THE REACTION BETWEEN GRIGNARD REAGENTS AND THE OXIRANE RING

NORMAN G. GAYLORD[1] AND ERNEST I. BECKER

Chemical Laboratories of the Polytechnic Institute of Brooklyn, Brooklyn, New York

Received April 12, 1951

CONTENTS

I. INTRODUCTION

Soon after the discovery of the Grignard reaction in 1900, E. E. Blaise (25) treated ethylene oxide with an organomagnesium compound in the hope of obtaining a primary alcohol. From that time to the present the reaction between ethylene oxide and substituted ethylene oxides has been the focus of a great deal of experimental investigation. It has been found useful for the preparation of primary, secondary, and tertiary alcohols, and in some cases aldehydes and ketones have been recovered from the reaction mixtures. These are the well-known facts regarding the course of the reaction. What is less generally known and understood is that the reaction is often accompanied by rearrangement of the oxide with the formation of unexpected products. The structure of the epoxy compound as well as that of the Grignard reagent and the reaction conditions appear to influence the course of the reaction. It is primarily the purpose of this paper to discuss the course of the reaction of Grignard reagents with epoxides.

Ethylene oxide will first be discussed, followed by separate discussion of

---

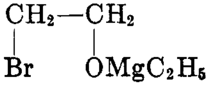
[1] Present address: Yerkes Research Laboratory, E. I. du Pont de Nemours & Co., Buffalo 7, New York.

epoxides as they become more complex. Finally, a general review of the mechanism will be given. The reaction of lithium and of sodium organometallics is included in this discussion, primarily because of the small number of such references and their close relation to the magnesium derivatives.

II. 1,2-Epoxy Compounds

A. *Ethylene oxide (see table 1)*

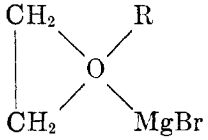
Blaise (25), in 1902, obtained ethylene bromohydrin as the predominant product from the reaction of ethylene oxide and ethylmagnesium bromide. To explain this product a new method of cleavage of organomagnesium compounds was postulated: namely, instead of the usual division into the groups R and MgBr, in this case a splitting into RMg and Br occurred with the subsequent formation of



$$\begin{array}{ll} CH_2 & —CH_2 \\ | & | \\ Br & OMgC_2H_5 \end{array}$$

which, upon hydrolysis with water, gave the bromohydrin, CH_2BrCH_2OH.

However, in 1903, Grignard (95, 96) found that if the ether is distilled from the reaction mixture an exothermic reaction takes place and, upon hydrolysis, 1-butanol is obtained in 82 per cent yield with no trace of bromohydrin. Similarly, isoamylmagnesium bromide gives a 75 per cent yield of 5-methyl-1-hexanol ("isoheptanol"). Grignard explained this by a two-phase mechanism. In the first phase of the reaction an addition complex is formed between the organomagnesium compound and ethylene oxide. This so-called "oxonium" compound was assigned the following formula:



I

Upon hydrolysis the ethylene oxide is liberated along with the hydrocarbon, magnesium bromide, and magnesium hydroxide. The ethylene oxide and magnesium bromide then react to give ethylene bromohydrin, according to the earlier report of Wurtz (228).

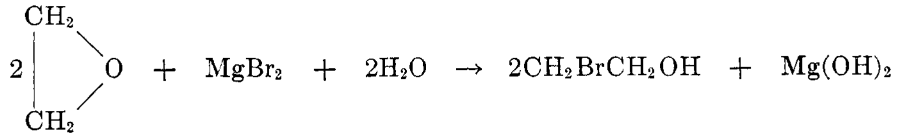


TABLE 1

Reaction of ethylene oxide with Grignard reagents

GRIGNARD REAGENT FROM ALKYL HALIDES	CONDITIONS*	PRODUCT	YIELD		REFERENCE
			Alcohol	Halohydrin	
			per cent	*per cent*	
RBr	A	RCH_2CH_2OH	Small amount		(25)
		Ethylene bromohydrin		Main product	
1-Bromoethane	C	1-Butanol	82	0	(95, 96)
	—	1-Butanol	Good	—	(108)
	A, E	Ethylene bromohydrin			(149)
	B, C	1-Butanol			
	B(2:1)	Ethylene bromohydrin	63.6	81	(167)
	E(2:1)	1-Butanol	60	81.6	
	A(2:1)	Ethylene bromohydrin	72	45	(117)†
	D(1:1)		79	11	
	F(2:1)	1-Butanol	88	0	
1-Chloroethane	A(1:1)	Ethylene chlorohydrin	54.6	22.0	(120)†
	A(2:1)		80.3	69.4	
	D(1:1)	1-Butanol	45.9	16.4	
1-Bromopropane	A(2:1)	Ethylene bromohydrin	75	43	(117)†
	D(1:1)		76	6	
	F(2:1)	1-Pentanol	90	0	
1-Chloropropane	A(1:1)	Ethylene chlorohydrin	39.5	31.5	(120)†
	A(2:1)		66.4	54.0	
	D(1:1)	1-Pentanol	49.9	32.0	
2-Bromopropane	A(2:1)	Ethylene bromohydrin	70	45	(117)†
	D(1:1)		74	7	
	F(2:1)	3-Methyl-1-butanol	85	0	
2-Chloropropane	A(1:1)	Ethylene chlorohydrin	34.5	35.1	(120)†
	A(2:1)		54.8	58.0	
	D(1:1)	3-Methyl-1-butanol	46.5	19.5	
	E	3-Methyl-1-butanol	60		(221)

TABLE 1—*Continued*

GRIGNARD REAGENT FROM ALKYL HALIDES	CONDITIONS*	PRODUCT	YIELD		REFERENCE
			Alcohol	Halohydrin	
			per cent	*per cent*	
1-Bromobutane....	D	1-Hexanol	50		(216)
	D	1-Hexanol	60–62		(57)
	A(2:1)	Ethylene bromohydrin	71	41	(117)†
	D(1:1)		70	5	
	F(2:1)	1-Hexanol	82	0	
	D	1-Hexanol	65		(46)
		2-Hexanol	10.1‡		
	F	1-Hexanol	43.5		
		2-Hexanol	0.8‡		
1-Chlorobutane....	A(1:1)	Ethylene chlorohydrin	39.0	25.5	(120)†
	A(2:1)		69.6	60.1	
	D(1:1)	1-Hexanol	45.8	36.8	
2-Bromobutane....	A(2:1)	Ethylene bromohydrin	65	51	(117)†
	D(1:1)		65	9	
	F(2:1)	3-Methyl-1-pentanol	70	0	
2-Chlorobutane....	A(1:1)	Ethylene chlorohydrin	25.6	30.9	(120)†
	A(2:1)		40.9	61.5	
	D(1:1)	3-Methyl-1-pentanol	35.1	23.9	
1-Bromo-2-methyl propane.........	—	4-Methyl-1-pentanol	—		(178)
	A(2:1)	Ethylene bromohydrin	69	41	(117)†
	D(1:1)		64	3	
	F(2:1)	4-Methyl-1-pentanol	80	0	
1-Chloro-2-methyl propane..........	A(1:1)	Ethylene chlorohydrin	23.6	34.6	(120)†
	A(2:1)		35.2	60.4	
	D(1:1)	4-Methyl-1-pentanol	29.8	25.0	
1-Chloro-2-methyl-3-methoxypropane............	D	4-Methyl-5-methoxy-1-pentanol	74		(59)
2-Bromo-2-methyl-propane..........	A(2:1)	Ethylene bromohydrin	0§	50	(117)†
	D(1:1)		0	60	

TABLE 1—*Continued*

GRIGNARD REAGENT FROM ALKYL HALIDES	CONDITIONS*	PRODUCT	YIELD		REFERENCE
			Alcohol	Halohydrin	
			per cent	*per cent*	
2-Chloro-2-methyl propane	D	Ethylene chlorohydrin		—	(116)
	A(1:1)	Ethylene chlorohydrin	0	21.3	(120)†
	A(2:1)		0	48.1	
	D(1:1)		0	23.3	
	D	3,3-Dimethyl-1-butanol	13.2		(148)
1-Bromopentane	D	1-Heptanol	58		(216)
	A(2:1)	Ethylene bromohydrin	60	40	(117)†
	D(1:1)		69	10	
	F(2:1)	1-Heptanol	75	0	
2-Bromopentane	A(2:1)	Ethylene bromohydrin	50	44	(117)†
	D(1:1)		63	5	
	F(2:1)	3-Methyl-1-hexanol	60	0	
1-Bromo-3-methyl butane	C	5-Methyl-1-hexanol	75 (crude)	0	(95)
	A(2:1)	Ethylene bromohydrin	56	41	(117)†
	D(1:1)		59	4	
	F(2:1)	5-Methyl-1-hexanol	70	0	
	D	5-Methyl-1-hexanol	52.5		(35)
1-Bromo-2-methyl butane	A(2:1)	Ethylene bromohydrin	53	35	(117)†
	D(1:1)		58	9	
	F(2:1)	4-Methyl-1-hexanol	68	0	
2-Bromo-2-methylbutane	A(2:1)	Ethylene bromohydrin	0	48	(117)†
	D(1:1)		0	42	
	F(2:1)		0	0	
2-Chloro-2-methylbutane	A(2:1)	Ethylene chlorohydrin	0	35	(117)†
	D(1:1)		0	39	
	F(2:1)		0	0	
2-Bromo-3-methylbutane	A(2:1)	Ethylene bromohydrin	46	41	(117)†
	D(1:1)		40	10	
	F(2:1)	3,4-Dimethyl-1-pentanol	45	0	

TABLE 1—*Continued*

GRIGNARD REAGENT FROM ALKYL HALIDES	CONDITIONS*	PRODUCT	YIELD		REFERENCE
			Alcohol	Halohydrin	
			per cent	*per cent*	
1-Bromo-2,2-dimethylpropane...	C	4,4-Dimethyl-1-pentanol	30		(148)
1-Bromohexane.....	D	1-Octanol	71		(216)
	A(2:1)	Ethylene bromohydrin 1-Octanol	47	30	(117)†
	D(1:1)		49	4	
	F(2:1)		50	0	
2-Bromohexane.....	A(2:1)	Ethylene bromohydrin 3-Methyl-1-heptanol	40	47	(117)†
	D(1:1)		43	6	
	F(2:1)		55	0	
1-Chloro-3,3-dimethylbutane....	D	5,5-Dimethyl-1-hexanol	67		(188)
1-Bromo-5-methylhexane...........	B	7-Methyl-1-octanol	40		(35)
1-Bromoheptane....	D	1-Nonanol	55		(216)
1-Bromoöctane.....	D	1-Decanol	52		(216)
1-Chloro-4-methylpentadecane.....	B	6-Methyl-1-heptadecanol	66		(36)
1-Bromo-2-cyclohexylethane......	D	4-Cyclohexyl-1-butanol	47–53		(115)
1-Bromo-2-cyclohexylbutane......	D	4-Cyclohexyl-1-hexanol	37		(115)
Benzyl chloride....	A(2:1)	Ethylene bromohydrin 3-Phenyl-1-propanol	79	5	(117)†
	D(1:1)		73	3	
	D	3-Phenyl-1-propanol 2-(*p*-Tolyl)ethanol	48.5		(78)
m-Xylyl bromide...	—	3-(*m*-Tolyl)-1-propanol	45		(151)

TABLE 1—*Continued*

GRIGNARD REAGENT FROM ALKYL HALIDES	CONDITIONS*	PRODUCT	YIELD		REFERENCE
			Alcohol	Halohydrin	
			per cent	*per cent*	
p-Xylyl bromide	—	3-(*p*-Tolyl)-1-propanol (80%) 2-(2,5-Dimethylphenyl)ethanol (20%)	—		(151)
o-Xylyl bromide	—	2-(3,4-Dimethylphenyl)ethanol (90%) 2-(2,3-Dimethylphenyl)ethanol (10%)			(151)
2-(2-Biphenylyl)-1-bromoethane	B	4-(2-Biphenylyl)-1-butanol	39‡		(56)
3-Phenylpropyl bromide	A	5-Phenyl-1-pentanol	68		(187, 212)
Olefinic halides:					
2-Bromo-6-methyl-5-heptene	A	3,7-Dimethyl-6-octen-1-ol (rhodinol)	—		(61)
Acetylenic compounds:					
Acetylene, monosodium derivative		3-Butyn-1-ol	52		(181)
1-Propyne	—	3-Pentyn-1-ol	95		(125)
1-Butyne	B	3-Hexyn-1-ol Ethylene bromohydrin	28 25		(195)†
1-Butyne, sodium derivative		3-Hexyn-1-ol	47		(191)
1-Hexyne	—	3-Octyn-1-ol Ethylene bromohydrin 2-Butyl-4,5-dihydrofuran	"Substantially same yields as in 1-heptyne reaction"		(49, 50)

TABLE 1—*Continued*

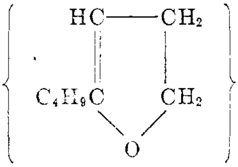
GRIGNARD REAGENT FROM ALKYL HALIDES	CONDITIONS*	PRODUCT	YIELD		REFERENCE
			Alcoho	Halohydrin	
			per cent	*per cent*	
1-Hexyne (*Continued*)	—		"Substantially same yields as in 1-heptyne reaction"		(49, 50)
1-Heptyne	B	3-Nonyn-1-ol	40		(62)
	—	3-Nonyn-1-ol	52		(6)
	—	3-Nonyn-1-ol	32‡	37‡	(49, 50)
		Ethylene bromohydrin			
		2-Amyl-4,5-dihydrofuran	30‡		
1-Octyne	B	3-Decyn-1-ol	40		(62)
Phenylacetylene	B	1-Phenyl-1-butyn-4-ol, $C_6H_5C{\equiv}C$-CH_2CH_2OH	40		(62)
	—	1-Phenyl-1-butyn-4-ol Ethylene bromohydrin 2-Phenyl-4,5-dihydrofuran	"Substantially same yield as with hexyne"		(49, 50)
Alicyclic halides:					
Chlorocyclopentane	—	2-Cyclopentylethanol	27		(158)
Bromocyclohexane	D	2-Cyclohexylethanol	44–53		(114, 115)
	A(2:1) D(1:1) F(2:1)	Ethylene bromohydrin 2-Cyclohexylethanol	45 50 60	42 8 0	(117)†
Aryl halides:					
Bromobenzene	D	2-Phenylethanol	"Approximating theory"		(1, 189)

TABLE 1—*Continued*

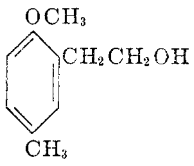
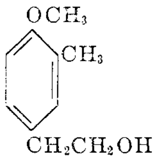
GRIGNARD REAGENT FROM ALKYL HALIDES	CONDITIONS*	PRODUCT	YIELD		REFERENCE
			Alcohol	Halohydrin	
			per cent	*per cent*	
Bromobenzene (*Continued*)....	A(2:1)	Ethylene bromohydrin	55	50	(117)†
	D(1:1)		58	42	
	F(2:1)	2-Phenylethanol	72	0	
	D	2-Phenylethanol			(104)
Chlorobenzene...	G	2-Phenylethanol	70 (95% pure)		(182)
	G	2-Phenylethanol	Good		(121)
4-Bromotoluene..	D	2-(*p*-Tolyl)ethanol	—		(1, 189)
2-Iodobiphenyl...	B	2-(2-Biphenylyl)-ethanol	76		(56)
m-(Trifluoromethyl)phenyl bromide........	—	2-(3-Trifluoromethylphenyl)ethanol	70		(197)
2-Bromoanisole...	D	2-(*o*-Anisyl)ethanol	35		(26)
	D	2-(*o*-Anisyl)ethanol	60		(103)
3-Bromoanisole..	D	2-(*m*-Anisyl)ethanol	62‡		(152)
	D	2-(*m*-Anisyl)ethanol	54		(70)
4-Bromoanisole..	D	2-(*p*-Anisyl)ethanol			(189)
2-Bromo-4-methylanisole..	D	2-(3-Methyl-6-methoxyphenyl)ethanol  	36		(26)
4-Bromo-2-methylanisole..	D	None	—		(26)
	D	2-(3-Methyl-4-methoxyphenyl)ethanol  	—		(1, 189)

TABLE 1—*Continued*

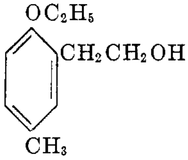
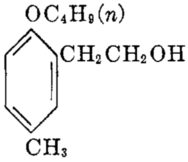
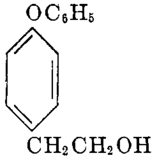
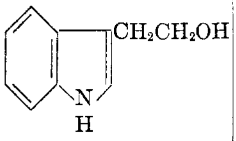
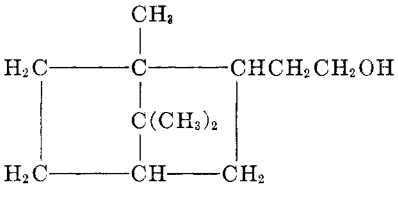
GRIGNARD REAGENT FROM ALKYL HALIDES	CONDITIONS*	PRODUCT	YIELD		REFERENCE
			Alcohol	Halo-hydrin	
			per cent	*per cent*	
2-Bromo-4-methylphenetole......	D	2-(6-Ethoxy-3-methylphenyl)-ethanol 	40		(26)
2-Bromo-4-(*n*-butoxy)toluene.	D	2-(6-Butoxy-3-methylphenyl)-ethanol 	37		(26)
4-Bromophenoxybenzene........	C	2-(4-Phenoxyphenyl)-ethanol 	52		(70)
1-Bromonaphthalene............	C	2-(1-Naphthyl)-ethanol	68, 63‡		(43, 175)
	—	2-(1-Naphthyl)-ethanol	—		(192)
1-Iodo-6-methoxynaphthalene..	C	2-(6-Methoxy-1-naphthyl)ethanol	51.5‡		(41)

TABLE 1—*Concluded*

GRIGNARD REAGENT FROM ALKYL HALIDES	CONDITIONS*	PRODUCT	YIELD		REFERENCE
			Alcohol	Halohydrin	
			per cent	*per cent*	
2-Bromonaphthalene.	C	2-(2-Naphthyl)ethanol	10 (crude)‡		(192)
9-Bromophenanthrene	B	2-(9-Phenanthryl)-ethanol	36–50‡		(21)
	B	2-(9-Phenanthryl)-ethanol	75		(161)
Miscellaneous:					
Indole	C	2-(β-Indolyl)ethanol	52		(157)
					
α-Methylindole	C	2-(β-Indolyl-α-methyl)ethanol	68		(157)
Pinene hydrochloride	A	No reaction			(29)
	D	"Camphane-2-ethanol	—		(29)
					
(Chloromethyl)-trimethylsilane.	D	(3-Hydroxypropyl)-trimethylsilane, $(CH_3)_3SiCH_2CH_2CH_2OH$	71		(190)
(2-Bromopropyl)-trimethylsilane.	E	(5-Hydroxypentyl)-trimethylsilane, $(CH_3)_3Si(CH_2)_4CH_2OH$	64		(190)

Footnotes to table 1

* Reaction conditions (where indicated, the ratios represent ethylene oxide:Grignard reagent):

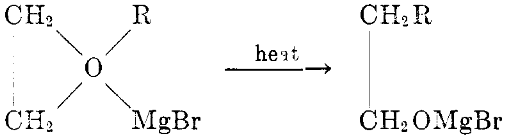
A. Ether solution decomposed without heating.
B. Ether refluxed before decomposition.
C. Ether distilled before decomposition.
D. Ether replaced by higher-boiling solvent before decomposition.
E. Ether solution allowed to stand at room temperature before decomposition.
F. Magnesium halide precipitated by dioxane and solution of dialkylmagnesium treated with ethylene oxide and allowed to stand at room temperature before decomposition.
G. Grignard reagent prepared in chlorobenzene and ethylene oxide in benzene (181) or chlorobenzene (121) added.

