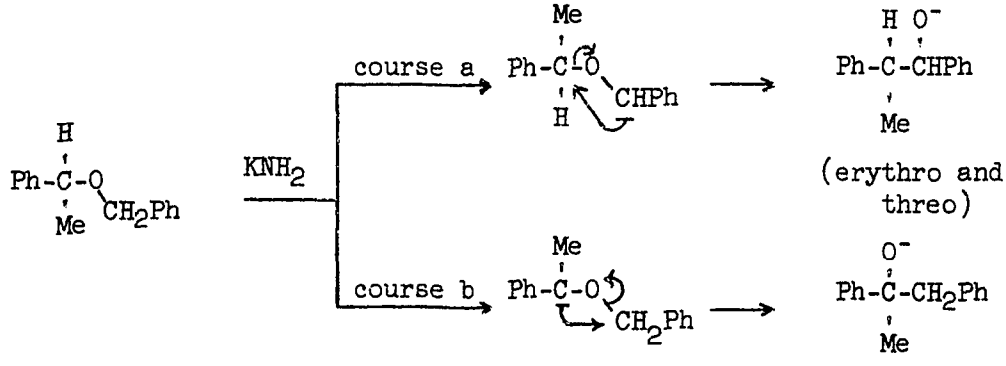
DISCUSSION

The ether selected for study of the stereochemical result in the migrating group in the Wittig rearrangement was benzyl-α-methylbenzyl ether. Selection of this compound was based on the premise that a high degree of stereospecificity might be observed in the migration of a benzylic group, which is inherently more susceptible to displacement reactions than are simple alkyl groups. It was also felt that this ether would rearrange readily even at low temperature, and thus lend itself to a practicable study of the effect of temperature on the stereochemistry of the migrating group.

A Williamson synthesis, based on the reaction between benzyl chloride and α-methylbenzyloxide ion, was developed for the preparation of the ether. The method finally selected employed the potassium alkoxide in liquid ammonia solvent, and led to excellent yields of ether in a reaction period of only a few hours. Use of the sodium alkoxide under the same conditions led to a slightly inferior yield of ether, whereas in ether as the reaction medium, a decidedly poorer yield was obtained after a reaction period as long as twenty hours.



Rearrangement of benzyl-α-methylbenzyl ether might be expected to give either a mixture of erythro- and threo-1,2-diphenylpropanols (course a), or benzylmethylphenyl carbinol (course b), or both, depending upon which benzyl group migrates.



From the results of earlier studies (2,5), in which dibenzyl ether was found to rearrange much more readily than bis (α-methylbenzyl) ether, it was expected that rearrangement via course a would be much faster than that proceeding via course b. In practice, it was found that the rearrangement proceeded smoothly in a few hours in liquid ammonia and exclusively by course a. There was no evidence from the distillation behavior of the product, its infrared spectrum, or other physical properties, of the presence of any of the tertiary alcohol which would be produced by course b. Since this alcohol was shown to be stable to the reaction conditions, the possibility of its formation and subsequent destruction by a fragmentation reaction could also be eliminated.

The ease of rearrangement of benzyl-α-methylbenzyl ether in liquid ammonia lies between that of dibenzyl ether (complete in less than one hour) and that of bis (α-methylbenzyl) ether (less than 50% reaction after six hours). This sequence suggests that the rate of rearrangement

depends upon the ease with which base can abstract a proton from the reacting benzyl group.

Optically active benzyl-α-methylbenzyl ether was prepared from active α-methylbenzyl alcohol using the Williamson method developed for the inactive ether. From alcohol of 98.3% optical purity, ether having a rotation of 80.3° was obtained. It was anticipated that the ether would have a lower optical purity than the starting alcohol, since its alkoxide salt, an intermediate in the ether synthesis, has been shown by Doering (26) to undergo rather extensive racemization in the presence of air. This optical instability is apparently due to the participation of the alkoxide in the Meerwein, Ponndorf-Oppenauer equilibrium with trace amounts of acetophenone resulting from air oxidation.

To determine the extent of racemization that had occurred in the present synthesis, the ether was submitted to catalytic hydrogenolysis in the presence of palladium-charcoal, for the purpose of determining the optical purity of the recovered α-methylbenzyl alcohol, which should be representative of the optical purity of the α-methylbenzyl group in the ether.

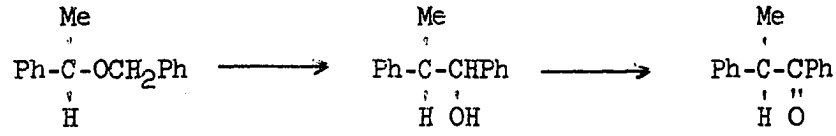
$$\mathrm{Ph\text{-}\overset{\overset{\mathrm{Me}}{|}}{\underset{\underset{\mathrm{H}}{|}}{C}}\text{-}OCH_2Ph} \xrightarrow[Pd.C]{H_2} \mathrm{Ph\text{-}\overset{\overset{\mathrm{Me}}{|}}{\underset{\underset{\mathrm{H}}{|}}{C}}\text{-}OH} + PhCH_3$$

In each of two experiments, the infrared spectrum of the recovered alcohol showed a trace of carbonyl absorption at 5.96 μ. In one case, the carbonyl contaminant was removed by reduction with lithium aluminum hydride, giving alcohol of 94.1% optical purity. If the carbonyl absorption had been due to acetophenone, the actual optical purity of the

alcohol derived from the ether would have been slightly greater than 94.1%, since the reduction would produce some racemic alcohol. In the other case, removal of the carbonyl contaminant using Girard's "T" reagent was attempted, but the recovered alcohol still showed a trace of carbonyl absorption. Its optical purity was 93.9%. On the basis of 94.1% optical purity in the recovered alcohol, and equivalent optical purity in ether having a rotation of 80.3°, optically pure benzyl-α-methylbenzyl ether was calculated to have a rotation of 85.3°.