† Yield of alcohol calculated from alkyl halide or hydrocarbon, and yield of halohydrin calculated from ethylene oxide.

‡ Calculated from author's data.

§ Filtrate gave on long standing a 9 per cent yield of 3,3-dimethyl-1-butanol.

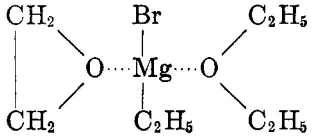
However, if the ether is removed, the temperature rises and the first product undergoes rearrangement (sceond phase).



II

II decomposes normally with water, giving the alcohol. This work has been confirmed by Henry (108) and many others.

The mechanism of the Grignard reaction with ethylene oxide has been the subject of a great deal of investigation in an effort to elucidate the structures of the intermediate compounds involved. At this point it may be mentioned that Meisenheimer proposed a modified formula for I (149)



and $C_2H_5CH_2CH_2OMgBr$ for the rearranged product.

In 1932 Ribas and Tapia (166, 167) presented analytical data in support of the identity of the product from an equimolar reaction of ethylene oxide with an ether solution of magnesium bromide and the product obtained by Grignard (97, 98) from ethylene bromohydrin and ethylmagnesium bromide. However, in 1941, Huston and Agett (117) presented data to show that the intermediate has the molecular formula $C_4H_8Br_2MgO_2$ instead of CH_2BrCH_2OMgBr as proposed by Ribas and Tapia. This compound reacts with dialkylmagnesium to form $(RCH_2CH_2O)_2Mg$, which is the precursor of the alcohol obtained by hydrolysis. Further studies with alkylmagnesium chlorides have been presented to support this view (120).

The fact that upon hydrolysis the same primary alcohol is obtained from the reaction between a Grignard reagent and a halohydrin as between the Grignard reagent and the corresponding ethylene oxide has found wide synthetic application (42, 97, 98, 99, 100).

Regardless of the exact mechanism of the formation of the primary alcohol from the reaction between ethylene oxide and the Grignard reagent, the overall effect is a cleavage of the epoxy ring. The active agent in any Grignard reaction may be RMgX, R_2Mg, or MgX_2, owing to the equilibrium which is characteristic of Grignard reagents (179, 180).

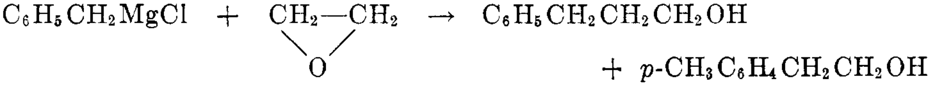
$$2RMgX \rightleftharpoons R_2Mg + MgX_2$$

The product or mixture of products which results from any Grignard reaction is thus a direct result of the reactivity of the constituents of the Grignard reagent towards the functional group involved, in this case the epoxy ring. Greater reactivity of any one of the components, e.g., R_2Mg, towards the oxide disturbs the equilibrium by conversion of the less active RMgX to R_2Mg. This may result in a preponderance of one product. This effect is observed in the reaction of ethylene oxide with tertiary Grignard reagents and in the case of substituted ethylene oxides assumes great importance, owing to the possibility of rearrangements. This will be discussed later.

Therefore it is apparent that the products arising in an attempted synthesis utilizing the Grignard reagent with an ethylene oxide are dependent upon the nature of the reagent, the nature of the oxide, factors governing their reactivity, and the conditions under which the synthesis is effected. Regarding the latter point, the literature contains references to syntheses carried out in the following manner:

1. After the oxide and the Grignard reagent have been permitted to react,
    - (*a*) the ether solution is decomposed without heating,
    - (*b*) the ether solution is refluxed before decomposition,
    - (*c*) the ether is distilled from the reaction mixture before decomposition,
    - (*d*) a higher-boiling solvent such as benzene or toluene is added and the ether is distilled before decomposition,
    - (*e*) the ether solution is allowed to stand at room temperature before decomposition;
2. The magnesium halide in the Grignard reagent is precipitated by dioxane, the mixture is filtered, and the solution of dialkylmagnesium is treated with the oxide;
3. The Grignard reagent is prepared in the absence of ether, e.g., in chlorobenzene, and the oxide in benzene or chlorobenzene is added;
4. The gaseous oxide is passed into a hot solution of the Grignard reagent in some solvent, such as benzene.

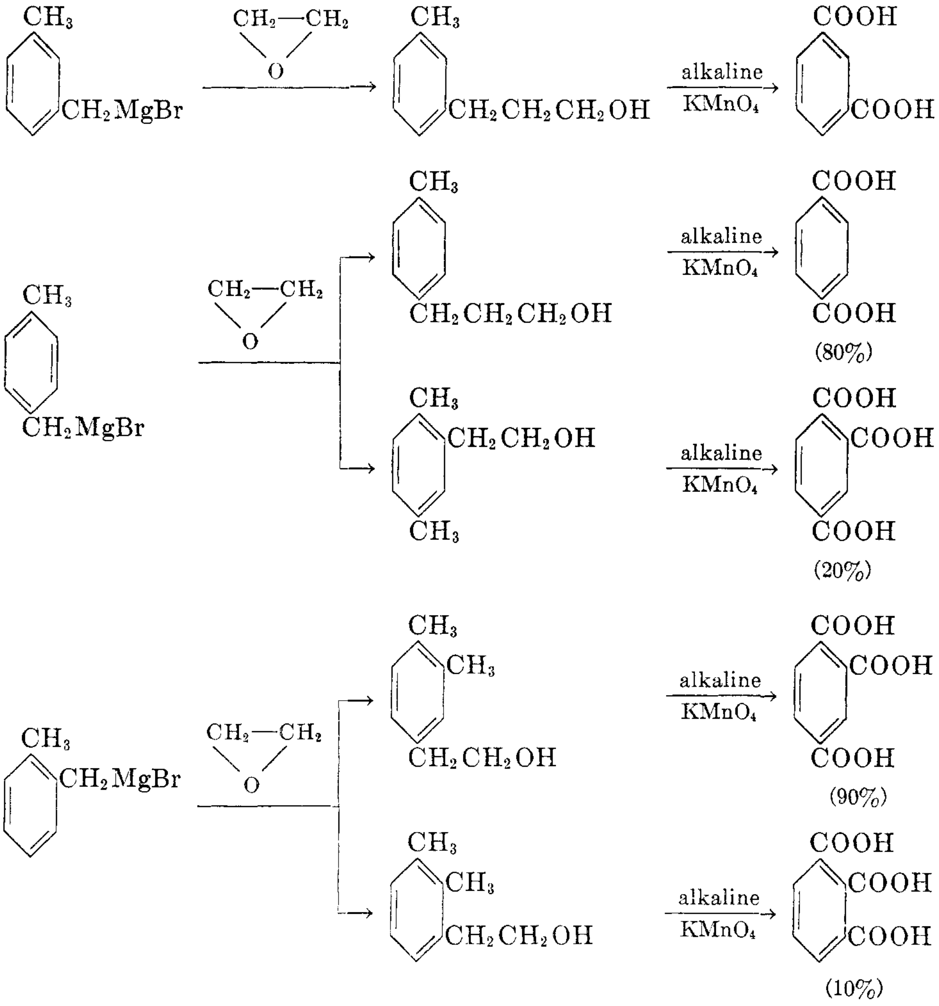
The reaction of ethylene oxide and the Grignard reagent has had wide application whenever it was desired to synthesize a primary alcohol containing two more carbon atoms than were present in the original alcohol or halide. Thus, the synthesis of 1-hexanol by the reaction between ethylene oxide and *n*-butylmagnesium bromide is described in *Organic Syntheses* (57). The synthesis of a series of primary alcohols containing six to ten carbon atoms was carried out utilizing ethylene oxide and the appropriate Grignard reagent (216). In addition to the use of primary and secondary alkyl Grignard reagents (35, 36, 57, 59, 96, 108, 117, 120, 178, 188, 190, 216, 221) the reaction has been used with tertiary reagents. It has been reported that with *tert*-butyl (116, 117, 120), *tert*-amyl, and *tert*-hexyl (117) Grignard reagents, only ethylene bromohydrin is formed regardless of whether one or two moles of ethylene oxide is used. Thus the initial product, in spite of the increase in temperature or distillation of the ether, does not undergo further change. However, on long standing, a *tert*-butyl Grignard reagent gives a small yield of 3,3-dimethyl-1-butanol. More recently, this alcohol has been obtained in 13.2 per cent yield by allowing the reaction mixture to stand for 24 hr., distilling the ether, adding toluene to the residue, and refluxing for several hours before decomposition (148). A discussion of the reaction between benzylmagnesium chloride and ethylene oxide is pertinent because of the known rearrangements which take place with benzylmagnesium halides and formaldehyde (223). Gilman and Kirby (78) obtained a product in 48.5 per cent yield from the reaction of benzylmagnesium chloride and ethylene oxide. Upon oxidation the product gave a 1:1 mixture of benzoic and terephthalic acids, but no phthalic acid. Therefore, the original product was a mixture of the normal product and a product rearranged to the para isomer.



$$C_6H_5CH_2MgCl + \underset{\diagdown\ \diagup \atop O}{CH_2\text{—}CH_2} \rightarrow C_6H_5CH_2CH_2CH_2OH + p\text{-}CH_3C_6H_4CH_2CH_2OH$$

In 1941 Huston and Agett (117) reported that this same reagent with one or two moles of ethylene oxide without heating or standing gives 73–79 per cent of 3-phenyl-1-propanol along with a very small quantity of ethylene chlorohydrin. This room-temperature reaction has been postulated as due either to reaction of dibenzylmagnesium with the intermediate from the initial reaction or to a direct reaction of benzylmagnesium chloride with ethylene oxide. It should be pointed out that no exhaustive attempt to isolate or identify a second product was made. In the light of this, then, it seems feasible that the product may have contained some isomeric 1-phenyl-2-propanol.

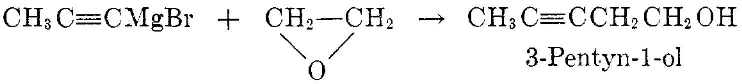
More recently, Mousseron and Du (151) carried out the reaction between ethylene oxide and methyl-substituted benzyl Grignard reagents. The products obtained varied with the position of the methyl group. Thus, *m*-methylbenzylmagnesium bromide gave a product, b.p. 140°C./20 mm., which upon oxidation with alkaline permanganate was converted to isophthalic acid as the only product. This product represents the expected course of addition. The reaction product from *p*-methylbenzylmagnesium bromide, b.p. 138–142°C./20 mm., on oxidation gave a mixture of acids which was identified as consisting of 80 per cent terephthalic acid and 20 per cent 1,2,4-benzenetricarboxylic acid. Here the major product arose from expected addition and the other product from ortho-rearrangement. The product from *o*-methylbenzylmagnesium bromide, b.p. 135–140°C./20 mm., gave a mixture of 90 per cent 1,2,4-benzenetricarboxylic acid and 10 per cent 1,2,3-benzenetricarboxylic acid. The major product arose from para-rearrangement and the second product from ortho-rearrangement, with no normal addition to the epoxy ring.



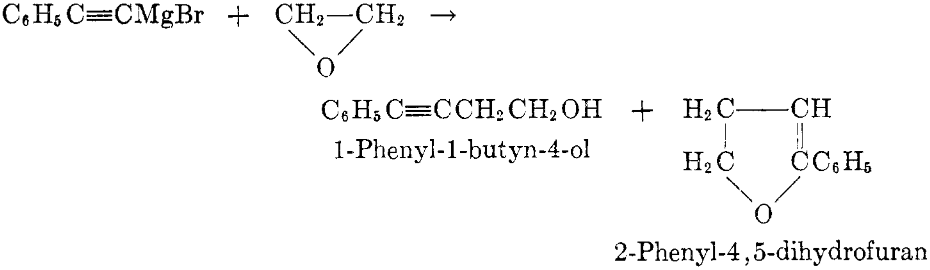
In a careful experiment Beeby and Mann (229) isolated normal and rearranged-coupled products in the reaction of *o*-bromobenzylmagnesium bromide (one mole) with ethylene oxide (two moles). The products were ethylene bromohydrin (58 per cent), 3-(*o*-bromophenyl)-1-propanol (49 per cent), 2,2′-dibromobibenzyl, and 2,2′-dihydroxyethylbibenzyl.

Unsaturated aliphatic Grignard reagents have also been investigated. Thus, a German patent (61) has been issued for the preparation of rhodinol, 3,7-dimethyl-6-octen-1-ol, by the action of the Grignard reagent prepared from 2-bromo-6-methyl-5-heptene upon ethylene oxide.

Acetylenic Grignard reagents have been utilized to prepare homologous series of primary alcohols. In 1907 Iotsitch and his coworkers (125) reported the preparation of 3-pentyn-1-ol in 95 per cent yield by the action of the Grignard reagent from methylacetylene upon ethylene oxide, according to the equation:



This work was apparently overlooked by subsequent workers, for, in 1934, Faucounau[2] (62) reported as a new reaction the preparation of 3-nonyn-1-ol, 3-decyn-1-ol, and 1-phenyl-1-butyn-4-ol by this method. The work of Faucounau was confirmed by Danehy, Vogt, and Nieuwland (49, 50) and by Bachman (6), the former adding 3-octyn-1-ol to the series of prepared alcohols and reporting (49) the isolation of 2-phenyl-4,5-dihydrofuran as a by-product in the preparation of 1-phenyl-1-butyn-4-ol.



Analogous compounds were isolated in the preparation of 3-octyn-1-ol and 3-nonyn-1-ol. The Grignard reaction to prepare 3-hexyn-1-ol has also been reported (195).

More recently the use of sodio derivatives of acetylene has been applied to the reaction with ethylene oxide. In this way treatment of ethylene oxide with sodium acetylide has given 3-butyn-1-ol (181) and reaction with the sodio derivatives of 1-butyne has given 3-hexyn-1-ol (191).

2-Cyclopentylethanol (158) and 2-cyclohexylethanol (114, 117) have been prepared by the Grignard reaction with ethylene oxide. Likewise, 4-cyclohexyl-1-butanol (115), 6-cyclohexyl-1-hexanol (117), 2-(2-biphenylyl)ethanol (56), 4-(2-biphenylyl)-1-butanol (56), 2-(1-naphthyl)ethanol (43, 175, 192), 2-(2-naphthyl)ethanol (192), 5-phenyl-1-pentanol (187, 212), 2-(6-methoxy-1-naphthyl)-ethanol (41), and 2-(9-phenanthryl)ethanol (21, 161) have been prepared by reaction of the appropriate Grignard reagent with ethylene oxide or ethylene halohydrin.

2-Phenylethanol has been the focus of several investigations (104, 121, 182) in which the Grignard reaction with ethylene oxide was carried out without the

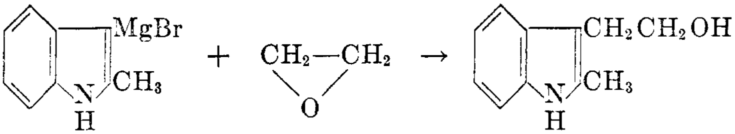
---

[2] See also Golse (232).

use of ether, thus superseding the original idea that the presence of ether was necessary before the reaction could take place. The reaction with ethylene chlorohydrin and phenylmagnesium bromide was also carried out without ether (182).

Substituted aryl Grignard reagents have been used to prepare substituted phenylethanols. Thus, bromoanisoles (1, 26, 70, 103, 152, 189), bromomethylanisoles (1, 26, 189), bromophenetoles, bromotolyl butyl ether (26), phenoxybromobenzene (70), and *m*-(trifluoromethyl)bromobenzene (197) have been converted into Grignard reagents and caused to react with ethylene oxide to produce the corresponding substituted phenylethanols.

The magnesylindoles, i.e., the Grignard reagents prepared from indole, have been used to prepare indolylethanols (tryptophols) (157). Thus, 2-(β-indolyl)-ethanol has been prepared in 52 per cent yield from indole, while 2-(β-indolyl-α-methyl)ethanol has been prepared in 68 per cent yield from α-methylindole.

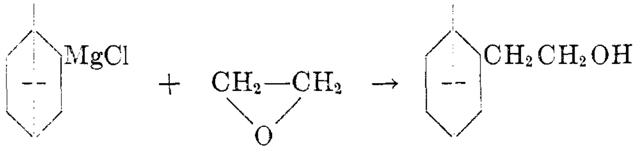


2-(β-Indolyl-α-methyl)ethanol

Grignard reagents prepared from silanes have also been used with ethylene oxide. The Grignard reagents from chloromethyltrimethylsilane and (2-bromopropyl)trimethylsilane have yielded, respectively, (3-hydroxypropyl)trimethylsilane and (5-hydroxypentyl)trimethylsilane (190).

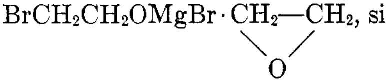
$$(CH_3)_3SiCH_2CH_2CH_2OH \qquad (CH_3)_3SiCH_2CH_2CH_2CH_2CH_2OH$$

The terpenes have also been utilized in this connection. Thus, Bousset (29) prepared from pinene hydrochloride the Grignard reagent which with ethylene oxide gave camphane-2-ethanol:



Camphane-2-ethanol

It was not certain whether this was bornylethanol, isobornylethanol, or a mixture of the two isomers.

An anomalous reaction of ethylene oxide and the Grignard reagent has been reported by Cottle and Hollyday (46). From a reaction of the oxide and *n*-butylmagnesium bromide, wherein the ether was replaced with benzene and refluxed before decomposition, there was obtained 65 per cent of 1-hexanol and 10.1 per cent of 2-hexanol. The 1-hexanol is the normal product expected by ring cleavage. Similarly, ethylene bromohydrin and the butyl Grignard reagent gave 50.6 per cent of 1-hexanol and 5.7 per cent of 2-hexanol. The formation of secondary alcohol is not explained by any of the intermediates that have been postulated, such as $(BrCH_2CH_2O)_2Mg$ or  $BrCH_2CH_2OMgBr \cdot \underset{\diagdown\,O\,\diagup}{CH_2{-}CH_2}$, since neither of these should give rearrangement. It was found that magnesium bromide and the oxide gave, in a violent reaction, an acetaldehyde resin, while dibutylmagnesium gave only 1-hexanol. The rearrangement of ethylene oxide and ethylene halohydrin to acetaldehyde had previously been observed. Thus, Kaschirsky (128) had observed that while potash and ethylene chlorohydrin gave ethylene oxide, zinc oxide gave acetaldehyde. This fact was utilized to explain the reaction of ethylene iodohydrin and dimethylzinc wherein the product obtained was 2-propanol instead of 1-propanol (34). Kaschirsky (127) postulated the initial formation of $CH_2ICH_2OZnCH_3$, then the splitting out of CH_3ZnI with formation of ethylene oxide, and the isomerization of the oxide at the instant of formation to acetaldehyde, which through reaction with dimethylzinc yields 2-propanol.

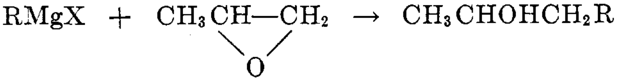
Cottle and Hollyday (46) explained the formation of 2-hexanol in the reaction with the butyl Grignard reagent as due to the loss of Br from $BrCH_2CH_2O^-$ as a result of the electrophilic attack by magnesium, rearrangement to acetaldehyde, and normal reaction with the Grignard reagent. It thus appears that the synthesis described in *Organic Syntheses* (57) probably yields a few per cent of 2-hexanol as well as 1-hexanol.

B. MONOSUBSTITUTED ETHYLENE OXIDES

The homologs of ethylene oxide react with the Grignard reagent in a manner dependent upon the structure of the epoxy compound and the structure of the Grignard reagent. This means that the extent to which rearrangement occurs during the course of the reaction is greater with increasing complexity of the carbon skeleton of the Grignard reagent in the vicinity of the attachment of magnesium. The following discussion will emphasize this concept.

1. Propylene oxide

Ethylmagnesium bromide is reported to react with propylene oxide without rearrangement to give 2-pentanol in 60 per cent yield (109). Likewise, *n*-propyl- (118, 143), *n*-butyl- (118, 148), and isobutylmagnesium (148) bromides react without reported rearrangement of the oxide. The secondary Grignard reagents isopropylmagnesium bromide (144) and *sec*-butylmagnesium bromide (118) also give products without rearrangement of the oxide, albeit in lower yields.



$$RMgX + CH_3\underset{\diagdown\,O\,\diagup}{CH{-}CH_2} \rightarrow CH_3CHOHCH_2R$$

R = primary or secondary aliphatic radical.

The reaction between *tert*-butylmagnesium halides and propylene oxide has been variously reported. In the first reference to this reaction Stevens and McCoubrey (194) reported that the sole product using *tert*-butylmagnesium chloride is 2,2-dimethyl-3-pentanol. This conclusion was supported by the following evidence:

1. The 3,5-dinitrobenzoate, m.p. 92.5–93°C., depressed the melting point of the known 3,5-dinitrobenzoate of 4,4-dimethyl-2-pentanol, 92.5–95.7°C. (224), to 87–90°C.
2. The 1-naphthylurethan melted at 107–108°C., as compared with a melting point of 86.5–87°C. reported for the same derivative of 4,4-dimethyl-2-pentanol (224).
3. The product was not 2,3,3-trimethyl-2-butanol, since the latter forms a hydrate upon shaking with moist ether, while the product does not.
4. The product was not 2,3,3-trimethyl-1-butanol, because its boiling point is appreciably below that of the latter compound, 137–138°C. and 159.5–162°C., respectively.

TABLE 2

The reaction of tert-butylmagnesium halide with propylene oxide

ALCOHOL REPORTED	BOILING POINT	$n_{D}^{20°}$	MELTING POINT OF 3,5-DINITROBENZOATE	MELTING POINT OF 1-NAPHTHYLURETHAN	REFERENCE
	°C.		°C.	°C.	
2,2-Dimethyl-3-pentanol	137–138		92.5–93	107–108	Stevens and McCoubrey (194)
4,4-Dimethyl-2-pentanol	65/40 mm.	1.4247	48–50		Huston and Bostwick (118)
4,4-Dimethyl-2-pentanol*	137–138.5	1.4188	92.5–95.7	86.5–87	Whitmore and Homeyer (224)

* Prepared by reduction of methyl neopentyl ketone.

On the other hand, Huston and Bostwick (118) reported that the reaction between *tert*-butylmagnesium bromide and propylene oxide gives only 4,4-dimethyl-2-pentanol. However, their 3,5-dinitrobenzoate melted at 48–50°C., whereas that reported by Whitmore and Homeyer melted at 95.2–95.7°C. Since no further chemical evidence was presented, it appears that the structure assigned by Huston and Bostwick may be in error (see table 2 for a summary of these reactions). The difference between the two reactions may be the use of *tert*-butylmagnesium chloride in one case (194) and of *tert*-butylmagnesium bromide in the other[3] (118). Work is now under way by one of us (N. G. G.) to clarify this point.

In contrast to the rearrangements observed with alkylmagnesium halides, no rearrangements have been observed with dialkylmagnesiums. Thus, dimethylmagnesium (94) gives 2-butanol and diethylmagnesium gives 2-pentanol (156), the expected products.

With aromatic Grignard reagents propylene oxide (see table 3) gives mainly

---

[3] *Note added in proof:* Recently, Huston and Tiefenthal (234) have reported that *tert*-butylmagnesium chloride also gives 4,4-dimethyl-2-pentanol, but the structure is still based on the same conflicting evidence reported above.

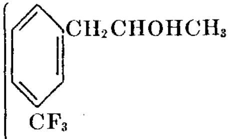
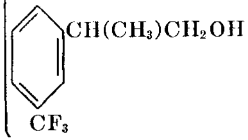
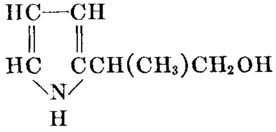
TABLE 3

Reaction of propylene oxide with Grignard reagents

GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCE
		per cent		
Dimethylmagnesium	2-Butanol	28	Reflux	(94)
Ethylmagnesium bromide	2-Pentanol	60	Distill ether	(111)
	2-Pentanol	12	Reflux	(156)
	2-Pentanol 1-Bromo-2-propanol	13 62	(1:1) Let stand 2 days	(118)
	2-Pentanol 1-Bromo-2-propanol	54 76	(2:1) Let stand 2 days	(118)
	2-Pentanol (60%) 2-Methyl-2-butanol (40%) 1-Bromo-2-propanol	24 10	(1:1) Replace ether with benzene	(118)
Diethylmagnesium	2-Pentanol	—	Let stand or reflux	(118)
	2-Pentanol	23	Reflux	(156)
n-Propylmagnesium bromide	2-Hexanol	—	Distill ether	(143)
	2-Hexanol 1-Bromo-2-propanol	4 69	(1:1) Let stand 2 days	(118)
	2-Hexanol 1-Bromo-2-propanol	51 74	(2:1) Let stand 6 days	(118)
Isopropylmagnesium bromide	4-Methyl-2-pentanol	—	Distill ether	(144)
	4-Methyl-2-pentanol 1-Bromo-2-propanol	7 50	(1:1) Let stand 2 days	(118)
	4-Methyl-2-pentanol 1-Bromo-2-propanol	38 76	(2:1) Let stand 7 days	(118)

n-Butylmagnesium bromide	2-Heptanol	30	Distill ether	(148)
	2-Heptanol 1-Bromo-2-propanol	5 67	(1:1) Let stand 2 days	(118)
	2-Heptanol 1-Bromo-2-propanol	56 70	(2:1) Let stand 8 days	(118)
sec-Butylmagnesium bromide	4-Methyl-2-hexanol 1-Bromo-2-propanol	4 62	(1:1) Let stand 2 days	(118)
	4-Methyl-2-hexanol 1-Bromo-2-propanol	31 62	(2:1) Let stand 2 days	(118)
Isobutylmagnesium bromide	5-Methyl-2-hexanol	20	Distill ether	(148)
	5-Methyl-2-hexanol 1-Bromo-2-propanol	4 64	(1:1) Let stand 2 days	(118)
	5-Methyl-2-hexanol 1-Bromo-2-propanol	15 28	(2:1) Let stand 25 days	(118)
tert-Butylmagnesium bromide	4,4-Dimethyl-2-pentanol 1-Bromo-2-propanol	4 62	(1:1) Let stand 2 days	(118)
	4,4-Dimethyl-2-pentanol 1-Bromo-2-propanol	15 52	(2:1) Let stand 45 days	(118)
tert-Butylmagnesium chloride	2,2-Dimethyl-3-pentanol	11	Let stand 7 weeks	(194)
Phenylmagnesium bromide	1-Phenyl-2-propanol	39	Distill ether	(143)
	1-Phenyl-2-propanol	60	Reflux	(153)
	1-Phenyl-2-propanol 1-Bromo-2-propanol	47 39	(1:1) Let stand 1 day	(118)
	1-Phenyl-2-propanol 1-Bromo-2-propanol	69 74	(2:1) Let stand 1 day	(118)

TABLE 3—*Concluded*

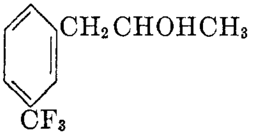
GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCE
		per cent		
Phenyllithium	1-Phenyl-2-propanol	58	(1:1.1) Reflux 15 min. or let stand overnight	(48)
p-Tolylmagnesium bromide	1-*p*-Tolyl-2-propanol	39	Replace ether with benzene	(185)
m-Tolylmagnesium bromide	1-*m*-Tolyl-2-propanol	—	Replace ether with benzene	(185)
Mesitylmagnesium bromide	1-Mesityl-2-propanol 1-Bromo-2-propanol	58 35	(1:1) Let stand 1 day	(118)
m-(Trifluoromethyl)phenylmagnesium bromide	 and 	43(total)	No details	(197)
Pyrrylmagnesium bromide	1-(α-Pyrryl)-2-propanol† +  $\overset{\text{HC}=\text{CH}}{\text{HC}=\text{CCH}(\text{CH}_3)\text{CH}_2\text{OH}}$ (N–H)	16	Reflux	(113)

---

* Ratios where given are oxide:Grignard reagent.

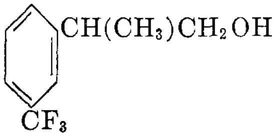
† Structure not proven.

products derived by attack at the 1-position. Thus, *m*- and *p*-tolylmagnesium bromides give only 1-(*p*-tolyl)-2-propanol and 1-(*m*-tolyl)-2-propanol, respectively, whether the oxide is added to the Grignard reagent or the filtered Grignard reagent is added to the oxide (185). However, the reaction of *m*-(trifluoromethyl)phenylmagnesium bromide (197) with propylene oxide (no conditions specified) gave a 43 per cent yield of a mixture of alcohols boiling over a ten-degree range. Fractional distillation partially separated the alcohols. The lower-boiling fractions gave a positive haloform reaction, while the higher-boiling fractions gave slight or negative tests. An Oppenauer oxidation of the mixture afforded *m*-(trifluoromethyl)phenylacetone (C). On the basis of this evidence structures A and B were assigned to the alcohols. It must be pointed out that the evidence does not rule out the possibility that D had been formed. D must be considered because of the work of Stevens and McCoubrey (194).



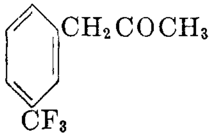
A

(lower-boiling)

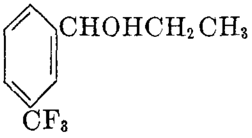


B

(higher-boiling)



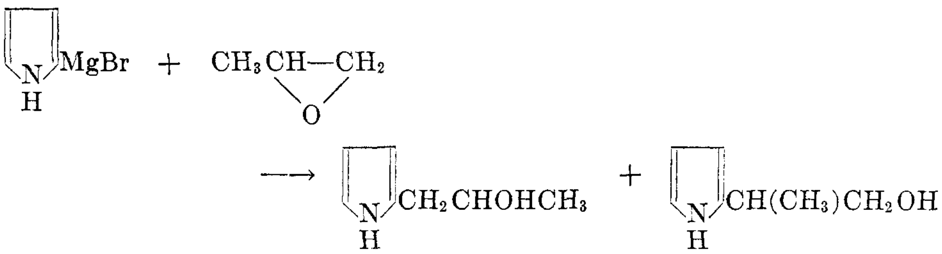
C



D

Phenyllithium gives 1-phenyl-2-propanol as the only isolable product (48).

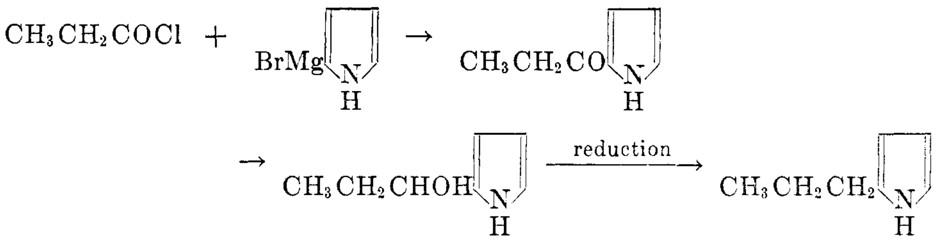
Only one heterocyclic Grignard reagent has been treated with propylene oxide (113). Pyrrylmagnesium bromide reacts with propylene oxide to give 1-(α-pyrryl)-2-propanol (I) and a substance assigned structure II. The structure of the secondary alcohol was assigned on the basis that (*1*) it could be reduced to 1-(α-pyrryl)propane, and (*2*) that it was different from the alcohol obtained



I (16 per cent)

II (5 per cent)

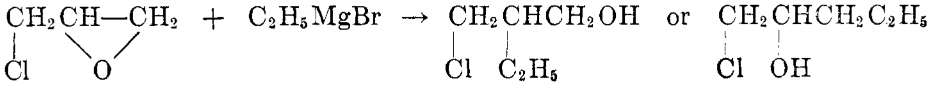
in the following series of reactions:



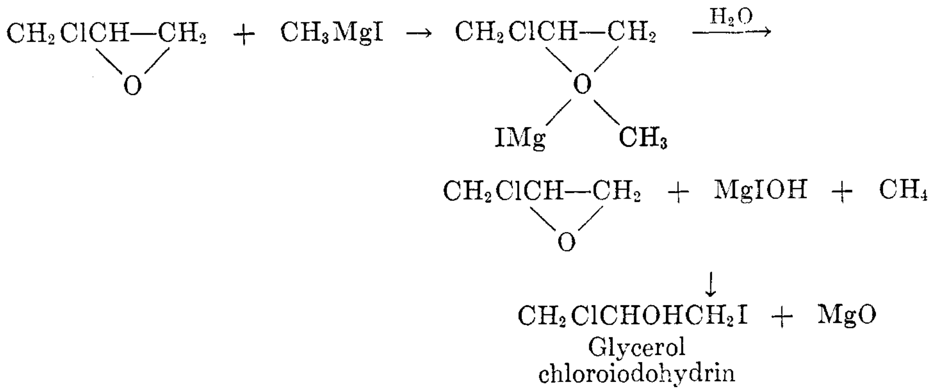
Structure II was assigned to the second product, because it was neither I nor 1-(α-pyrryl)-1-propanol.

2. *Epihalohydrins*

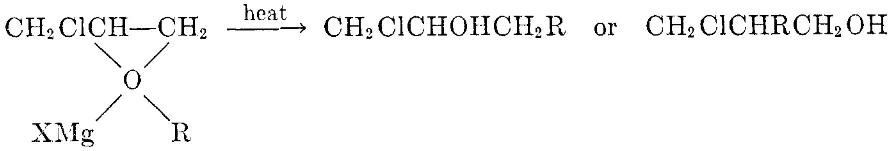
The effect of substituting various groups in the methyl group of propylene oxide has been widely studied (see table 4). 3-Chloro-1,2-epoxypropane (epichlorohydrin), in particular, has been the focus of a great deal of investigation and reinvestigation. Iotsitch (122) reported, in 1902, that ethylmagnesium bromide and epichlorohydrin gave a 58 per cent yield of a chloroalcohol when the reaction mixture was warmed on the water bath. Two possible structures were advanced for the chloroalcohol, but no proof of structure was given.



Kling (135, 136) found that if the reaction mixture obtained from epichlorohydrin and methylmagnesium iodide without heating was immediately decomposed with dilute acetic acid the product, in almost quantitative yields, was glycerol chloroiodohydrin. To explain this result Kling had recourse to the work and theory of Grignard (95, 96):



The substances obtained by Iotsitch at an elevated temperature arose from rearrangement of the addition compound:

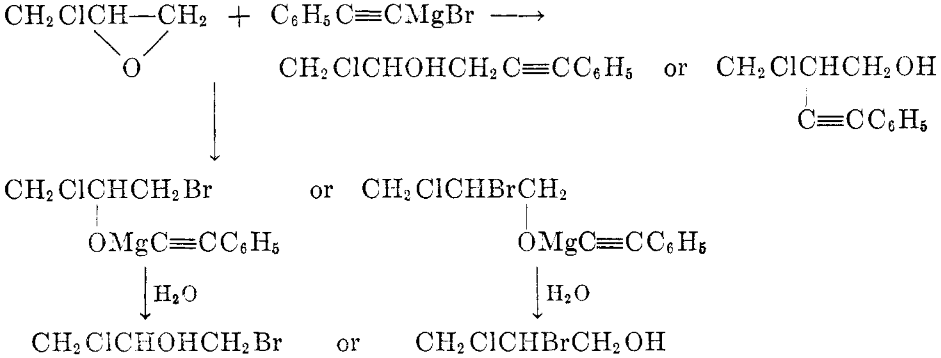


However, no proof of structure of the chloroiodohydrin obtained in the reaction in the cold was given by Kling.

At this time, Fourneau obtained a French patent on the reaction between epichlorohydrin and the phenyl, anisyl, and benzyl Grignard reagents (160), respectively. An identical patent was obtained at the same time in Germany (169). It was stated that a repetition of the reaction of the aliphatic Grignard reagents with epichlorohydrin confirmed Kling's findings that only glycerol chlorobromohydrin was formed. It was suggested that Iotsitch had actually obtained the chlorobromohydrin.