It might be noted that no special precautions for the exclusion of air were taken in the ether synthesis, and that the level of racemization observed was quite low in view of the earlier experience of Doering, who used solvents other than ammonia. The more favorable outcome in the present study may be due to a more or less automatic exclusion of air by the rapidly evaporating ammonia, and to the low temperature of reaction.

Rearrangement of the optically active ether produced an alcohol fraction showing a significant degree of optical activity. However, since the product contained a new asymmetric center, and presumably was a mixture of diastereomers whose optical rotations are known (27) to be different, it was impossible to evaluate the stereochemical change occurring in the migrating α-methylbenzyl group from the alcohols directly. Accordingly, the new asymmetric center was eliminated by chromic acid oxidation of the alcohols to the corresponding ketone, in which the lone center of asymmetry was that present in the ether itself. Since this oxidation had been shown previously (27) to not racemize the resulting ketone, the configuration and optical purity of the α-methyl-



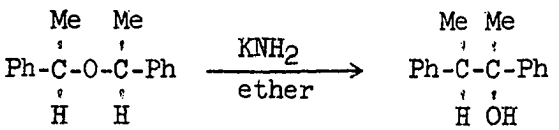
benzyl group in this compound could be compared with those of the same group in the starting ether. Starting with D-(-) ether of 34.4% optical purity, rearrangement and oxidation led to D-(+)-α-methyl deoxybenzoin of 21.8% optical purity. This corresponds to 63% retention of optical purity, and predominant retention of configuration in the rearrangement step.

The above rearrangement was conducted in liquid ammonia at its boiling point, -33°. The rearrangement was also conducted in liquid ammonia maintained at -60°, and in diethyl ether at its reflux temperature, 35°. The stereochemical result in the low temperature run was practically identical with that in boiling ammonia, ether of 32.2% optical purity leading, after oxidation of the alcohol, to α-methyldeoxybenzoin of 21.3% optical purity. Thus, 64% of the optical activity was retained, with predominant retention of configuration in the migrating group. In ether at the higher temperature, predominant retention of configuration was again observed, but the degree of retention of optical activity was 70%.

The relatively high degree of retention of configuration of the migrating group in these rearrangements 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 Schöllkopf (3). However the racemized portion of the product may well have been formed by the

mechanism he suggested. Additional evidence bearing on the possible operation of both mechanisms was obtained in the rearrangement of optically active bis (α-methylbenzyl) ether.

The rearrangement of this ether had been studied previously by Weinheimer (5), who demonstrated that the separate d,l and meso modifications rearranged predominantly to the threo and erythro forms of 2,3-diphenyl-2-butanol, respectively.



The ethers, rather high boiling liquids exhibiting very little difference in boiling point, were prepared by the sulfuric acid catalyzed dehydration of α-methylbenzyl alcohol. As would be anticipated by the method of synthesis, the product was a mixture of the two diastereomeric forms, now shown to be roughly 1:1 in composition. Weinheimer separated the two diastereomers by extremely tedious fractional distillation of large quantities of the mixture, finally obtaining small portions of both the low boiling form, n_D^{25} 1.5363, and the high boiling form, n_D^{25} 1.5400. In all probability, even these specimens were still contaminated to some extent by the alternate isomers. The low boiling ether was demonstrated to be the d,l modification by the distillation behavior of partially active ether, which was prepared from active α-methylbenzyl alcohol, and which showed a steady decline in optical activity of successive fractions.

In the present work, the stereochemical result of rearrangement of optically active bis (α-methylbenzyl) ether was investigated. The

active ether was prepared as before, but no attempt was made to separate the mixture of isomers so obtained. Instead, the rearrangement was conducted with the mixture, the optical purity and configuration of the products being evaluated after their separation and purification by chromatography.

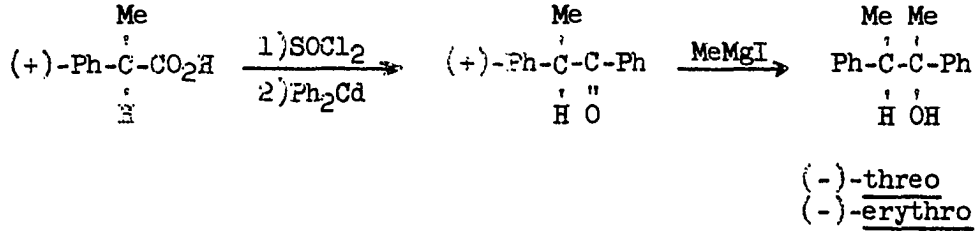
The configuration of the active ether in the starting mixture was expected to be the same as that of the alcohol from which it was synthesized. This expectation was confirmed by the following hydrogenolysis experiment, which also provided data for calculation of the optical purity of the active ether present in the mixture.

The partially active ether employed in this hydrogenolysis was prepared from 56.6% optically pure (-)-α-methylbenzyl alcohol, and exhibited α_D^{25} -20.22 and n_D^{25} 1.5384. Hydrogenolysis of this ether was interrupted at 50% completion, the unreacted ether then exhibiting α_D^{25} -26.74 and n_D^{25} 1.5373. The increased activity of the recovered ether was interpreted as the result of faster hydrogenolysis and destruction of the meso form, and was supported also by the change in refractive index in the direction expected on enrichment in the d,l ether. The (-)-α-methylbenzyl alcohol produced in the hydrogenolysis had an optical purity of 4.5%, which represented the composite purity of active alcohol derived from active d,l ether, and the necessarily inactive alcohol derived from meso ether.

A sample of inactive ether having n_D^{25} 1.5391 was shown in a gas chromatographic analysis (courtesy of the Barber-Colman Company) to be composed of 53% of one and 47% of the other ether. The major component was eluted first, and was considered to be the d,l isomer on the basis

that this isomer is the lower boiling of the two. Using this knowledge on the composition-refractive index relationship, and the results of the hydrogenolysis experiment described above, it was calculated (see last section of Experimental) that the active ether employed in the hydrogenolysis was 11.2% optically pure d,l form, that the refractive indices of pure d,l and meso ethers were n_D^{25} 1.5360 and n_D^{25} 1.5418, respectively, and that optically pure ether has a rotation of 307°.

The configurations and rotations of the alcohols produced in the rearrangement were established by their preparation from (+)-hydratropic acid via (+)-methyldeoxybenzoin.



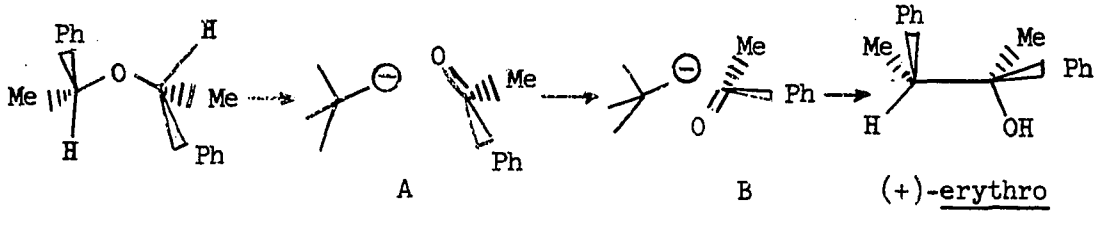
From the rotations of the individual alcohols obtained after chromatographic separation, the optically pure threo and erythro forms were calculated to have rotations of -47.4° and -53.6° (EtOH), respectively.

The configuration of the α-methylbenzyl group in the two (-)-alcohols is necessarily the same as that in (+)-hydratropic acid. It has also been shown (15) that this group has identical configurations in (+)-hydratropic acid and (-)-α-methylbenzyl alcohol, from which (-)-bis(α-methylbenzyl) ether was prepared. The ether, in turn, produced (-)-α-methylbenzyl alcohol on hydrogenolysis, confirming the expectation that no configurational change occurred in the synthesis of the ether.

The rearrangement was conducted with a sample of mixed ethers

having α_D^{30} + 28.83 and n_D^{25} 1.5388, and calculated to contain d,l ether of 18.2% optical purity. The resulting mixture of alcohols was separated by chromatography, and the (+)-threo isomer was found to have retained 74.2% of the activity of the starting ether. Again, the α-methylbenzyl group had migrated predominantly with retention of configuration. Surprisingly, the erythro alcohol from this rearrangement displayed optical activity at a level of 9.7% of that of the starting ether. Clearly, the active alcohol could not have arisen from the meso ether, and must have been derived from the d,l form. It is noteworthy that this isomer had a positive rotation, and thus the same configuration in the migrating group as present in the active starting ether.

The high degrees of retention of configuration observed in the rearrangements of benzyl α-methylbenzyl ether and bis (α-methylbenzyl) ether appear, at first, to support the S_Ni interpretation of this reaction. However, the formation of optically active erythro-2,3-diphenyl-2-butanol from the latter ether can be rationalized best in terms of the fragmentation-recombination mechanism, involving reorientation of the acetophenone fragment relative to the α-methylbenzyl carbanion, which retains its configuration during this process:



If the carbanion can maintain asymmetry during the reorientation of A to B, 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.

EXPERIMENTAL

All melting points and boiling points are uncorrected.

Optical rotations were obtained with a Gaertner L-320 Polarimeter. The symbol α_D refers to rotations of neat samples in a one decimeter tube. Alcohol refers to 95% ethanol.

Preparation of (±)-Benzyl-α-Methylbenzyl Ether in Ethyl Ether as Solvent.--A mixture of 0.51 mole (65 g.) of benzyl chloride and 0.5 mole of sodium α-methylbenzylate, prepared from 61 g. of α-methylbenzyl alcohol and 0.5 mole of sodium amide (from 11.5 g. of sodium), in 300 ml. of dry ethyl ether was refluxed gently on a steam bath for 12 hours. After adding an additional 29.5 g. of benzyl chloride, reflux was continued for another 22 hours. The ether solution was washed with water and dried over sodium sulfate, solvent was removed and excess benzyl chloride, 30.48 g., b. p. 42-45° at 4.2 mm., was distilled from the mixture. Distillation of the residue gave (i) forerun, 5.56 g., b. p. to 55° and 0.9 mm., (ii) 2.95 g., b.p. 130-136° at 5.8 mm., n_D^{25} 1.5480, and (iii) 77.23 g., b.p. 136° at 5.4 mm., n_D^{25} 1.5492. A viscous brown residue remained in the pot.

Fractions (ii) and (iii) were combined and redistilled giving (i') 1.30 g., b. p. 88-91.5° at 0.5 mm., n_D^{25} 1.5464, (ii') 4.21 g., b. p. 91-97° at 0.5 mm., n_D^{25} 1.5484, and (iii') 73.20 g., b. p. 93-95° at 0.5 mm., 1.5492. Fraction (iii') represents 69% yield of benzyl-α-methyl-

benzyl ether.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 85.00; H, 7.36.