The situation with the aryl Grignard reagents was entirely different. There, in addition to the chlorobromohydrin, a large yield of a chloroaryl alcohol was obtained. Analogous structures were assigned to the products from the phenyl, *p*-anisyl, and benzyl reagents, i.e., $CH_2ClCHArCH_2OH$, but no proof of structure was given.

Iotsitch extended his work with epichlorohydrin, using the Grignard reagent from phenylacetylene (123). The products included chlorobromohydrin and a phenylacetylene chlorohydrin as well as diphenyldiacetylene and phenylacetylene. The formation of these products was explained as follows:

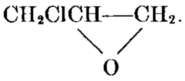


Iotsitch did not assign a specific structure to either the chlorohydrin or the chlorobromohydrin. However, the course of the reaction leading to the chlorobromohydrin was in error. It has been shown that RMgX participates in its reaction upon ethylene oxides as the fragments R and MgX rather than as the RMg and X postulated above. The dihalohydrin arises from decomposition of the addition compound from the oxide and the Grignard reagent.

A repetition of the work with ethylmagnesium bromide (124) gave, on decomposition with water, chlorobromohydrin, formulated as $CH_2BrCHOHCH_2Cl$,

TABLE 4

Reaction of Grignard reagents with epihalohydrins

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCES
			per cent		
 $CH_2ClCH\text{—}CH_2$ with O bridging (epoxide)	RMgX	1-Chloro-3-halo-2-propanol	—	Immediate decomposition	(135, 160, 169)
	Methylmagnesium iodide	1-Chloro-3-iodo-2-propanol	Quantitative	Immediate decomposition	(136)
	Ethylmagnesium bromide	1-Chloro-2-pentanol	58	Heat on water bath	(122)
		1-Chloro-2-pentanol	—	—	(111)
		3-Bromo-1-chloro-2-propanol 1-Chloro-2-pentanol	—	Heat on water bath	(124)
		3-Bromo-1-chloro-2-propanol	—	Oxide added to Grignard reagent; replace ether with toluene	(66)
		3-Bromo-1-chloro-2-propanol 1-Chloro-2-pentanol	68 19	Grignard reagent added to oxide; reflux and let stand	(138)
		3-Bromo-1-chloro-2-propanol 1-Chloro-2-pentanol	— Small amount	Replace ether with benzene	(138)
		3-Bromo-1-chloro-2-propanol	—	Reflux with *n*-butyl ether	(138)

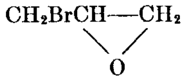
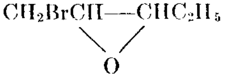
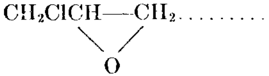
		3-Bromo-1-chloro-2-propanol 1-Chloro-2-pentanol	— 19	Grignard reagent added to oxide; reflux and let stand	(139)
		3-Bromo-1-chloro-2-propanol 1-Chloro-2-pentanol	87 49	Oxide added to Grignard reagent (2:1); reflux	(167)
		3-Bromo-1-chloro-2-propanol 1-Chloro-2-pentanol	78 35	Oxide added to Grignard reagent; reflux	(146)
		3-Bromo-1-chloro-2-propanol 1-Chloro-2-pentanol	61 13	Oxide added to Grignard reagent (1:1); immediate hydrolysis	(146)
		3-Bromo-1-chloro-2-propanol 1-Chloro-2-pentanol Cyclopropanol Tar	36 4.5	Oxide added to Grignard reagent (1:1); let stand 7 days	(146)
		3-Bromo-1-chloro-2-propanol 1-Chloro-2-pentanol Cyclopropanol Tar	41 8.7	Oxide added to Grignard reagent (1:1); let stand 25 days	(146)
	Diethylmagnesium	1-Chloro-2-pentanol	70–83	Oxide added to Grignard reagent (2:1); reflux	(146)
	Ethylmagnesium bromide	1,3-Dibromo-2-propanol	—	—	(124)

TABLE 4—*Continued*

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCES
			per cent		
 $CH_2BrCH—CHC_2H_5$ (O)	Ethylmagnesium bromide	1,3-Dibromo-2-pentanol	40	Oxide added to Grignard reagent; let stand overnight	(51)
		1,3 Dibromo-2-pentanol	—	Oxide added to Grignard reagent; distill ether	(51)
		1,3-Dibromo-2-pentanol	—	—	(52)
 $CH_2ClCH—CH_2$ (O)........	*n*-Propylmagnesium bromide	3-Bromo-1-chloro-2-propanol	—	Oxide added to Grignard reagent; replace ether with toluene	(66)
	n-Propylmagnesium iodide	1-Chloro-3-iodo-2-propanol 1-Chloro-2-hexanol	3.9	Grignard reagent added to oxide; reflux and let stand	(139)
	Isopropylmagnesium iodide	1-Chloro-3-iodo-2-propanol 1-Chloro-4-methyl-2-pentanol	— —	Grignard reagent added to oxide; reflux and let stand	(139)
	Isopropylmagnesium bromide	3 Bromo-1-chloro-2-propanol 1-Chloro-4-methyl-2-pentanol	— 0	Grignard reagent added to oxide; reflux and let stand	(139)
	n-Butylmagnesium bromide	3-Bromo-1-chloro-2-propanol	—	Oxide added to Grignard reagent; replace ether with toluene	(66)

n-Butylmagnesium chloride	1,3-Dichloro-2-propanol 1-Chloro-2-heptanol	— 16	Grignard reagent added to oxide; reflux and let stand	(139)
sec-Butylmagnesium chloride	1,3-Dichloro-2-propanol 1-Chloro-4-methyl-2-hexanol	— 9	Grignard reagent added to oxide; reflux and let stand	(139)
tert-Butylmagnesium chloride	1,3-Dichloro-2-propanol 1-Chloro-5,5-dimethyl-3-hexanol	— 0	Grignard reagent added to oxide; reflux and let stand	(139)
n-Amylmagnesium bromide	3-Bromo-1-chloro-2-propanol	—	Oxide added to Grignard reagent; replace ether with toluene	(66)
n-Amylmagnesium chloride	1,3-Dichloro-2-propanol 1-Chloro-2-octanol	— 29.8	Grignard reagent added to oxide; reflux and let stand	(139)
3-Amylmagnesium chloride	1,3-Dichloro-2-propanol 1-Chloro-4-ethyl-2-hexanol	— 10.9	Grignard reagent added to oxide; reflux and let stand	(139)
Cyclohexylmagnesium chloride	1,3-Dichloro-2-propanol 1-Chloro-3-cyclohexyl-2-propanol	— 15.3	Grignard reagent added to oxide; reflux and let stand	(139)
Cyclohexylmethylmagnesium chloride	1,3-Dichloro-2-propanol 1-Chloro-4-cyclohexyl-2-butanol	— 29.9	Grignard reagent added to oxide; reflux and let stand	(139)
1-Methyl-1-cyclohexylmagnesium chloride	1,3-Dichloro-2-propanol 1-Chloro-3-(1-methylcyclohexyl)-2-propanol	— 0	Grignard reagent added to oxide; reflux and let stand	(139)

TABLE 4—*Continued*

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCES
			per cent		
	2-Phenylacetylenemagnesium bromide	3-Bromo-1-chloro-2-propanol	—	—	(123)
		1-Chloro-5-phenyl-4-penten-2-ol or 2-chloromethyl-4-phenyl-3-butyn-1-ol	—		
	Benzylmagnesium chloride	1,3-Dichloro-2-propanol	—	Grignard reagent added to oxide; reflux and let stand	(139)
		1-Chloro-4-phenyl-2-butanol	32		
		1,3-Dichloro-2-propanol	—	Oxide added to Grignard reagent (1:1); immediate decomposition	(66, 160)
		1-Chloro-4-phenyl-2-butanol†	—		(68, 169)
	2-Phenylethylmagnesium chloride	1,3-Dichloro-2-propanol		Grignard reagent added to oxide; reflux and let stand	(139)
		1-Chloro-5-phenyl-2-pentanol	12.8		
	3-Phenylpropylmagnesium chloride	1,3-Dichloro-2-propanol	—	Grignard reagent added to oxide; reflux and let stand	(139)
		1-Chloro-6-phenyl-2-hexanol	25		
	Phenylmagnesium bromide	3-Bromo-1-chloro-2-propanol	—	—	(124)
		1-Chloro-3-phenyl-2-propanol	—		
		3-Bromo-1-chloro-2-propanol	—	Oxide added to Grignard reagent (1:1); immediate decomposition	(66, 68, 160, 169)
		1-Chloro-3-phenyl-2-propanol†	—		

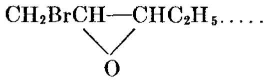
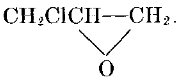
		1-Chloro-3-phenyl-2-propanol	—	Reflux	(69)
		3-Bromo-1-chloro-2-propanol 1-Chloro-3-phenyl-2-propanol	— 18.2	Grignard reagent added to oxide; reflux and let stand	(139)
		3-Bromo-1-chloro-2-propanol 1-Chloro-3-phenyl-2-propanol	87 67.7	Oxide added to Grignard reagent (2:1); reflux	(167)
		3-Bromo-1-chloro-2-propanol 1-Chloro-3-phenyl-2-propanol	*ca.* 40 *ca.* 30	Oxide added to Grignard reagent (1:1); reflux	(167)
		3-Bromo-1-chloro-2-propanol Methylstilbene	—	Oxide added to Grignard reagent (1:1); replace ether with toluene	(198)
	m-(Trifluoromethyl)-phenylmagnesium bromide	3-Chloro-1-(3-trifluoromethylphenyl)-2-propanol	70	None given	(197)
 $CH_2BrCH\overset{O}{—}CHC_2H_5$.....	Phenylmagnesium bromide	1,3-Dibromo-2-pentanol 1-Bromo-3-phenyl-2-pentanol	50	Let stand	(51)

TABLE 4—*Concluded*

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCES
			per cent		
 $CH_2ClCH—CH_2$ (—O—)	Anisylmagnesium bromide	3-Bromo-1-chloro-2-propanol 3-Anisyl-1-chloro-2-propanol†	— —	Oxide added to Grignard reagent; immediate decomposition	(66, 68, 160, 169)
	p-Anisylmagnesium bromide	3-(*p*-Anisyl)-1-chloro-2-propanol	—	Reflux	(69)
	o-Anisylmagnesium bromide	3-(*o*-Anisyl)-1-chloro-2-propanol	25–30	"Ordinary"	(155)
	1-Naphthylmagnesium bromide	1-Chloro-3-(1-naphthyl)-2-propanol	45	Reflux	(69)
	4-Methoxy-1-naphthylmagnesium bromide	1-Chloro-3-(4-methoxy-1-naphthyl)-2-propanol	49	Reflux	(69)

---

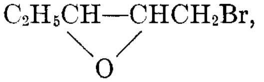
* Ratios where indicated are oxide:Grignard reagent.

† Erroneously assigned the isomeric structure $CH_2ClCHRCH_2OH$.

and a chloropentanol, $CH_2ClCHOHCH_2C_2H_5$ or $CH_2ClCH(C_2H_5)CH_2OH$. Phenylmagnesium bromide gave chlorobromohydrin and a phenylchloropropanol analogous to the chloropentanol above. Ethylmagnesium bromide and epibromohydrin gave only the dibromohydrin $CH_2BrCHOHCH_2Br$. No proofs of structure were given for any of the products obtained.

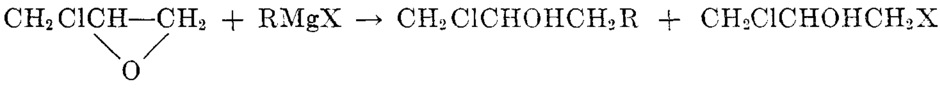
In 1907 Henry reported (111), without giving experimental details or proof of structure, that ethylmagnesium bromide gave $CH_2ClCH(C_2H_5)CH_2OH$. In the same year Fourneau and Tiffeneau (66, 68) reported in journals the findings which had been patented earlier. With aliphatic Grignard reagents, regardless of changing conditions, i.e., refluxing several days with ether or with toluene, only glycerol chlorobromohydrin was isolated when ethyl, propyl, butyl, and amyl Grignard reagents were used.

With aromatic Grignard reagents, in addition to glycerol chlorobromohydrin, an aromatic chlorohydrin was obtained. In this case, the structure was proved and shown to be that of the secondary alcohol rather than the primary alcohol set forth in the patents and earlier publications. Thus, phenylmagnesium bromide gave 3-chloro-1-phenyl-2-propanol, $C_6H_5CH_2CHOHCH_2Cl$, while *p*-anisylmagnesium bromide and benzylmagnesium chloride gave, respectively, 1-(*p*-anisyl)-3-chloro-2-propanol and 1-benzyl-3-chloro-2-propanol. In all these cases, however, some chlorobromohydrin was always formed except with the benzylmagnesium chloride, in which case the by-product was the dichlorohydrin.

No further work was done on the problem until 1923 when Delaby (51, 52) reported that ethylmagnesium bromide and ethylglycerol epibromohydrin,  $C_2H_5\underset{\diagdown O \diagup}{CH\text{—}CH}CH_2Br$, reacted to form 1,3-dibromo-2-pentanol in 40 per cent yield, while phenylmagnesium bromide gave 50 per cent of the dibromohydrin as well as a phenylbromohydrin. This corresponded to the results of Kling and of Fourneau and Tiffeneau.

The problem was further investigated in 1929 by Koelsch and McElvain (138), who obtained a chloroamyl alcohol as well as glycerol chlorobromohydrin when ethylmagnesium bromide was added to epichlorohydrin. When the reagents were allowed to stand at room temperature before hydrolysis, a 19 per cent yield of the chloropentanol was obtained and the remainder of the product was glycerol chlorobromohydrin (68 per cent). If the ether was replaced by benzene, only a small amount of chloroalcohol was obtained. The chloroalcohol was proved to be 1-chloro-2-pentanol. These results indicated that Iotsitch's observations were correct rather than those of Fourneau and Tiffeneau.

In a later communication, Koelsch and McElvain (139) reported the reaction of higher alkyl and amyl Grignard reagents with epichlorohydrin and found that when the Grignard reagent was added to a solution of an equivalent amount of epichlorohydrin, refluxed, and then allowed to stand with glycerol dihalohydrin at room temperature for 24 hr. before decomposition, a chlorohydrin was obtained:



$$CH_2Cl\underset{\diagdown O \diagup}{CH\text{—}CH_2} + RMgX \rightarrow CH_2ClCHOHCH_2R + CH_2ClCHOHCH_2X$$

The chlorohydrin was formed when the Grignard reagent was derived from primary and secondary (except isopropyl) alkyl halides and aromatic halides.

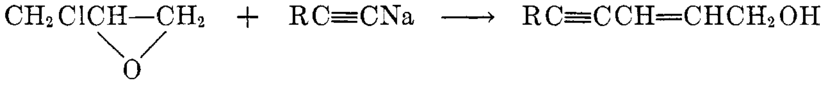
Ribas and Tapia (165) found that when zinc chloride was added to a solution of phenylmagnesium bromide and the resulting precipitate was refluxed with epichlorohydrin, the product on hydrolysis contained glycerol dichlorohydrin as well as chlorobromohydrin. Reactions of epichlorohydrin with the etherates of magnesium bromide and zinc chloride also gave dihalohydrins.

In 1932, Ribas and Tapia (167) made an attempt to reconcile the results of Koelsch and McElvain with those of Fourneau and Tiffeneau. It was stated that the former added the RMgX to epichlorohydrin so that RMgX was in the presence of an excess of epichlorohydrin, making possible the reaction of R_2Mg, while the latter carried out the reverse addition. Since this was equivalent to carrying out the reaction with different proportions of reactants, Ribas and Tapia repeated Fourneau and Tiffeneau's method of adding the oxide to the Grignard reagent but utilized two moles of oxide per mole of reagent. After refluxing and decomposing the addition product there was obtained 87 per cent of glycerol chlorobromohydrin and 49 per cent of 1-chloro-2-pentanol, the yield being calculated considering one mole of oxide reacting with $MgBr_2$ and the other reacting with R_2Mg. On this basis the yield obtained by Koelsch and McElvain is raised to 36.7 per cent. It was further observed that with epichlorohydrin and phenylmagnesium bromide in a 2:1 ratio, 87 per cent of the chlorobromohydrin was obtained along with 67.7 per cent of 1-chloro-3-phenyl-2-propanol. With a 1:1 ratio of reactants the yields were one-half those in the other case.

Magrane and Cottle (146) obtained a 70.83 per cent yield of 1-chloro-2-pentanol from epichlorohydrin and diethylmagnesium (2:1). When epichlorohydrin was added to ethylmagnesium bromide (1:1) and the product was hydrolyzed immediately upon coming to room temperature, there was obtained 13 per cent of chloropentanol and 61 per cent of the bromochlorohydrin. However, if the reaction mixture was allowed to stand (7 days and 24 days) before hydrolysis, a fraction containing cyclopropanol and a tar were obtained. If the ethyl Grignard reagent was treated with excess epichlorohydrin, refluxed for 2 hr., and hydrolysis carried out immediately, the yield of chloropentanol was increased to 35 per cent and that of the bromochlorohydrin to 78 per cent.

Stahl and Cottle (193) showed that epichlorohydrin and ethylmagnesium bromide (1:2) gave 6 per cent cyclopropanol but if the Grignard reagent was made from distilled and sublimed magnesium no cyclopropanol was obtained. However, if a 1:1 ratio of epichlorohydrin and magnesium bromide with 0.0014 mole ferric chloride was used, a 31–43 per cent yield of cyclopropanol was obtained.

In an interesting disclosure Heilbron and Jones (233) have shown that the reaction between epichlorohydrin and sodium derivatives of acetylenes gives rise to primary ene-yne-ols.

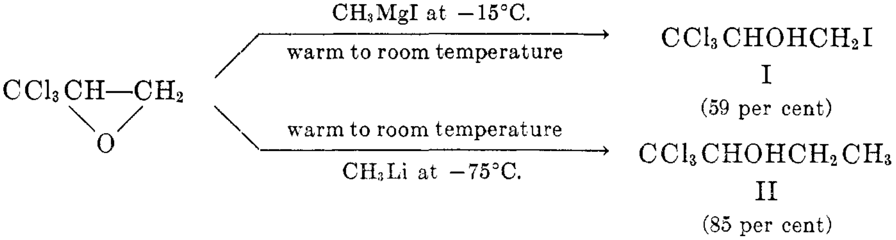


$$\underset{\text{O}}{\text{CH}_2\text{ClCH—CH}_2} + \text{RC}{\equiv}\text{CNa} \longrightarrow \text{RC}{\equiv}\text{CCH}{=}\text{CHCH}_2\text{OH}$$

R = H, C_6H_5, and *n*-C_4H_9.