Preparation of (±)-Benzyl-α-Methylbenzyl Ether in Liquid Ammonia as Solvent.--Racemic α-Methylbenzyl alcohol (61 g., 0.5 mole) dissolved in 100 ml. of dry ethyl ether was added to 1 l. of liquid ammonia containing 0.5 mole of potassium amide prepared from 19.55 g. (0.5 mole) of potassium. After stirring 1/4 hour, 94.5 g. (0.75 mole) of benzyl chloride was added to the mixture and the ammonia was evaporated at room conditions (about 3 hours). The reaction mixture was decomposed with 100 ml. of water and extracted with ether. The ether extract was washed three times with 50 ml. portions of water, twice with 20 ml. of N hydrochloric acid, and again, three times with 50 ml. portions of water. The solution was dried over sodium sulfate, solvent was removed, and excess benzyl chloride (25.42 g.) was distilled from the mixture. Distillation of the residue gave (i) 2.77 g. of forerun, b. p. 90-94° at 0.45 mm.; (ii) 9.52 g., b. p. 94-97° at 0.45-0.4 mm., $n_D^{25.8}$ 1.5484; (iii) 6.81 g., b. p. 97° at 0.4 mm., $n_D^{25.5}$ 1.5488; (iv) 69.42 g., b. p. 96-99.5° at 0.4-0.5 mm., $n_D^{25.5}$ 1.5490; (v) 6.13 g., b. p. 99.5-101° at 0.5-0.55 mm., n_D^{25} 1.5492. The combined fractions, (ii) through (v), represent an 86.6% yield of ether.

In a similar experiment, 0.5 mole of sodium α-methylbenzylate was treated with 0.75 mole of benzyl chloride. The mixture was stirred overnight and worked up by the procedure described below. Distillation gave (i) 59.50 g. of unreacted benzyl chloride and alcohol b. p. to 89° at 0.75 mm.; (ii) 3.13 g., b. p. 91-101° at 0.7 mm., n_D^{25} 1.5462; (iii)

4.39 g., b. p. 101-102° at 0.7 mm., n_D^{25} 1.5488; and (iv) 63.18 g., b. p. 102° at 0.7 mm., n_D^{25} 1.5495. Fractions (iii) and (iv) represent a 63.7% yield of ether.

Preparation of (-)-Benzyl-α-Methylbenzyl Ether.--Optically active (-)-α-methylbenzyl alcohol, b. p. 66-66.8° at 2.95 mm., n_D^{25} 1.5247, and α_D^{25} -42.94° (neat), was prepared by the method of Downer and Kenyon (28). The reported (29) values for optically pure alcohol are b. p. 93.8° at 12 mm., n_D^{25} 1.5248, and α_D^{25} -43.7° (neat). The alcohol (15.45 g., 0.126 mole), in 60 ml. of dry ethyl ether was added to 0.126 mole potassium amide (from 4.93 g. of potassium) in 600 ml. of liquid ammonia in 8 minutes and the mixture was stirred 5 minutes. Benzyl chloride (63.76 g., 0.5 mole) was added in 15 minutes and the mixture was stirred at room conditions until the ammonia evaporated (about 5 hours). Water (100 ml.) was added, the layers were separated, and the aqueous layer was extracted three times with 50 ml. portions of ether. The combined organic material was washed with 25 ml. of water, 10 ml. of N hydrochloric acid and finally three times with 25 ml. portions of water. The solution was dried over sodium sulfate and, after removal of solvent, excess benzyl chloride (42.63 g.) was distilled from the mixture. Distillation of the residue gave (i) 0.71 g. of forerun, b. p. to 68° at 3.4 mm.; (ii) 1.27 g., b. p. 117-118° at 2.2 mm., n_D^{25} 1.5432; (iii) 22.17 g., b. p. 118° at 2.2 mm., n_D^{25} 1.5486, α_D^{25} -79.19° (neat); (iv) 1.12 g., b. p. 118° at 2.2 mm., n_D^{25} 1.5510. Fraction (iii) was redistilled giving (i') 1.71 g. of forerun, b. p. 106-110° at 1.15 mm., n_D^{25} 1.5458; (ii') 1.66 g., b. p. 110-104.2° at 1.15-0.95 mm., n_D^{25} 1.5482, α_D^{25} -79.99° (neat); (iii') 16.54 g., b. p. 104.2-106° at 1 mm., n_D^{25} 1.5489, α_D^{25} -80.32° (neat); (iv') 1.40 g.,

b. p. 106° at 1 mm., n_D^{25} 1.5500. Fraction (iii') represents a 61.9% yield of ether, and was shown to be at least 94.1% optically pure as indicated below.

Hydrogenolysis of (-)-Benzyl-α-Methylbenzyl Ether.--Optically active (-)-benzyl-α-methylbenzyl ether (5.91 g., α_D^{25} -8.35°) in a mixture of 10 ml. of ethanol and 10 ml. of acetic acid was catalytically reduced with hydrogen in the presence of 0.5 g. of 5% palladium on charcoal. After absorption of 650 ml. of hydrogen in 4 hours (27°, 738 mm.), the reaction was stopped. The mixture was filtered, treated with 15 g. of potassium carbonate in 150 ml. of water, and extracted with 50 ml. of ether. The extract was washed three times with 20 ml. of water and was dried over sodium sulfate. After solvent was removed distillation of the residue to 60° (bath temperature) at 0.7 mm. afforded 1.0 g. in the α-methylbenzyl alcohol fraction. The distillate, which showed a trace of carbonyl absorption in the infrared, was treated with 0.1 g. of lithium aluminum hydride in 15 ml. of ethyl ether. Excess reducing agent was decomposed with methanol, water was added and the mixture was extracted with ether. After drying and removal of solvent, distillation to 91° (bath temperature) at 9.5 mm. gave 0.43 g. of (-)-α-methylbenzyl alcohol which had α_D^{25} -4.28° (neat), calculated to be 9.79% optically pure. Its infrared spectrum showed no carbonyl group absorption. Based on the activity of the recovered alcohol, the ether having α_D^{25} -80.3° has an optical purity of 94.1%; and the calculated value for the optically pure ether is α_D^{25} -85.3° (neat).

The impurity showing absorption in the carbonyl region of the infrared spectrum may have been either acetophenone or the acetate of

the alcohol. Lithium aluminum hydride reduction would not affect the asymmetric center of the acetate. However, reduction of acetophenone would give racemic alcohol resulting in a slightly low value for the calculated optical purity of the ether.

In another experiment, 8.53 g. of (-)-benzyl-α-methylbenzyl ether having α_D^{25} -12.02° was submitted to hydrogenolysis by the procedure described above. The reaction was stopped after absorption of 1204 ml. of hydrogen (26.5°, 739 mm.) in 5 hours. The mixture was filtered and the filtrate was treated with 30 g. of sodium carbonate and 350 ml. of water. After extraction with ether, phases were separated, and the ether layer was dried over sodium carbonate. Solvent was removed, and distillation of the residue gave 1.18 g., b. p. 60° at 1.7 mm., α_D^{25} -6.08° (neat) in the α-methylbenzyl alcohol fraction.

The infrared spectrum of the distillate indicated a trace of carbonyl absorption. Treatment of the distillate with Girard's "T" reagent followed by distillation at 83° (bath temperature) at 4.8 mm. gave 0.52 g. of 14.05% optically active α-methylbenzyl alcohol having α_D^{25} -6.14° (neat). The infrared spectrum obtained on a relatively thick film (0.025 mm.) showed a very weak, broad absorption peak at about 5.99μ indicating incomplete removal of the carbonyl compound.

The rotation of the alcohol affords a calculated value of 93.9% optical purity for the ether having α_D^{25} -80.3°.

Rearrangement of (-)-Benzyl-α-Methylbenzyl Ether in Liquid Ammonia at -33°.--The ether [18.0 g., 0.085 mole, α_D^{25} -29.32° (neat), 34.4% optical purity] in 28 ml. of ethyl ether was added to 0.17 mole of potassium amide (from 6.64 g. of potassium) in 300 ml. of liquid ammonia,

and the mixture was stirred three hours. Ether (100 ml.) was added, and excess amide was decomposed by addition of 100 ml. of water. Layers were separated and the water layer was extracted one time with 100 ml. of ether. The combined ether solution was washed 8 times with 50 ml. of water in an attempt to remove benzamide, which forms by reaction of excess base with the cleavage product, benzaldehyde (2). The ether solution was dried over sodium sulfate and solvent was removed. Distillation of the residue gave (i) 0.53 g. of forerun, b. p. to 60° at 2.5 mm., (ii) 2.08 g., b. p. 118° at 0.9-0.7 mm., (iii) 2.98 g., b. p. 118-117° at 0.7-0.65 mm., (iv) 3.79 g., b. p. 117-115° at 0.62-0.58 mm., α_D^{25} -21.21° (neat), (v) 1.31 g., b. p. 115° at 0.58 mm. The presence of benzamide was indicated by carbonyl absorption in the infrared spectrum of the distillate. Fractions (iii), (iv), and (v) were combined in 30 ml. of hexane and washed ten times with 10 ml. of water, dried over sodium sulfate, and solvent was removed. Distillation of the residue gave (i') 1.86 g., b. p. 119-116° at 0.86 mm., (ii') 2.02 g., b. p. 116° at 0.65 mm., $[\alpha]_D^{25}$ -12.1 ± 0.2° (c 4.28, chloroform), (iii') 1.46 g., b. p. 116-115° at 0.65 mm., α_D^{25} -21.61° (neat) and $[\alpha]_D^{25}$ -11.9 ± 0.2° (c 4.28, chloroform), (iv) 0.97 g., b. p. 115° at 0.65 mm. The infrared spectra of fractions (ii') and (iii') indicated that less than 0.5% benzamide remained.

(+)-Methyldeoxybenzoin by Oxidation of Alcohols from Rearrangement of (-)-Benzyl-α-Methylbenzyl Ether at -33° (27).--The diastereomeric mixture of 1,2-diphenyl-1-propanols (2.12 g.) from fractions (ii') and (iii') of the above rearrangement in 10 ml. of benzene was added at room temperature over a period of 2 1/2 hours to a stirred solution of 4.76 g. of sodium chromate, 6.3 ml. of sulfuric acid, 3.5 ml. of acetic acid, and

21 ml. of water. Stirring was continued for 2 hours, layers were separated, and the aqueous phase was extracted with 10 ml. of benzene. The combined organic material was washed with three 10 ml. portions of water, one time with 20 ml. of saturated sodium carbonate solution, and again three times with 10 ml. of water. The solution was dried over sodium sulfate and the solvent was removed. Distillation of the residue at 128° (bath temperature) at 1 mm. gave 0.96 g. (45.7%) of 21.8% optically pure methyldeoxybenzoin which melted at 45-50°, and showed $[\alpha]_D^{25}$ +45.2 ± 0.2° (c 4.36, chloroform). The reported values for optically pure methyldeoxybenzoin are b. p. 114-116° at 1 mm. (27), m. p. 34-35°, $[\alpha]_D^{17}$ 207° (c 1.07, chloroform) (30). The reported melting point of the (±)-ketone is 50-52° (30).

Since the ether was 34.4% optically pure, the level of activity in the ketone represents 63% retention of optical activity in the rearrangement.

Rearrangement of (-)-Benzyl-α-Methylbenzyl Ether in Liquid Ammonia at -60°.--To 300 ml. of a solution of 0.158 mole of potassium amide (from 6.16 g. of potassium) in liquid ammonia at -65 to -60° was added 16.7 g. (0.0788 mole) of 33.2% optically pure (-)-benzyl-α-methylbenzyl ether, α_D^{25} -28.36°, in 28 ml. of dry ethyl ether. The temperature of the stirred mixture was maintained at -65 to -60° for four hours. Ether (100 ml.), followed by 100 ml. of water, was added and stirring was continued overnight. The reaction mixture was worked up as described above in the rearrangement at -33°. Distillation of the reaction mixture gave (i) 8.06 g., b. p. 102-117° at 0.76 mm. and (ii) 3.56 g., b. p. 117-119° at 0.75 mm. The infrared spectrum of fraction (i) showed that it was

unreacted ether containing some alcohol. Absorption at 9.1μ in the infrared spectrum of fraction (ii) indicated the presence of some ether.