The reaction with aryl Grignard reagents has been used for the synthesis of chlorohydrins containing an aromatic nucleus, including the naphthalene series (69) as well as the benzene series (69, 155). However, an anomalous result was reported by Tapia and Hernandez (198) in the reaction of epichlorohydrin and phenylmagnesium bromide wherein the ether was replaced by toluene before hydrolysis. The products obtained were glycerol chlorobromohydrin and, instead of 1-chloro-3-phenyl-2-propanol, methylstilbene, $C_6H_5CH{=}C(CH_3)C_6H_5$. The identity of the latter was proven by synthesis and mixed melting point.

The effect of further substitution of the hydrogen in the methyl group of propylene oxide with chlorine as well as the effect of temperature is seen in the work of Gilman and Abbott (76) on 3,3,3-trichloro-1,2-epoxypropane. Thus, when the oxide was added to methylmagnesium iodide at −15°C. and the mixture was allowed to come to room temperature and stirred for 30 min. before hydrolysis, the product was the trichloroiodohydrin (I), while with methyllithium at −75°C., warmed to room temperature before hydrolysis, the product was 1,1,1-trichloro-2-butanol (II).



$$\underset{\text{O}}{\text{CCl}_3\text{CH—CH}_2} \xrightarrow[\text{warm to room temperature}]{\text{CH}_3\text{MgI at }-15°\text{C.}} \text{CCl}_3\text{CHOHCH}_2\text{I}$$

I

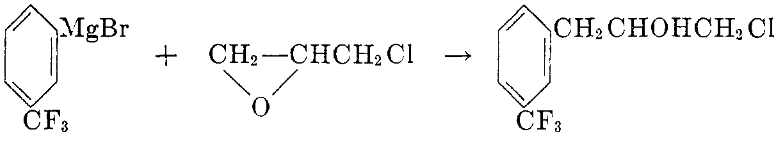
(59 per cent)

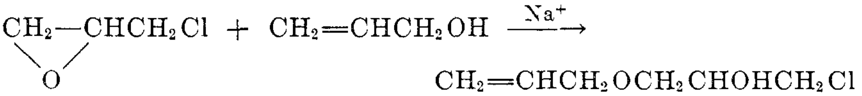
$$\underset{\text{O}}{\text{CCl}_3\text{CH—CH}_2} \xrightarrow[\text{CH}_3\text{Li at }-75°\text{C.}]{\text{warm to room temperature}} \text{CCl}_3\text{CHOHCH}_2\text{CH}_3$$

II

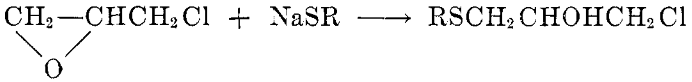
(85 per cent)

The only use of a fluorine-containing compound in the reaction of Grignard reagents with epoxides was recently reported by Szmant *et al.* (197). *m*-(Trifluoromethyl)phenylmagnesium bromide with epichlorohydrin gave 3-chloro-1-(3-trifluoromethylphenyl)-2-propanol. No synthetic evidence was presented for the structure assigned to the product; its structure was based upon analogy with other ring-opening reactions of epichlorohydrin:

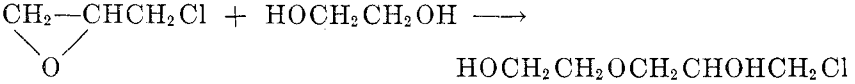




$$\underset{\text{O}}{\text{CH}_2\text{—CHCH}_2\text{Cl}} + \text{CH}_2{=}\text{CHCH}_2\text{OH} \xrightarrow{\text{Na}^+} \text{CH}_2{=}\text{CHCH}_2\text{OCH}_2\text{CHOHCH}_2\text{Cl} \quad (196)$$



$$\underset{\text{O}}{\text{CH}_2\text{—CHCH}_2\text{Cl}} + \text{NaSR} \longrightarrow \text{RSCH}_2\text{CHOHCH}_2\text{Cl} \quad (77)$$

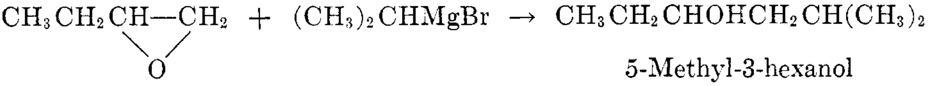


$$\underset{\diagdown O \diagup}{CH_2\text{—}CHCH_2Cl} + HOCH_2CH_2OH \longrightarrow HOCH_2CH_2OCH_2CHOHCH_2Cl \quad (134)$$

It should be pointed out that the lack of synthetic evidence leaves the structure of the product in doubt, since the nature of the reactions used for comparison is quite different.

3. Other 1-substituted ethylene oxides

Replacement of a hydrogen of the methyl group of propylene oxide or of the chlorine of epichlorohydrin with alkyl, alkoxy, or aryloxy groups gives products resulting from ring cleavage to the secondary alcohol (see table 5). Thus, 1,2-epoxybutane (1,2-butylene oxide) and the isopropyl Grignard reagent give 5-methyl-3-hexanol by cleavage of the oxirane ring at the terminal carbon atom (144).

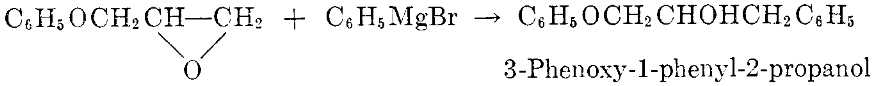


$$CH_3CH_2\underset{\diagdown O \diagup}{CH\text{—}CH_2} + (CH_3)_2CHMgBr \rightarrow CH_3CH_2CHOHCH_2CH(CH_3)_2$$

5-Methyl-3-hexanol

Analogous carbinols are obtained from *n*-propyl and phenyl Grignard reagents (144). 1,2-Epoxy-3-methylbutane (isoamylene oxide) and ethylmagnesium bromide give 2-methyl-3-hexanol (147) and analogous products are formed from isopropyl and *n*-propyl Grignard reagents.

From 1,2-epoxy-3-methoxypropane and phenylmagnesium bromide, Ribas (164) obtained 3-methoxy-1-phenyl-2-propanol and 1-bromo-3-methoxy-2-propanol. The yield of alcohol was increased when the ether was replaced with benzene or toluene. Under these conditions 1-chloro-3-methoxy-2-propanol and the phenyl Grignard reagent yield 90 per cent of the methoxyphenylpropanol. Analogous results were obtained from the oxide and ethylmagnesium bromide (167). Boyd and Vineall (31) similarly obtained 3-phenoxy-1-phenyl-2-propanol from phenylmagnesium bromide and 1,2-epoxy-3-phenoxypropane:

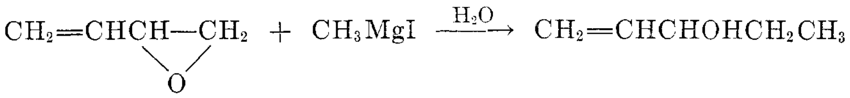


$$C_6H_5OCH_2\underset{\diagdown O \diagup}{CH\text{—}CH_2} + C_6H_5MgBr \rightarrow C_6H_5OCH_2CHOHCH_2C_6H_5$$

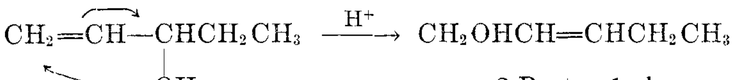
3-Phenoxy-1-phenyl-2-propanol

Heating was found to be a critical factor, as the yield of alcohol was reduced and 1-bromo-3-phenoxy-2-propanol was obtained if the addition compound was not heated before decomposition. Therefore, the influence of a methyl, ethyl, alkoxy, or phenoxy group attached to propylene oxide is not very pronounced, since these oxides react by simple ring opening.

Recently, Semeniuk and Jenkins (184) investigated the reaction between 3,4-epoxy-1-butene (butadiene monoxide) and various Grignard reagents. From acid hydrolysis of the addition product of the oxide and methylmagnesium iodide they obtained 2-penten-1-ol. The product was assumed to be as indicated without degradative or synthetic proof but solely on the comparison of its boiling point with that of the known carbinol as reported in the literature. The formation of the product was explained as follows:



Here normal ring cleavage, as in the case of the analogous saturated compound (144), has occurred. However, in the acid-catalyzed hydrolysis, the secondary alcohol is claimed to undergo an allylic rearrangement to the β-substituted allyl alcohol:



$$CH_2{=}CH{-}\underset{OH}{\underset{|}{C}}HCH_2CH_3 \xrightarrow{H^+} CH_2OHCH{=}CHCH_2CH_3$$

2-Penten-1-ol

The "1,4-addition" of the Grignard reagent to 3,4-epoxy-1-butene is also advanced as a possible reaction mechanism. On the basis of the general formula evolved for the reaction product from the methyl Grignard reagent, analogous structures were proposed for the reaction products from cyclohexylmagnesium chloride, phenyl- and 1-naphthylmagnesium bromides, and *o*-ethoxyphenylmagnesium chloride (from *o*-chlorophenetole).

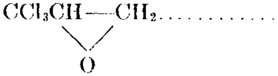
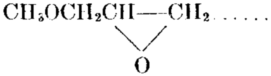
However, it has been shown that the major product of the reaction of 3,4-epoxy-1-butene with 1-naphthylmagnesium bromide is actually 1-(1-naphthyl)-3-buten-2-ol (75). The structure was proved by degradation to the corresponding hydrocarbon and also by comparison of the semicarbazone of the ketone obtained in the degradation and that prepared from the same ketone resulting from an unequivocal synthesis. The physical constants of the butenol obtained in this work and that reported by Semeniuk and Jenkins are in sufficient agreement to justify the assumption that they are identical. With thienylmagnesium bromide the major product has been shown to result from "1,4-addition," but with α-thienylsodium the product is analogous to that obtained with α-naphthylmagnesium bromide (80).

Additional work still in progress has shown that the chief product of the reaction of methylmagnesium bromide and 3,4-epoxy-1-butene is indeed 2-penten-1-ol. However, 2-methyl-3-buten-1-ol has also been separated from the reaction products (173). The physical constants agree with those reported (171) and its 3,5-dinitrobenzoate did not depress the melting point of the 3,5-dinitrobenzoate of the previously synthesized alcohol. In view of the disparity in size of the two hydrocarbon moieties of the Grignard reagents employed, it appears that the size of the Grignard reagent must be considered in any prediction of the course of the reaction.

Diethylmagnesium and 3,4-epoxy-1-butene react to give a mixture of alcohols in 70 per cent yield. Fractionation separates only two products: namely, 2-hexen-1-ol (26 per cent) and 2-ethyl-3-buten-1-ol (74 per cent) (71). With ethylmagnesium bromide the overall yield of alcohols was *ca.* 75 per cent. 2-Hexen-1-ol (30 per cent), 2-ethyl-3-buten-1-ol (35 per cent), and 1-hexen-4-ol (22 per cent)

TABLE 5

Reaction of Grignard reagents with 1-substituted ethylene oxides (other than propylene oxide and epihalohydrins)

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCE
			per cent		
 $CCl_3CH—CH_2$ (epoxide, O)	Methylmagnesium iodide	1,1,1-Trichloro-3-iodo-2-propanol	59	Oxide added to Grignard reagent (1:1); stir 1/2 hr.	(76)
 $CH_3OCH_2CH—CH_2$ (epoxide, O)	Ethylmagnesium bromide	1-Methoxy-2-pentanol	60–62	Oxide added to Grignard reagent (1:2)	(167)
		1-Bromo-3-methoxy-2-propanol	83.5	Oxide added to Grignard reagent (1:2); reflux	(167)
		1-Bromo-3-methoxy-2-propanol	41	Oxide added to Grignard reagent (2:1); replace ether with benzene	(167)
		1-Methoxy-2-pentanol	57		
		1-Bromo-3-methoxy-2-propanol	69	Oxide added to Grignard reagent (2:1); reflux	(167)
		1-Methoxy-2-pentanol	48		
	Phenylmagnesium bromide	1-Bromo-3-methoxy-2-propanol	60	Oxide added to Grignard reagent (1:1); let stand overnight	(164)
		3-Methoxy-1-phenyl-2-propanol	25		
		1-Bromo-3-methoxy-2-propanol	—	Oxide added to Grignard reagent (1:1); distill ether or replace with benzene	(164)
		3-Methoxy-1-phenyl-2-propanol	>25		

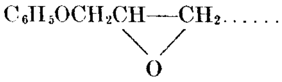
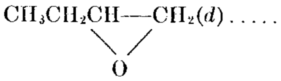
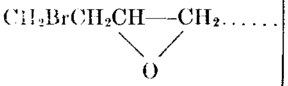
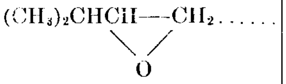
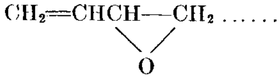
 $C_6H_5OCH_2CH\underset{O}{-}CH_2$......	Phenylmagnesium bromide	3-Phenoxy-1-phenyl-2-propanol	75	Oxide added to Grignard reagent (1:1); distill ether; heat to 100°C.	(31)
		3-Phenoxy-1-phenyl-2-propanol 1-Bromo-3-phenoxy-2-propanol	>75 —	Oxide added to Grignard reagent (1:1); distill ether	(31)
 $CH_3CH_2CH\underset{O}{-}CH_2(d)$.....	*n*-Propylmagnesium bromide	*l*-3-Heptanol	—	Oxide added to Grignard reagent (1:1); let stand 10 days	(144)
	Isopropylmagnesium bromide	*l*-5-Methyl-3-hexanol	—	Oxide added to excess Grignard reagent; let stand 6 days	(144)
	Phenylmagnesium bromide	*l*-1-Phenyl-2-butanol	—	Oxide added to Grignard reagent (1:1); let stand 4 days	(144)
 $CH_2BrCH_2CH\underset{O}{-}CH_2$......	Methylmagnesium chloride	—	—	—	(157a)
 $(CH_3)_2CHCH\underset{O}{-}CH_2$......	Ethylmagnesium bromide	2-Methyl-3-hexanol	63	Oxide added to Grignard reagent; let stand 48 hr.; distill ether	(147)
	n-Propylmagnesium bromide	2-Methyl-3-heptanol	38	Oxide added to Grignard reagent; let stand 48 hr.; distill ether	(147)

TABLE 5—*Continued*

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCE
 $CH_2{=}CHCH{-}CH_2$ (epoxide, O)			*per cent*		
	Isopropylmagnesium bromide	2,5-Dimethyl-3-hexanol	41	Oxide added to Grignard reagent; let stand 48 hr.; distill ether	(147)
	Methylmagnesium bromide	2-Penten-1-ol	35.7	Oxide added to Grignard reagent (1:1); let stand 6 hr.	(184)
		2-Penten-1-ol 2-Methyl-3-buten-1-ol	—	Oxide added to Grignard reagent (1:1); let stand 1 hr.	(173)
	Ethylmagnesium bromide	2-Hexen-1-ol (*ca.* 30%) 2-Ethyl-3-buten-1-ol (*ca.* 35%) 1-Hexen-4-ol (*ca.* 22%) Unsaturated bromohydrin (*ca.* 10%)	*ca.* 75% total alcohols	Oxide added to Grignard reagent (1:1); let stand 1 hr.	(71)
	Diethylmagnesium	2-Hexen-1-ol (26%) 2-Ethyl-3-buten-1-ol (74%)	70% total alcohols	Oxide added to Grignard reagent (1:1); let stand 1 hr.	(71)
	Cyclohexylmagnesium chloride	4-Cyclohexyl-2-buten-1-ol†	34	Stir 6 hr.	(184)
	Phenylmagnesium bromide	4-Phenyl-2-buten-1-ol†	38	Stir 6 hr.	(184)

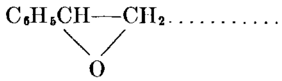
	o-Ethoxyphenylmagnesium chloride	4-*o*-Ethoxyphenyl-2-buten-1-ol†	14.7	Stir 6 hr.	(184)
	α-Naphthylmagnesium bromide	4-(α-Naphthyl)-2-buten-1-ol†	30.2	Oxide added to Grignard reagent (1:1); stir 12 hr.	(184)
	α-Naphthylmagnesium bromide	1-(α-Naphthyl)-3-buten-2-ol	55–58	Oxide added to Grignard reagent (1:1); stir 8 hr.; let stand 12 hr.	(75)
	α-Thienylmagnesium bromide	4-(α-Thienyl)-2-buten-1-ol	26	Oxide added to Grignard reagent; let stand 7 hr.	(80)
	α-Thienylsodium	1-(α-Thienyl)-3-buten-2-ol	16.2	Stir until cooled to room temperature	(80)
	RMgBr	$C_6H_5CHOHCH_2R$	—	—	(68)
	RMgX	$C_6H_5CH_2CHOHR$	—	—	(206)
	Methylmagnesium bromide	1-Phenyl-2-propanol	—	—	(206)
	Methylmagnesium iodide	1-Phenyl-2-propanol	53	Oxide added to Grignard reagent (1:1); distill ether	(94)
		1-Phenyl-2-propanol 1-Iodo-1-phenyl-2-propanol	51 Trace	Oxide added to Grignard reagent (1:1); reflux	(94)