Redistillation of fraction (ii) to 130° (bath temperature) at 0.65 mm. gave (i') 2.08 g. and (ii') 1.23 g. The total rotation of fraction (ii'), α_D^{25} -22.3° (neat), was slightly high because of incomplete removal of the unreacted ether as indicated by the infrared spectrum of the compound.

(+)-Methyldeoxybenzoin by Oxidation of the Alcohols from Rearrangement in Liquid Ammonia at -60°.--A benzene solution (8 ml.) of 1.20 g. of fraction (ii') from the above rearrangement was oxidized by the procedure described earlier with a mixture of 2.69 g. of sodium chromate, 3.56 ml. of sulfuric acid, 1.98 ml. of acetic acid, and 11.88 ml. of water. Distillation of the reaction mixture to 130° (bath temperature) at 0.8 mm. gave 0.39 g. (24%) of 21.3% optically active (+)-methyldeoxybenzoin which melted at 45-49° and showed $[\alpha]_D^{25}$ +44.1° (c 4.6, chloroform). The infrared spectrum of the ketone showed no absorption characteristic of benzyl-α-methylbenzyl ether which was present in the rearrangement product before oxidation.

The level of activity of the ketone represented 64% retention of optical activity in the rearrangement.

Rearrangement of (-)-Benzyl-α-Methylbenzyl Ether in Ethyl Ether at 35°.--To 0.124 mole of potassium amide (from 4.83 g. of potassium) in 50 ml. of ethyl ether was added 13.12 g. (0.0618 mole) of 8.1% optically active (-)-benzyl-α-methylbenzyl ether, α_D^{25} -6.91°, in 20 ml. of ethyl ether. The mixture was refluxed on a steam bath 16 hours, and worked up as described earlier for the rearrangement in liquid ammonia at -33°.

Distillation gave (i) 0.08 g. of forerun, (ii) 6.33 g., b. p. 118-121° at 0.75 mm., and 4.10 g. of viscous residue. Because of carbonyl absorption in the infrared spectrum, fraction (ii) in 20 ml. of hexane was washed ten times with 10 ml. portions of water and redistilled. The alcohol mixture, 4.93 g., collected at 118° at 0.65 mm. showed carbonyl absorption at 5.96 μ. Treatment of the mixture with Girard's "T" reagent and redistillation gave (i') 0.92 g., b. p. 125-127° at 1.1-1.5 mm., (ii') 2.04 g., b. p. 127° at 1.5 mm., α_D^{25} -5.83° (neat), and (iii') forced, 0.63 g. The infrared spectra of fractions (i') -(iii') showed weak absorption bands at 5.95 μ, indicating a trace of impurity still remained in the mixture of the alcohols.

(+)-Methyldeoxybenzoin by Oxidation of the Alcohols from Rearrangement in Ether at 35°.--A benzene solution (10 ml.) of 1.83 g. of fraction (ii') from the above rearrangement was oxidized by the procedure described earlier with a mixture of 4.76 g. of sodium chromate, 6.3 ml. of sulfuric acid, 3.5 ml. of acetic acid and 21 ml. of water. Distillation of reaction product to 124° (bath temperature) at 1 mm. gave 0.56 g. (31%) of 5.7% optically active (+)-methyldeoxybenzoin which melted at 43-49° and showed $[\alpha]_D^{25}$ +11.9° (c 9.32, chloroform).

The activity of the ketone represented 70% retention of activity in the rearrangement.

Test of Optical Stability of (-)-1,2-Diphenyl-1-propanol with Potassium Amide.--Optically active (-)-1,2-diphenyl-1-propanol 5.16 g., 0.024 mole, α_D^{25} -2.15° (neat) in 60 ml. of ethyl ether was stirred with 0.048 mole of potassium amide (from 1.89 g. of potassium) in 300 ml. of liquid ammonia until the ammonia evaporated and stirring was continued

at room temperature for a total of 12 hours. The mixture was decomposed with water and extracted with ether. After removal of the solvent, distillation at 130° (bath temperature) at 0.7 mm. gave 4.35 g. (84%) of distillate. The recovered alcohol had an optical rotation of α_D^{25} -2.14° (neat); and its infrared spectrum (liquid) was identical with that of the starting alcohol.

Test of Stability of Benzylmethylphenyl Carbinol with Potassium Amide.--Benzylmethylphenyl carbinol was prepared in a yield of 54% from benzyl magnesium bromide and acetophenone. The alcohol melted at 49-50°; the reported m.p. is 51° (31). A solution of 4.24 g. (0.02 mole) of the alcohol in 20 ml. of ether was added to 0.04 mole of potassium amide (from 1.56 g. of potassium) in 125 ml. of liquid ammonia. After two hours, when most of the ammonia had evaporated, 50 ml. of ether was added and stirring was continued at room temperature for 1 1/2 hours. The mixture was decomposed by the addition of 50 ml. of water. Ether extraction afforded about 4 g. of recovered alcohol which had an infrared spectrum (supercooled liquid) that was identical with the starting material.

Preparation of Optically Active bis (α-Methylbenzyl) Ether.--Optically active (+)-α-methylbenzyl alcohol had b. p. 90.5-91.2° at 13.25 mm., n_D^{25} 1.5242 and α_D^{26} +38.94° (neat). The maximum rotation value of α_D^{25} +43.7° (27) was used to calculate an optical purity of 89.1% on the basis of a negligible difference in rotation between 25 and 27° C. Thus, a sample of levo alcohol showed α_D^{25} -42.94° (neat) and α_D^{27} -42.91° (neat).

A mixture of 18.10 g. (0.148 mole) of the active alcohol, and

6.4 ml. of a 1:1 (volume) solution of sulfuric acid and water was allowed to stand at room temperature for 72 hours with occasional shaking. A hexane extract of the mixture was washed with water, sodium carbonate solution, again with water, and then dried over sodium sulfate. After removal of the solvent, distillation gave (i) 1.11 g., b. p. 97-100° at 1.75 mm., n_D^{25} 1.5365; (ii) 1.19 g., b. p. 100-108° at 1.75 mm., n_D^{25} 1.5379; and (iii) 12.85 g., b. p. 105-108° at 1.75 mm., n_D^{25} 1.5388, α_D^{30} +28.83° (neat). Fraction (iii) represents a yield of 76.7% of the diastereomeric mixture of ethers. By reaction of 72.5% optically active (-)-α-methylbenzyl alcohol as described above for 20 hours, Weinheimer (5) obtained the ether having b. p. 133-134° at 7 mm., n_D^{25} 1.5383, and α_D^{25} -22.56° (neat).

Hydrogenolysis of Optically Active bis (α-Methylbenzyl) Ether.--Optically active ether was prepared as described above from 56.6% optically pure (-)-α-methylbenzyl alcohol which had n_D^{25} 1.5249 and α_D^{25} -24.72° (neat). The ether [9.20 g., $n_D^{25.6}$ 1.5382, and α_D^{25} -20.22° (neat)] in 20 ml. of a mixture of acetic acid and ethanol (1:1, volume) was catalytically reduced with hydrogen in the presence of 0.5 g. of 5% palladium on charcoal. After absorption of 800 ml. of hydrogen (30° C., 737 mm.) in 5 1/2 hours, the reaction was stopped and the mixture was filtered. Acetic acid was removed by adding 15 g. of sodium carbonate in 150 ml. of water. The aqueous solution was twice extracted with 50 ml. portions of ether. The combined organic material was washed three times with 50 ml. of water, dried over sodium sulfate and solvent was removed. Distillation of the residue gave (i) forerun, 0.76 g., b. p.

59-54° at 53-35 mm.; (ii) 0.27 g., b. p. 55-59° at 3.7-4.0 mm.; α_D^{25} -1.98° (neat); (iii) 0.64 g., b. p. to 119° at 3.3 mm.; (iv) 4.02 g., b. p. 119-120° at 3.3 mm., n_D^{25} 1.5373, α_D^{25} -26.74° (neat).

The recovered α-methylbenzyl alcohol, fraction (ii), was 4.5% optically active and its infrared spectrum showed only a trace of carbonyl absorption.

Rearrangement of Optically Active bis (α-Methylbenzyl) Ether.--The ether [12.58 g., 0.556 mole, n_D^{25} 1.5388, α_D^{30} +28.83° (neat)] in 50 ml. of ethyl ether was added to 0.111 mole of potassium amide (from 4.35 g. of potassium) in 150 ml. of liquid ammonia. The mixture was stirred until the ammonia evaporated (about 1 hour) and then was heated with a mantle until the ethyl ether refluxed gently. Ether was allowed to distil from the flask, and the stirred mixture was heated at 50-60° for 96 hours. Ether (50 ml.), followed by 50 ml. of water was added to the reaction flask, the layers separated, and the aqueous layer extracted four times with 30 ml. portions of ether. The organic solution was dried over sodium sulfate and the solvent was removed. The light brown residue 9.52 g. was chromatographed on alkaline alumina (75 x 3.5 cm.) as indicated in the table below.

Fractions (85-87) had $[\alpha]_D^{30}$ +6.41° (c 4.13, ethanol), (88-100) had $[\alpha]_D^{28}$ +6.31° (c 11.03, ethanol), and (101-122) had $[\alpha]_D^{28}$ +4.97° ± 0.3 (c 5.90, ethanol). An alcohol solution of fractions (101-122) was treated with activated charcoal, filtered, and evaporated to dryness on a steam bath. The residue showed $[\alpha]_D^{31}$ +5.70° (c 3.46, ethanol) and $[\alpha]_D^{31}$ +18.97° (c 3.74, chloroform).

Solvent	Volume (l)*	Fraction Numbers	Wt. of Eluted Material (g)	Melting Point**
Hexane	17.7	1-11	trace	oil
Hexane-Ether (19:1)	6.7	12-14	0.11	(oily solid)
"	3.25	15-21	0.79	79-85.5
"	11.9	22-76	2.65	84-86
"	1.15	77-78	0.10	57-79
" (9:1)	0.7	79-80	0.07	(oily solid)
"	1.85	81-84	0.67	45-65
"	13.4	85-117	2.85	65-67
"	4.75	118-128	0.81	63-66
Ether	0.7	129-130	0.33	63-64

*The volume collected for most of the individual fractions 15-130 was 0.35 l.
**Minimum and maximum observed in indicated fractions.

Fractions (23-28) showed $[\alpha]_D^{29}$ +0.61° (c 0.83, ethanol), and fractions (60-70) had $[\alpha]_D^{30}$ +0.87° (c 3.47, ethanol). Combined fractions of the higher melting alcohol (0.75 g.) flash distilled with a flame at 0.3 mm. gave 0.45 g. of distillate which melted at 85-86° and had $[\alpha]_D^{30}$ +0.95° (c 8.40, ethanol).

The melting points of the alcohols were not depressed by admixture with the corresponding racemic alcohols prepared from methyldeoxybenzoin by Mr. W. E. Marsico of this laboratory.