TABLE 5—*Concluded*

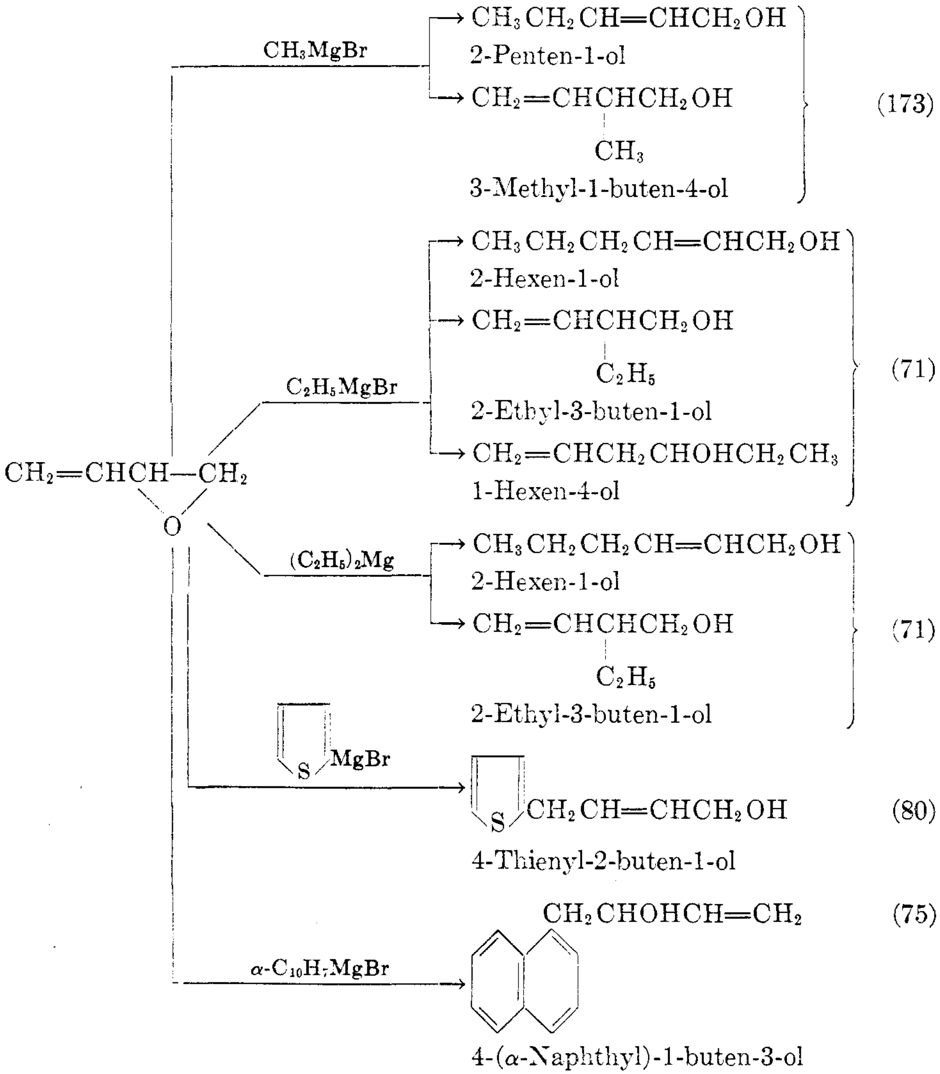
OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCE
			per cent		
	Dimethylmagnesium	2-Phenyl-1-propanol	60	Excess oxide added to Grignard reagent; reflux 5 hr.; let stand 1 week	(94)
	Ethylmagnesium bromide	1-Phenyl-2-butanol	—	—	(206)
	Phenylmagnesium bromide	2,2-Diphenylethanol	90	Oxide added to Grignard reagent; reflux 1 hr.	(133)
	Phenylmagnesium bromide	1,2-Diphenylethanol	Oil	Grignard reagent added to oxide; reflux	(133)
	p-Anisylmagnesium bromide	2-(*p*-Anisyl)-2-phenylethanol	Oil	Oxide added to Grignard reagent; reflux	(133)
		1-(*p*-Anisyl)-2-phenylethanol	Isolated as $C_6H_5CH{=}CHC_6H_4OCH_3$-*p*	Grignard reagent added to oxide; reflux	(133)
	Phenyllithium	Phenylbenzylcarbinol Stilbene	70–72 2–4	Oxide added to Grignard reagent; reflux 15 min. or let stand overnight	(48)

---

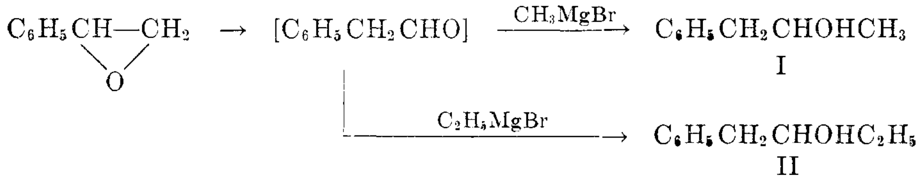
* Ratios where indicated are oxide:Grignard reagent.

† Structure assigned on basis of formula advanced for reaction product from methylmagnesium bromide.

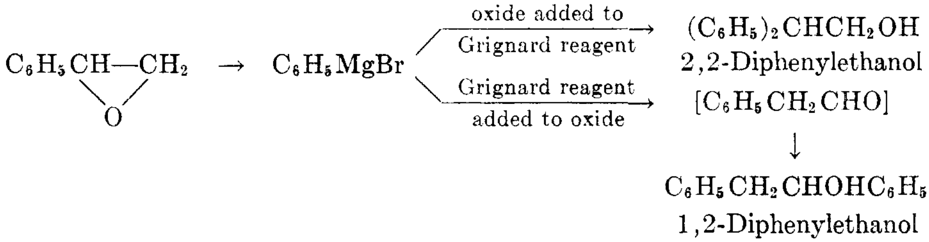
were identified in the product mixture. The latter compound can be considered as derived from vinylacetaldehyde formed upon rearrangement of the oxide. Since in all the reactions carried out by Becker and coworkers neutralized ammonium chloride solutions had been employed to hydrolyze the Grignard adducts, the alcohols were probably formed as such without acid-catalyzed rearrangements during hydrolysis.



The substitution of an aromatic nucleus, such as a phenyl group, into the molecule of ethylene oxide results in anomalous behavior with the Grignard reagent. Phenylethylene oxide (styrene oxide) was reported by Fourneau and Tiffeneau (67), in 1907, to yield, with the organomagnesium compound, the alcohol $C_6H_5CHOHCH_2R$. However, one year later they reported (206) that the oxide actually reacted as if rearrangement to the corresponding aldehyde had taken place before addition of the Grignard reagent to form the corresponding benzylcarbinol. Thus, by the action of methyl- and ethylmagnesium bromide, respectively, there are formed 1-phenyl-2-propanol (I) and 1-phenyl-2-butanol (II):



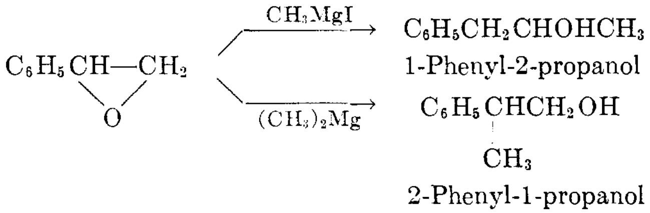
Kharasch and Clapp (133) found that the order of addition of reagents determines the nature of the products formed when styrene oxide reacts with an arylmagnesium halide. Addition of phenylmagnesium bromide to the oxide gives 1,2-diphenylethanol, whereas the addition of the oxide to the Grignard reagent gives 2,2-diphenylethanol. In each case the presence of small quantities of the isomeric alcohol was detected:



While 2,2-diphenylethanol distills unchanged at reduced pressure, 1,2-diphenylethanol decomposes into stilbene and water. As in the case of the phenyl Grignard reagent, addition of *p*-anisylmagnesium bromide to styrene oxide gives 1-(*p*-anisyl)-2-phenylethylene, resulting from the dehydration of the secondary alcohol, while reverse addition gives 2-(*p*-anisyl)-2-phenylethanol.

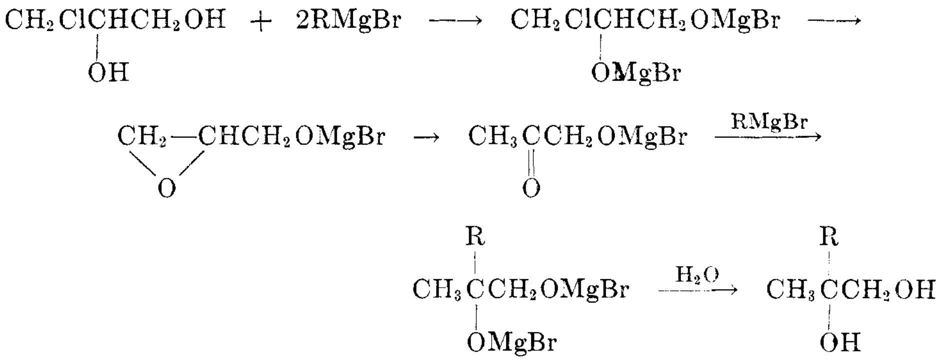
Golumbic and Cottle (94) found that styrene oxide and methylmagnesium iodide give 1-phenyl-2-propanol as does 2-iodo-2-phenylethanol with the methyl Grignard reagent. If the oxide is added to magnesium iodide before treatment with the Grignard reagent, the yield of alcohol is decreased from 51 per cent to 15 per cent. The alcohol is obtained in substantially the same yield from the oxide whether the ether is distilled from the reaction mixture or not.

With dimethylmagnesium, however, the product is 2-phenyl-1-propanol:



Phenyllithium gives 2–4 per cent of stilbene and 70–72 per cent of phenylbenzylcarbinol, indicating terminal addition only (48). Here it is observed that the absence of the magnesium halide which is present in an equilibrium mixture of the Grignard reagent has caused cleavage of the ring to occur without isomerization of the oxide to the aldehyde. The fact that it is actually the presence of the magnesium halide which causes isomerization is indicated by the findings of Tiffeneau and Tchoubar (209) that styrene oxide treated in the cold with the etherate of magnesium bromide or iodide and then hydrolyzed gives 2-bromo-2-phenylethanol or the 2-iodo compound. However, if the reaction mixture is heated, phenylacetaldehyde is obtained. This isomerization is also reported to occur on heating with zinc or lead chloride or over powdered alumina and in some cases by simple distillation (30).

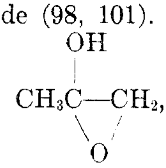
An instance in which a 1,2-epoxy compound was assumed to react through isomerization to a ketone was postulated by Grignard. The reaction of glycerol α-monochlorohydrin with a Grignard reagent was found to give, in addition to the normal glycol $RCH_2CHOHCH_2OH$ (99), formed by a Wurtz-type coupling reaction of the Grignard reagent, the glycol of the structure $CH_3C(R)(OH)CH_2OH$ (97, 98). The mechanism suggested involves oxide formation with subsequent formation of a ketone, which then reacts normally (100):



$$CH_2ClCH(OH)CH_2OH + 2RMgBr \longrightarrow CH_2ClCH(OMgBr)CH_2OMgBr \longrightarrow$$

$$\underset{\diagdown O \diagup}{CH_2{-}CHCH_2OMgBr} \rightarrow CH_3\underset{\overset{\|}{O}}{C}CH_2OMgBr \xrightarrow{RMgBr}$$

$$CH_3\overset{R}{\underset{OMgBr}{C}}CH_2OMgBr \xrightarrow{H_2O} CH_3\overset{R}{\underset{OH}{C}}CH_2OH$$

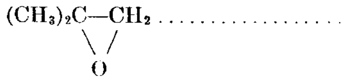
This mechanism was justified by the isolation of acetol, CH_3COCH_2OH, by heating $CH_2ClCH(OMgBr)CH_2OMgBr$, formed by treating glycerol monochlorohydrin with exactly two moles of ethylmagnesium bromide (98, 101). Earlier Kling had shown that while acetol in solution reacted as  anhydrous acetol in ether reacts with Grignard reagents as a ketone, CH_3COCH_2OH, to yield $CH_3C(R)(OH)CH_2OH$ (135, 137).

C. 1,1-DISUBSTITUTED ETHYLENE OXIDES (SEE TABLE 6)

L. Henry (107, 108), in 1907, obtained an 80 per cent yield of 3-methyl-2-butanol by the action of methylmagnesium bromide on 1,2-epoxy-2-methylpropane (isobutylene oxide). The same product is formed by the action of the

TABLE 6

Reaction of the Grignard reagent with polysubstituted ethylene oxides

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCES
A. 1,1-Disubstituted					
			per cent		
 $(CH_3)_2C—CH_2$ ………………	Methylmagnesium bromide	3-Methyl-2-butanol	80	—	(107, 108)
		1-Bromo-2-methyl-2-propanol 3-Methyl-2-butanol	40.2 40.8	1:2†	(119)
	Dimethylmagnesium	3-Methyl-2-butanol	—	1:1†	(119)
	Ethylmagnesium bromide	2-Methyl-3-pentanol	21	Reflux	(156)
		1-Bromo-2-methyl-2-propanol 2-Methyl-3-pentanol	28.3 42.2	1:1†	(119)
		1-Bromo-2-methyl-2-propanol 2-Methyl-3-pentanol 2-Methyl-2-pentanol Polymer (trimer of $(CH_3)_2CHCHO$) 2-Methyl-1-propanol	51.2 13.2 17.9 14 —	2:1†	(119)
		1-Bromo-2-methyl-2-propanol 2-Methyl-3-pentanol	40.4 51.4	1:2†	(119)
		1-Bromo-2-methyl-2-propanol 2-Methyl-3-pentanol Polymer (trimer of $(CH_3)_2CHCHO$)	27.3 13.8 5.0	Grignard reagent added to oxide (1:1); stir 2 hr.; let stand overnight	(119)

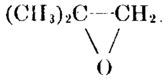
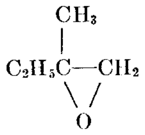
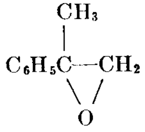
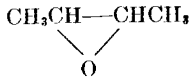
		1-Bromo-2-methyl-2-propanol	33.1	Grignard reagent added to oxide (2:1); stir 2 hr.; let stand overnight	(119)
		2-Methyl-2-pentanol			
		2-Methyl-1-propanol	8.5		
		Polymer (trimer of	6.0		
		(CH₃)₂CHCHO)	16.0		
	Diethylmagnesium	2-Methyl-2-pentanol	27.5	Reflux	(156)
		2-Methyl-2-pentanol	35.0	1:1†	(119)
	n-Propylmagnesium bromide	1-Bromo-2-methyl-2-propanol 2-Methyl-3-hexanol	30.5 39.4	1:1†	(119)
		1-Bromo-2-methyl-2-propanol	57.2	2:1†	(119)
		2-Methyl-3-hexanol	12.8		
		2-Methyl-2-hexanol	15.2		
		Polymer (trimer of (CH₃)₂CHCHO)	28		
		2-Methyl-1-propanol	—		
 $(CH_3)_2C—CH_2$	*n*-Propylmagnesium bromide	1-Bromo-2-methyl-2-propanol 2-Methyl-3-hexanol	23.0 44.5	1:2†	(119)
	Di-*n*-propylmagnesium	2-Methyl-2-hexanol	25.5	1:1†	(119)
	sec-Propylmagnesium bromide	1-Bromo-2-methyl-2-propanol 2,4-Dimethyl-3-pentanol	60.0 21.5	1:2†	(119)
	n-Butylmagnesium bromide	1-Bromo-2-methyl-2-propanol 2-Methyl-2-heptanol	41.0 20.1	1:2†	(119)
	Di-*n*-butylmagnesium	2-Methyl-2-heptanol	11.5	1:1†	(119)

TABLE 6—*Continued*

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCES
			per cent		
	tert-Butylmagnesium bromide	1-Bromo-2-methyl-2-propanol 2,2,4-Trimethyl-3-pentanol Polymer (trimer of $(CH_3)_2CHCHO$)	56.0 0.0 —	1:2†	(119)
	Di-*tert*-butylmagnesium	2,2,4-Trimethyl-2-pentanol	6.0	1:1†	(119)
	Ethylmagnesium bromide	4-Methyl-3-hexanol	—	—	(68)
	*tert*-Butylmagnesium chloride	4,4-Dimethyl-2-phenyl-3-pentanol	34	Stir 12 hr. in cold	(132)
	Phenylmagnesium bromide	1,2-Diphenyl-1-propanol	—	—	(201, 204)

B. 1,2-Disubstituted

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCES
	Methylmagnesium bromide	2-Methyl-2-butanol	—	—	(110)
		2-Methyl-2-butanol 3-Methyl-2-butanol	44 7	Reflux; let stand overnight	(47)

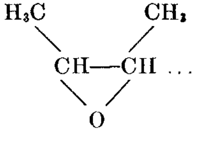
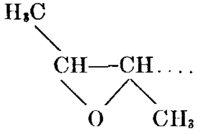
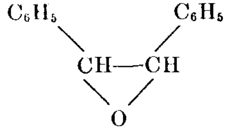
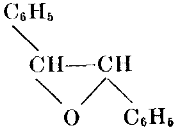
	Dimethylmagnesium	3-Methyl-2-butanol	35	Reflux	(47)
	Ethylmagnesium iodide	3-Methyl-2-pentanol 3-Methyl-3-pentanol	Trace 27	Reflux	(47)
	Ethylmagnesium bromide	3-Methyl-2-pentanol 3-Methyl-3-pentanol	2 31	Reflux	(47)
	Ethylmagnesium chloride	3-Methyl-2-pentanol 3-Methyl-3-pentanol	27 30	Reflux	(47)
	Diethylmagnesium	3-Methyl-2-pentanol	79	Reflux	(47)
 (*cis*)	Ethylmagnesium bromide	3-Methyl-3-pentanol	17.5	Reflux	(156)
	Diethylmagnesium	3-Methyl-2-pentanol	61	Reflux	(156)
 (*trans*)	Ethylmagnesium bromide	3-Methyl-3-pentanol	49	Reflux	(156)
	Diethylmagnesium	3-Methyl-2-pentanol	21.8	Reflux	(156)

TABLE 6—*Continued*

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCES
			per cent		
Isostilbene oxide 	Methylmagnesium bromide	α-1,2-Diphenyl-1-propanol	—	Reflux and let stand	(131)
	Methylmagnesium iodide	Oil	—	Reflux and let stand	(131)
	Ethylmagnesium bromide	α-1,2-Diphenyl-1-butanol	—	Reflux and let stand	(131)
	Benzylmagnesium chloride	α-1,2,3-Triphenyl-1-propanol	—	—	(129)
		α 1,2,3-Triphenyl-1-propanol	50	Reflux	(131)
trans-Stilbene oxide 	Methylmagnesium bromide	β-1,2-Diphenyl-1-propanol	—	Oxide added to Grignard reagent (1:1)	(131)
		—	—	Oxide added to Grignard reagent (2:1)	(131)
	Methylmagnesium iodide	A product melting at 133°C. and stilbene	—	Oxide added to Grignard reagent; reflux	(131)
		Stilbene	—	Grignard reagent added to oxide; reflux	(131)
		Complex mixture	—	Oxide added to Grignard reagent; high-purity magnesium used; reflux	(131)