Rotations of the various chromatography fractions of the individual alcohols differ because of the presence of impurities. This was indicated by increase in rotation after treatment with activated charcoal.

The corresponding levo alcohols, prepared from (+)-hydratropic acid (described below) afforded optical purities of approximately 1.6% for the erythro alcohol (m. p. 85°) and 12.2% for the threo alcohol (m. p. 65°). These percentages are based on the maximum observed rotations of the respective carbinols from the rearrangement. However, they are probably slightly high because the (+)-methyldeoxybenzoin, on which the calculated maximum rotations of the synthetic alcohols are based, was not pure.

Synthesis of Optically Active erythro and threo 2,3-Diphenyl-2-butanols.*--Reaction of diphenyl cadmium with hydratropyl chloride, prepared from 4.4 g. of (+)-hydratropic acid (27) afforded 4.02 g. of (+)-methyldeoxybenzoin which boiled at 111° at 0.3 mm. and had $[\alpha]_D^{26}$ +57.46° (c 5.96, chloroform). The reported (30) maximum rotation is $[\alpha]_D^{17}$ +207° (c 1.07, chloroform). The observed rotation is low because of contamination of the ketone with biphenyl, separated later. Cleavage of ethyl ether by the diphenyl cadmium reagent provides an alcohol for the formation of ethyl hydratropate, (32), which is probably also an impurity in the ketone. An infrared spectrum was not obtained, thus, the presence of the ester was not verified.

Reaction of the ketone with methyl magnesium iodide and chromatography of 2.5 g. of the product on alumina in hexane gave (i) 0.25 g. of biphenyl, identified by melting point and mixed melting point with an authentic specimen; elution with 5% ether in hexane gave 0.25 g. of erythro (-)-2,3-diphenyl-2-butanol m. p. 80-83°, $[\alpha]_D^{34}$ -16.5° (c 4.0, ethanol); (iii) 0.65 g., m. p. 62-65°; and (iv) 0.23 g. of threo (-)-

*This experiment was performed by Mr. J. O. Bledsoe.

2,3-diphenyl-2-butanol, m. p. 65-67°, $[\alpha]_D^{34}$ -14.6° (c 3.6, ethanol) and $[\alpha]_D^{34}$ -48.5° (c 4.02, chloroform).

On the basis of the methyldeoxybenzoin being 27.8% optically active, optically pure erythro (-)-2,3-diphenyl-2-butanol has a calculated rotation $[\alpha]_D^{25}$ -59.7° (ethanol) and the threo alcohol has a calculated maximum rotation $[\alpha]_D^{25}$ -52.5° (ethanol).

Test of Optical Stability of threo-2,3-Diphenyl-2-butanol with Potassium Amide.--Several fractions from the above rearrangement of bis (α-methylbenzyl) ether, which were contaminated with some dust, were combined to give 0.9 g. (0.004 mole) of the threo alcohol (m. p. 65°) which had an optical rotation of $[\alpha]_D^{29.5}$ +5.80° (c 4.4, ethanol). The alcohol was heated at 60-80° with 0.008 mole of potassium amide (from 0.31 g. of potassium) for 5 days by the procedure in the bis (α-methylbenzyl) ether rearrangement described above. An ethanol solution of the recovered material (0.9 g.) was treated with activated charcoal and evaporated to dryness on a hot plate. The observed rotation of $[\alpha]_D^{33}$ +6.29° (c 4.1, ethanol) of the recovered alcohol was higher than that of the starting material because treatment with charcoal afforded some purification.

Calculation of Rotation of Optically Pure (+)-bis (α-Methylbenzyl) Ether.--The mixed ether submitted to hydrogenolysis had $[\alpha]_D^{25}$ -20.22° and n_D^{25} 1.5384. Recovered ether had $[\alpha]_D^{25}$ -26.74° and n_D^{25} 1.5373. Ordinary ether having n_D^{25} 1.5391 was shown by gas chromatography to be composed of 53% d,l and 47% meso isomers.

Let x = fraction of d,l ether in mixture after hydrogenolysis.

Let y = fraction of d,l ether in mixture before hydrogenolysis

Let z = total difference in refractive indices of the two ethers.

Let α = rotation of d,l ether present in the ether mixture.

1. Then: $x\alpha = -26.74$; $y\alpha = -20.22$; and $x = 1.32\ y$

2. Also: $xz = yz = 1.5373 - 1.5384 = -0.0011$

3. And: $xz - 0.53z = 1.5373 - 1.5391 = -0.0018$

4. Next: $xz - \frac{xz}{1.32} = -0.0011$ or $z = \frac{-0.00454}{x}$

Substituting in 3, and solving, $x = 0.87$

$y = 0.66$

$z = 0.0052$

Calculation of the amounts of α-methylbenzyl alcohol produced from the meso and d,l forms of ether leads to the conclusion that 1.12 g. of a total of 2.49 g. formed in 50% reaction was derived from the d,l ether. Since the alcohol produced was 4.5% optically pure, it can be shown that the d,l ether was 10% optically pure, and that 100% pure ether would have $[\alpha]_D^{25}$ -307°.

SUMMARY

1. In two cases, a study of the stereochemistry of the migrating group in the Wittig rearrangement showed that migration occurred with predominant retention of configuration, but also with significant racemization. Optically active (-)-benzyl-α-methylbenzyl ether was rearranged by potassium amide with 63-70% retention of optical activity. A mixture of optically active and meso bis (α-methylbenzyl) ethers rearranged to threo and erythro 2,3-diphenyl butanols both of which were optically active.

   An interpretation of the results supports both S_Ni and cleavage-recombination courses which have been previously proposed for the rearrangement.

2. Preparation of (-)-benzyl-α-methylbenzyl ether with a high degree of optical purity was accomplished by the Williamson synthesis in liquid ammonia as solvent.

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