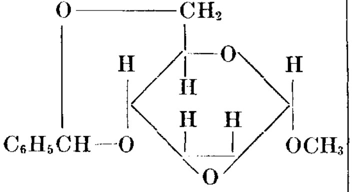
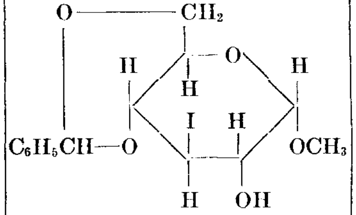
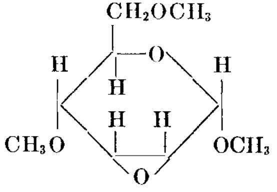
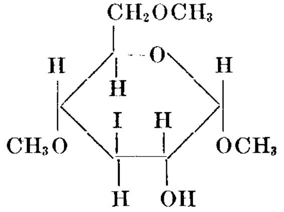
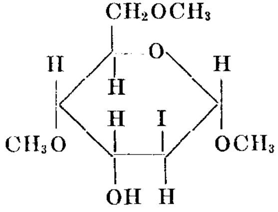
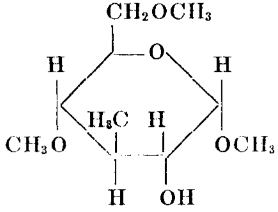
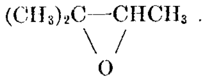
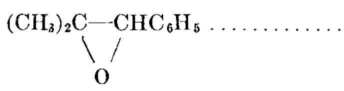
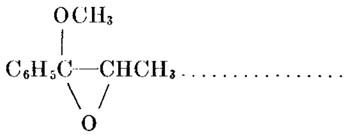
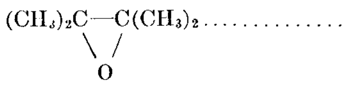
	Ethylmagnesium bromide	β-1,2-Diphenyl-1-butanol Stilbene	25 —	Reflux 2.5 hr.; let stand overnight	(131)
	Benzylmagnesium chloride	β-1,2,3-Triphenyl-1-propanol	—	—	(129)
		β-1,2,3-Triphenyl-1-propanol	50	Reflux	(131)
		β-1,2,3-Triphenyl-1-propanol	70	High-purity magnesium; reflux	(131)
4,6-Benzylidene-α-methyl-2,3-anhydroalloside............... 	Methylmagnesium iodide	4,6-Benzylidene-α-methyl-3-iodo-3-deoxyglucoside 	80	Oxide in tetrahydropyran added to Grignard reagent prepared in tetrahydropyran; reflux 2 hr.	(154)
4,6-Dimethyl-α-methyl-2,3-anhydroalloside................. 	Methylmagnesium iodide	4,6-Dimethyl-α-methyl-3-iodo-3-deoxyglucoside 	(I) 5.8 (II) 36.8 (III) 42.3	Oxide in ether added to Grignard reagent in ether; (I) reflux 2 hr.; (II) – 15°C.	(154)

TABLE 6—*Concluded*

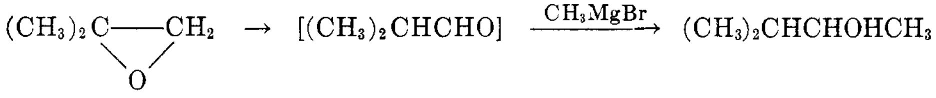
OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS*	REFERENCES
			per cent		
		4,6-Dimethyl-α-2-iodo-2-deoxyaltroside 	Isolated as acetyl derivative: (I) 6.8	(III) Oxide in tetrahydropyran added to Grignard reagent in tetrahydropyran; reflux 1 hr.	
		4,6-Dimethyl-α-methyl-3-methyl-3-deoxyglucoside 	Isolated as acetyl derivative: (I) 15.9		
		C. 1,1,2-Trisubstituted			
 $(CH_3)_2C\underset{O}{—}CHCH_3$	Methylmagnesium bromide	2,3-Dimethyl-2-butanol	30	Distill ether	(106, 112)
	Ethylmagnesium bromide	2,3-Dimethyl-3-pentanol	50	Reflux 20 min.	(156)
	Diethylmagnesium	2,3-Dimethyl-2-pentanol	21	Reflux 20 min.	(156)

 $(CH_3)_2C$—CHC_6H_5 (oxide)	Ethylmagnesium bromide	1-Phenyl-2,2-dimethyl-1-butanol (50%) 2-Methyl-3-phenyl-2-pentanol	—	—	(159)
 $C_6H_5C(OCH_3)$—$CHCH_3$ (oxide)	CH_3MgX	2-Methoxy-2-phenyl-3-butanol	85	Add oxide to Grignard reagent; room temperature; 15 min.	(193a)
	C_6H_5MgX	1-Methoxy-1,1-diphenyl-2-propanol	88	Add oxide to Grignard reagent; room temperature; 15 min.	(193a)
	tert-C_4H_9MgX	1-Methoxy-2,3,3-trimethyl-.phenyl-2-butanol	70	.Add oxide to Grignard reagent; room temperature; 15 min.	(193a)
		D. 1,1,2,2-Tetrasubstituted			
 $(CH_3)_2C$—$C(CH_3)_2$ (oxide)	Methylmagnesium bromide	2,3,3-Trimethyl-2-butanol	Quantitative	Distill ether	(112)
	Ethylmagnesium bromide	2,2,3-Trimethyl-3-pentanol	38	Reflux	(156)
	Diethylmagnesium	2,3,3-Trimethyl-2-pentanol	34.6	Reflux	(156)

* Evaluated where possible from descriptions given.

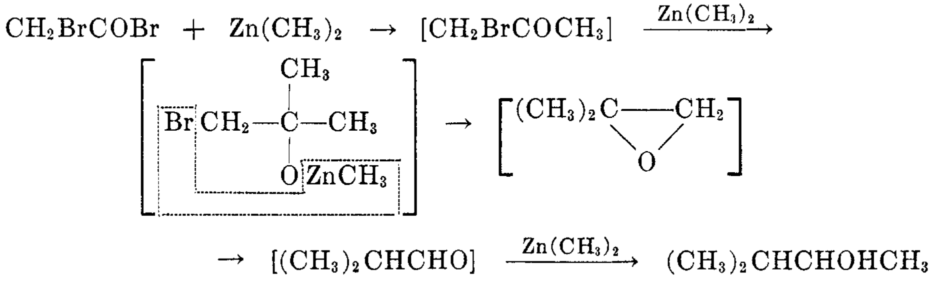
† Ratios where indicated are oxide : Grignard reagent.

methyl Grignard reagent on isobutyraldehyde. Therefore an initial isomerization of the oxide to isobutyraldehyde was postulated:



Isobutylene oxide Isobutyraldehyde 3-Methyl-2-butanol

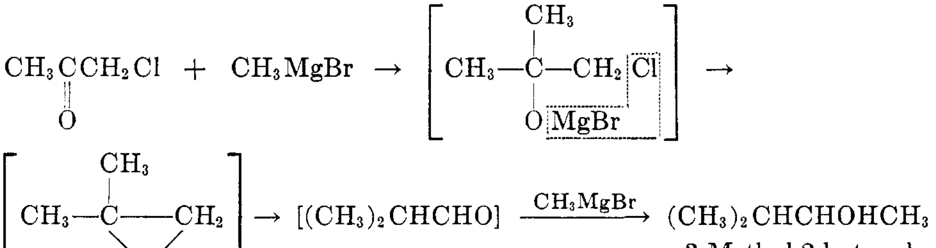
This alcohol had earlier been obtained by the action of dimethylzinc on bromoacetyl bromide (33, 226) and chloroacetyl chloride (27, 28). Kaschirsky (127) had postulated the intermediate formation of an oxide according to the following scheme:



3-Methyl-2-butanol

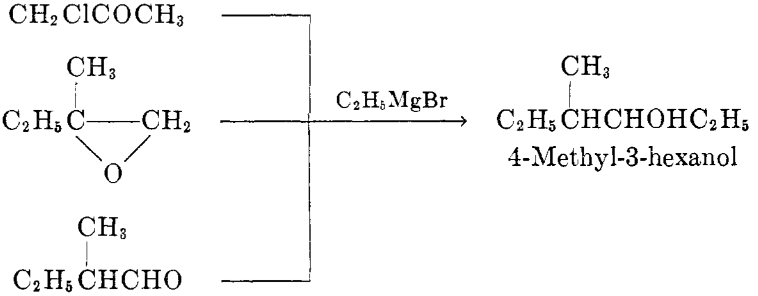
An analogous alcohol was reported by the action of diethylzinc on bromoacetyl bromide (226). On the basis of his work with isobutylene oxide and isobutyraldehyde and methylmagnesium bromide, Henry (107) advanced the same scheme for the organozinc reactions as well as that of chloroacetyl chloride and methylmagnesium bromide.

3-Methyl-2-butanol is obtained by the reaction of the methyl Grignard reagent (68, 107) upon chloroacetone, along with the chlorohydrin CH_2Cl-$C(CH_3)_2OH$. The proposed mechanism is analogous to that given for the acyl halide reaction.

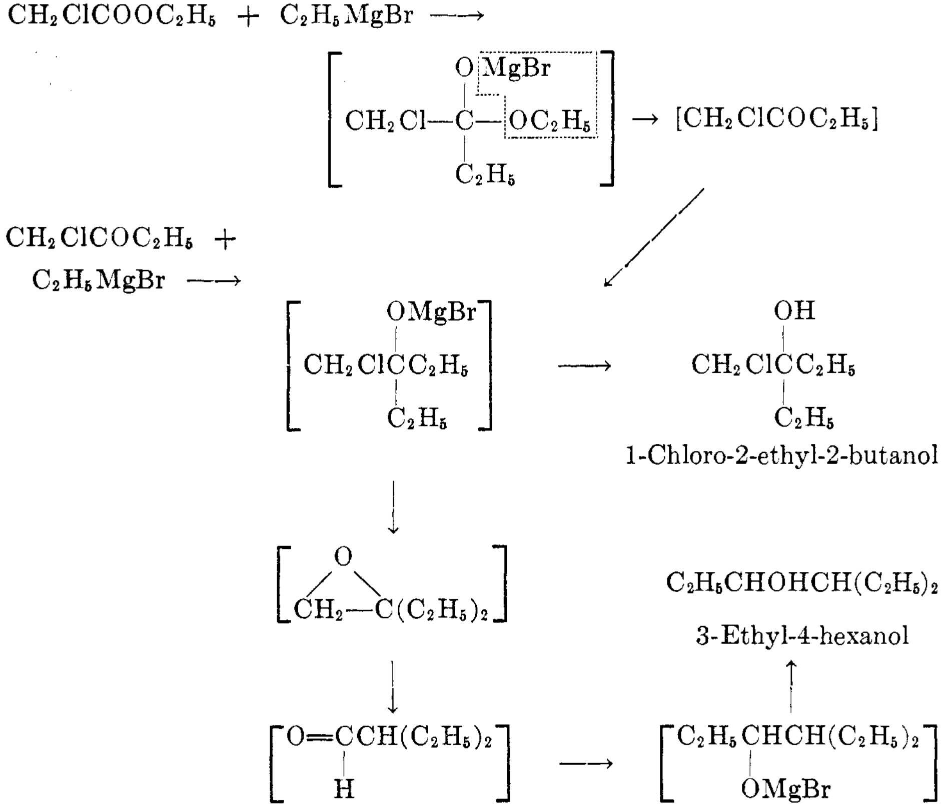


3-Methyl-2-butanol

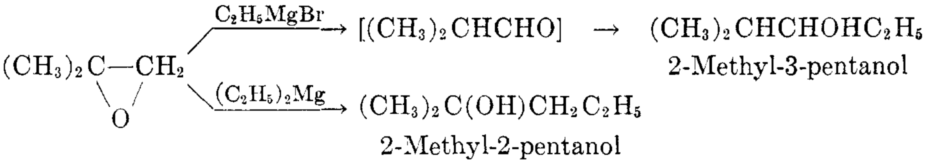
The main product of the reaction with chloroacetone is the halohydrin and the secondary product is the carbinol (64). In a similar manner, 1-chloro-2-methyl-2-butanol was prepared by the action of ethylmagnesium bromide on chloroacetone (67). The secondary product was 4-methyl-3-hexanol, which probably arose from 1,2-epoxy-2-methylbutane, since this forms the same alcohol with ethylmagnesium bromide as does 2-methylbutyraldehyde.



1-Chloro-2-ethyl-2-butanol, which gives an oxide, 1,2-epoxy-2-ethylbutane, is obtained from ethylmagnesium bromide and ethyl chloroacetate or 1-chloro-2-butanone, from which it is isolated along with 3-ethyl-4-hexanol:



Norton and Hass (156) obtained 2-methyl-3-pentanol from 1,2-epoxy-2-methylpropane and ethylmagnesium bromide. However, the oxide and diethylmagnesium gave 2-methyl-2-pentanol. Here again it is seen that the Grignard reagent causes isomerization, while the dialkylmagnesium gives a product by ring cleavage without isomerization.



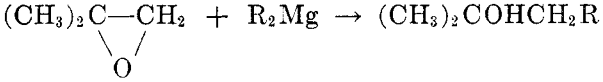
$$\underset{O}{(CH_3)_2C{-}CH_2} \xrightarrow{C_2H_5MgBr} [(CH_3)_2CHCHO] \rightarrow (CH_3)_2CHCHOHC_2H_5$$

2-Methyl-3-pentanol

$$\underset{O}{(CH_3)_2C{-}CH_2} \xrightarrow{(C_2H_5)_2Mg} (CH_3)_2C(OH)CH_2C_2H_5$$

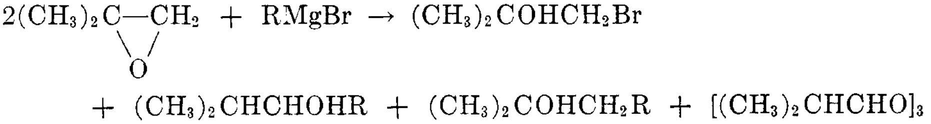
2-Methyl-2-pentanol

In an extensive paper Huston and Brault (119) have reported on the reaction between isobutylene oxide and Grignard reagents and also with the corresponding dialkylmagnesiums. The results are summarized in the following statements: (*1*) A single product, the tertiary alcohol resulting by the expected ring opening (156), is formed with dimethyl-, diethyl-, di-*n*-propyl, di-*n*-butyl-, and di-*tert*-butylmagnesium bromides.



$$\underset{O}{(CH_3)_2C{-}CH_2} + R_2Mg \rightarrow (CH_3)_2COHCH_2R$$

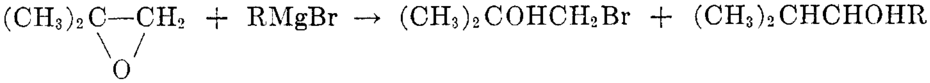
(*2*) Upon treating the oxide with a one-half molecular equivalent of alkylmagnesium bromide, the major product is 1-bromo-2-methyl-2-propanol. Smaller quantities of alkylisopropylcarbinol, dimethyl(alkylmethyl)carbinol, and a trimer of isobutyraldehyde are formed.



$$2\underset{O}{(CH_3)_2C{-}CH_2} + RMgBr \rightarrow (CH_3)_2COHCH_2Br + (CH_3)_2CHCHOHR + (CH_3)_2COHCH_2R + [(CH_3)_2CHCHO]_3$$

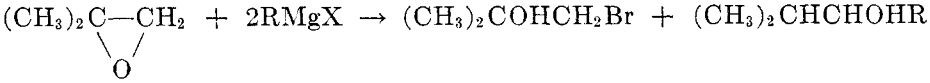
$R = C_2H_5$ or $n\text{-}C_3H_7$.

(*3*) In the 1:1 proportions of oxide to Grignard reagent the bromohydrin and the secondary alcohol are formed. An interesting point in this work was the isolation of the trimer of isobutyraldehyde from the product mixture, analogous to the earlier reported isolation of acetaldehyde resins from the reaction of ethylene oxide (46). (*4*) With two molecular equivalents of Grignard reagent only the bromohydrin and the secondary alcohol are formed. Only bromohydrin is obtained with *tert*-butylmagnesium bromide.



$$\underset{O}{(CH_3)_2C{-}CH_2} + RMgBr \rightarrow (CH_3)_2COHCH_2Br + (CH_3)_2CHCHOHR$$

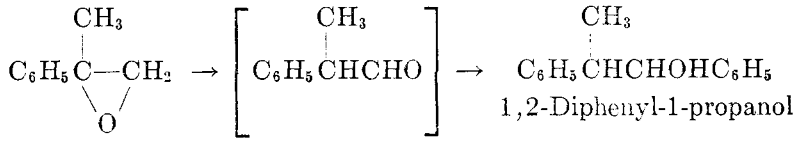
$R = C_2H_5$ or $n\text{-}C_3H_7$.



$$\underset{O}{(CH_3)_2C{-}CH_2} + 2RMgX \rightarrow (CH_3)_2COHCH_2Br + (CH_3)_2CHCHOHR$$

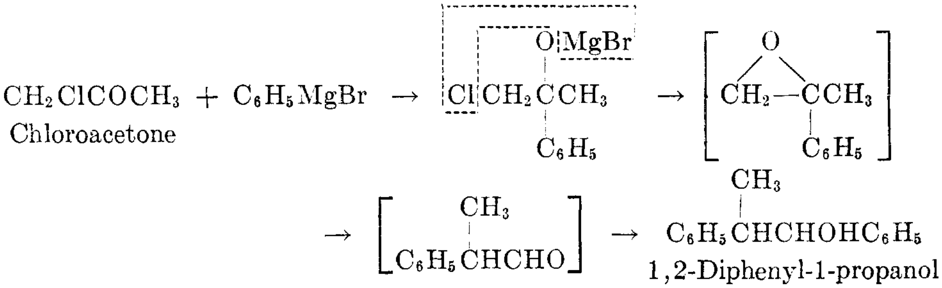
$R = CH_3$, C_2H_5, $n\text{-}C_3H_7$, $sec\text{-}C_3H_7$, or $n\text{-}C_4H_9$.

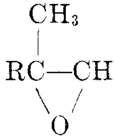
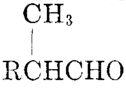
A similar rearrangement was observed by Tiffeneau (201, 204) in the reaction of 1,2-epoxy-2-phenylpropane (α-methylstyrene oxide) with phenylmagnesium bromide. A secondary alcohol was obtained by initial isomerization of the oxide to the aldehyde:

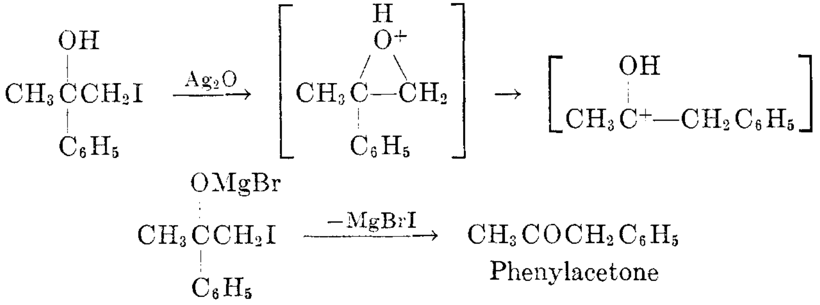


This isomerization had been observed to occur by atmospheric distillation of the oxide (65, 201) and the same alcohol was obtained by treating 2-phenylpropanal with the phenyl Grignard reagent (204). Khaletzkiĭ (132) observed the same initial isomerization to the aldehyde in the reaction with *tert*-butylmagnesium chloride.

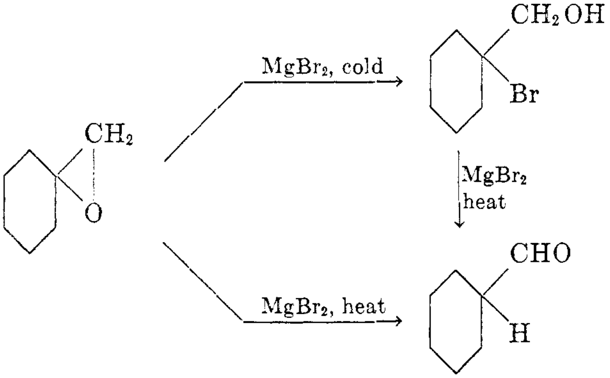
A different situation occurs in the reaction of phenylmagnesium bromide with chloroacetone. Here the product obtained is 1,2-diphenyl-1-propanol, presumably going through the oxide intermediate (203):



This is in accord with the results obtained with chloroacetone and the methyl and ethyl Grignard reagents previously mentioned. However, it was found that if $CH_3C(R)(OMgBr)CH_2Cl$, obtained by the addition of one mole of Grignard reagent to chloroacetone, is heated there is loss of MgBrCl, probably with intermediate formation of , and isolation of  $R\overset{CH_3}{\overset{|}{C}}HCHO$, where R = ethyl, amyl, or benzyl. However, where R is phenyl the ketone $CH_3COCH_2C_6H_5$ is isolated instead of the aldehyde (200, 202). This rearrangement can be shown to proceed through an oxonium intermediate, since it is known that with either mercuric oxide or silver oxide 1-iodo-2-phenyl-2-propanol rearranges to phenylacetone (201).



A 1,1-disubstituted oxide in which the carbon atom concerned is part of a ring is seen in methylenecyclohexane oxide. Here the action of magnesium bromide in the cold gives the halohydrin, while heating this product or the oxide with magnesium bromide or zinc chloride gives hexahydrobenzaldehyde as the sole product (209, 210, 211).



Hexahydrobenzaldehyde

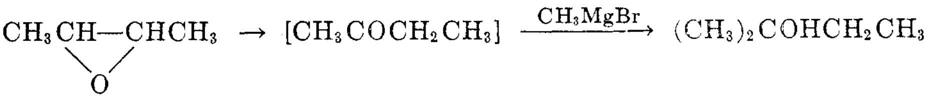
Although no Grignard reactions with this oxide were reported, it is probable that the product would arise through the intermediate aldehyde except in the case where a dialkylmagnesium would be expected to open the ring without initial isomerization.

1,1-Diphenylethylene oxide and phenyllithium give a combined 48–67 per cent yield of triphenylethylene and diphenylbenzylcarbinol, indicating only terminal addition in this instance (48).

III. 2,3-Epoxy Compounds

A. 1,2-DISUBSTITUTED ETHYLENE OXIDES (SEE TABLE 6)

Henry (110), in 1907, obtained the tertiary alcohol 2-methyl-2-butanol by the action of methylmagnesium bromide on 2,3-epoxybutane (2,3-butylene oxide). Since the same alcohol results from the action of the methyl Grignard reagent upon 2-butanone, while the oxide as such would give, by ring cleavage, 3-methyl-2-butanol, it was assumed that the magnesium compound caused the oxide to isomerize into the ketone, which then reacted normally with the Grignard reagent:



$$\underset{\diagdown\, O \,\diagup}{CH_3CH\text{—}CHCH_3} \rightarrow [CH_3COCH_2CH_3] \xrightarrow{CH_3MgBr} (CH_3)_2COHCH_2CH_3$$

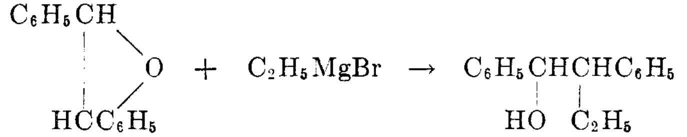
2,3-Epoxybutane 2-Methyl-2-butanol

In addition to the tertiary alcohol (44 per cent), Cottle and Powell (47) obtained the secondary alcohol (7 per cent) from this oxide and methylmagnesium bromide. With dimethylmagnesium the oxide gives 3-methyl-2-butanol with no isomerization, while with magnesium bromide alone the product is 2-butanone, indicating the source of the tertiary alcohol in the reaction of the Grignard reagent. Similarly, diethylmagnesium gives the secondary alcohol 3-methyl-2-pentanol, while the ethyl Grignard reagent gives both a secondary alcohol and a tertiary alcohol, 3-methyl-3-pentanol. The yields of secondary and tertiary alcohols appeared dependent upon the halide used for the Grignard reagent. While the yield of tertiary alcohol was fairly constant (27–31 per cent) regardless of the halide, the amount of secondary alcohol varied greatly: iodide, trace; bromide, 20 per cent; chloride, 27 per cent.

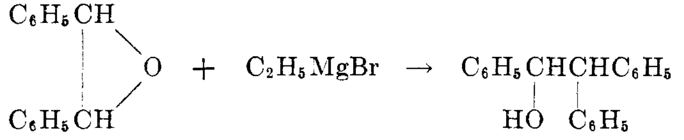
3-Bromo-2-butanol with ethylmagnesium bromide gave a 26 per cent yield of the tertiary alcohol 3-methyl-3-pentanol, through the oxide and ketone, along with a small amount of 2-butanone. A hexene fraction was also isolated (94). It was identified by reaction with bromine and potassium permanganate and by its boiling point, 69–70°C., as 3-methyl-2-pentene (45).

Norton and Hass (156) examined the behavior of *cis*- and *trans*-2,3-epoxybutanes with the Grignard reagent. While the *cis*-epoxide gives a 60 per cent yield of a racemic mixture of the secondary alcohol 3-methyl-2-pentanol, with diethylmagnesium the *trans*-epoxide gives only a 21.8 per cent yield of a different racemic mixture. With ethylmagnesium bromide, wherein initial isomerization to the ketone apparently occurs, the situation is reversed. Thus, while the *cis*-epoxide gives a 17.5 per cent yield of the tertiary alcohol 3-methyl-3-pentanol, the *trans*-epoxide gives a 49 per cent yield.

Kayser (129, 130, 131) also worked with isomeric oxides. The *cis* and *trans* isomers of stilbene oxide (isostilbene and stilbene oxide, respectively) were treated with methyl, ethyl, and benzyl Grignard reagents. The products from the reaction of the ethyl and benzyl reagents were the result of normal ring cleavage rather than initial isomerization to the ketone, as in 2,3-epoxybutane. Thus, ethylmagnesium bromide and *trans*-stilbene oxide give a racemic mixture of the *d*- and *l*-forms of *β*-1,2-diphenyl-1-butanol, while with isostilbene oxide a different racemic mixture of the *d*- and *l*-forms of *α*-1,2-diphenyl-1-butanol is obtained:



dl-*β*-1,2-Diphenyl-1-butanol

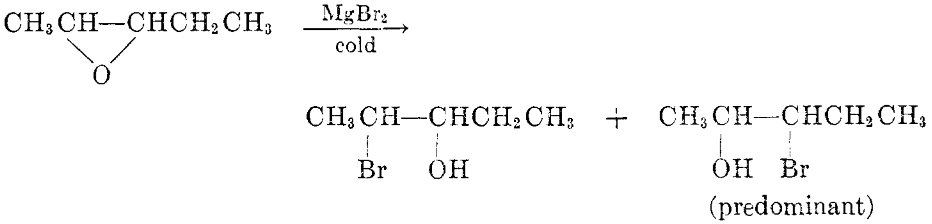


dl-*α*-1,2-Diphenyl-1-butanol

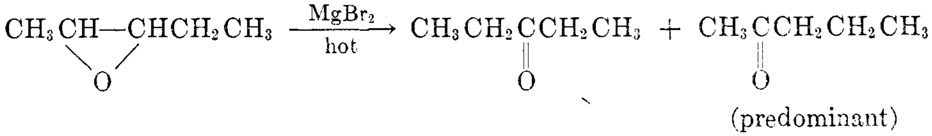
Similarly, benzylmagnesium chloride gives *dl*-*β*-1,2,3-triphenyl-1-propanol with *trans*-stilbene oxide and *dl*-*α*-1,2,3-triphenyl-1-propanol with isostilbene oxide.

While methylmagnesium bromide gives analogous 1,2-diphenylpropanols, methylmagnesium iodide gives complex mixtures of products.

The variety of products made possible by the isomerization of epoxy compounds is noted in the work of Tiffeneau and Tchoubar (209). 2,3-Epoxypentane and the etherate of magnesium bromide in the cold, on hydrolysis, give a mixture of bromohydrins.



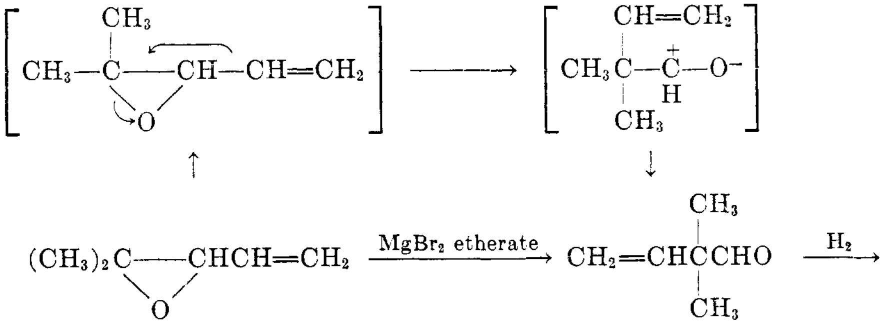
Under the influence of heat a mixture of ketones is obtained.

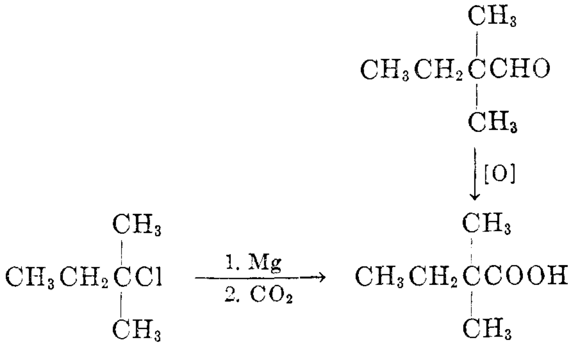


It would be expected that the reaction with the Grignard reagent would proceed through the ketone. However, as is shown in the next section, this does not follow necessarily. While the reaction with the halide may be indicative of the behavior with the Grignard reagent, it may at the same time bear no relationship to the latter.

Although it is not within the scope of this paper to consider the rearrangements brought about by magnesium bromide other than where they are connected with the behavior of oxides with Grignard reagents, certain rearrangements are worthy of mention and even more worthy of experimental attention as regards their behavior with Grignard reagents.

Among these interesting rearrangements are those involving shifting of groups. Thus, the migration of a vinyl group is postulated in the observed rearrangement of 2,3-epoxy-2-methyl-4-pentene to 2,2-dimethyl-3-buten-1-ol in the presence of magnesium bromide etherate (54):





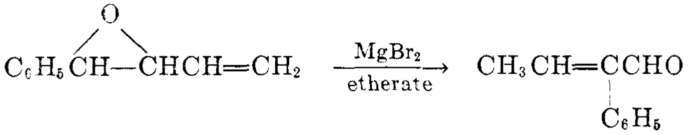
$$CH_3CH_2C(CH_3)_2CHO \xrightarrow{[O]} CH_3CH_2C(CH_3)_2COOH$$

$$CH_3CH_2C(CH_3)_2Cl \xrightarrow[2.\ CO_2]{1.\ Mg} CH_3CH_2C(CH_3)_2COOH$$

2,2-Dimethylbutanoic acid

The structure of the product was established by saturating the double bond and oxidizing to the acid. This acid proved to be identical with 2,2-dimethylbutanoic acid.

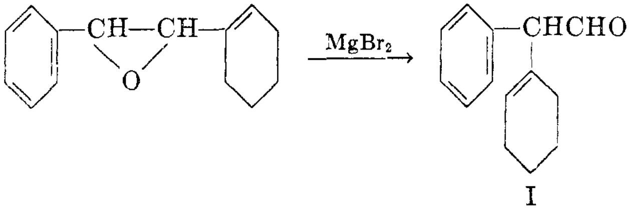
A similar migration may be responsible for the conversion of 1,2-epoxy-1-phenyl-3-butene to α-phenylcrotonaldehyde in the presence of magnesium bromide (55):



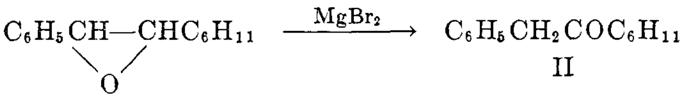
$$C_6H_5CH\overset{O}{—}CHCH{=}CH_2 \xrightarrow[\text{etherate}]{MgBr_2} CH_3CH{=}C(C_6H_5)CHO$$

Here the migration of the vinyl group (or the phenyl group) is followed by an allylic shift of the double bond.

The rearrangement of substituted styrene oxides presents interesting facets. β-Cyclohexenylstyrene oxide rearranges to an aldehyde (I), while β-cyclohexylstyrene oxide rearranges to a ketone (II) (207).



I

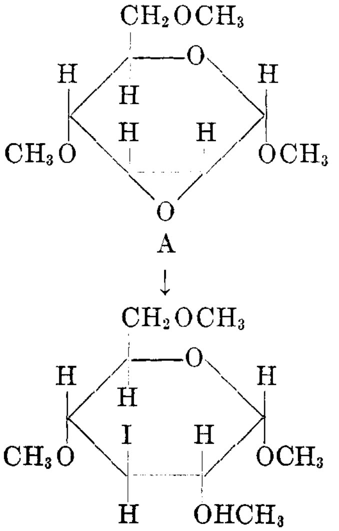


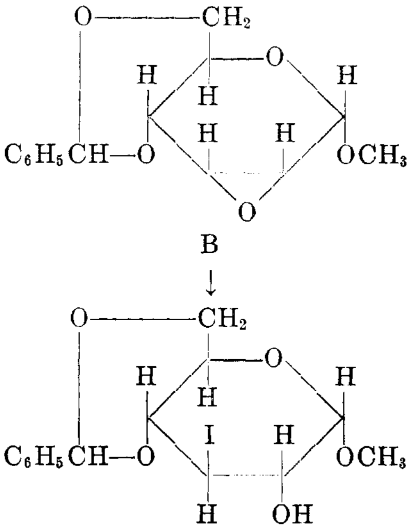
$$C_6H_5CH\underset{O}{—}CHC_6H_{11} \xrightarrow{MgBr_2} C_6H_5CH_2COC_6H_{11}$$

II

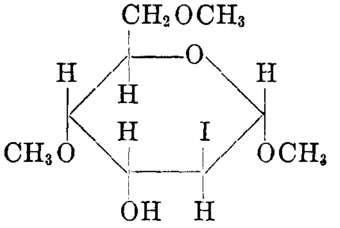
Further rearrangements of ethylene oxides are indicated in the recent review by Winstein and Henderson (227).

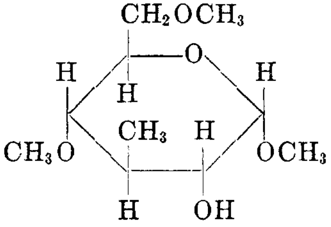
Only one report of the reaction of sugar epoxides with the Grignard reagent has been published (154). 4,6-Dimethyl-α-methyl-2,3-anhydroalloside (A) and


A


B

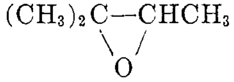
4,6-benzylidene-α-methyl-2,3-anhydroalloside (B) both give mainly analogous solid 3-iodo-3-deoxyglucosides. In addition, 3-acetyl-4,6-dimethyl-α-methyl-2-deoxyaltroside was isolated, indicating the formation of the corresponding hydroxy compound (C). 4,6-Dimethyl-α-methyl-3-methyl-3-deoxyglucoside (D) was tentatively identified among the products at the same time.


C


D

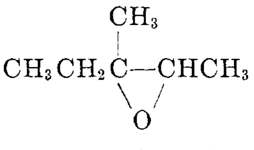
B. 1,1,2-TRISUBSTITUTED ETHYLENE OXIDES (SEE TABLE 6)

Fourneau and Tiffeneau (68) found that 3-chloro-2-methyl-2-butanol, which forms the oxide 2,3-epoxy-2-methylbutane,



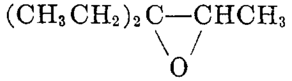
$$(CH_3)_2\underbrace{C{-}CH}_{O}CH_3$$

is obtained from 3-chloro-2-butanone and methylmagnesium bromide, along with a tertiary alcohol. Similarly, 2-chloro-3-methyl-3-pentanol, forming 2,3-epoxy-3-methylpentane,



$$CH_3CH_2\underbrace{\overset{CH_3}{C}{-}CH}_{O}CH_3$$

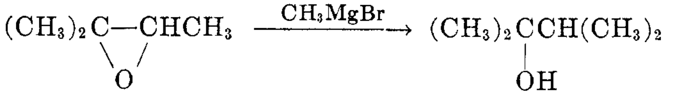
is obtained from 3-chloro-2-butanone and ethylmagnesium bromide, with a tertiary alcohol as an attendant product. Also, 2-chloro-3-ethyl-3-pentanol, forming 2,3-epoxy-3-ethylpentane,



$$(CH_3CH_2)_2C\underset{O}{—}CHCH_3$$

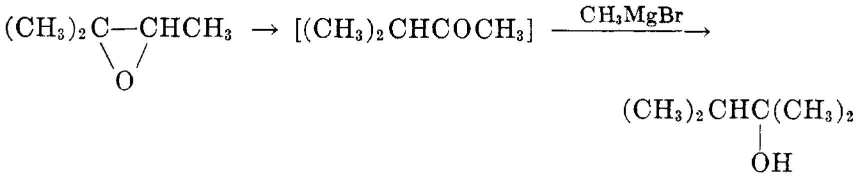
obtained from ethylmagnesium bromide and ethyl α-chloropropionate, gives a tertiary alcohol. The tertiary alcohols obtained in this series were not identified by physical properties, derivatives, or comparison with unequivocally prepared alcohols.

Henry (106, 112) found that 2,3-epoxy-2-methylbutane readily forms 2,3-dimethyl-2-butanol by reaction with methylmagnesium bromide in the usual way. This result, however, can be interpreted either by ring cleavage or by isomerization to the ketone, depending on the nature of the Grignard reagent used:



$$(CH_3)_2C\underset{O}{—}CHCH_3 \xrightarrow{CH_3MgBr} (CH_3)_2\underset{OH}{C}CH(CH_3)_2 \qquad (a)$$

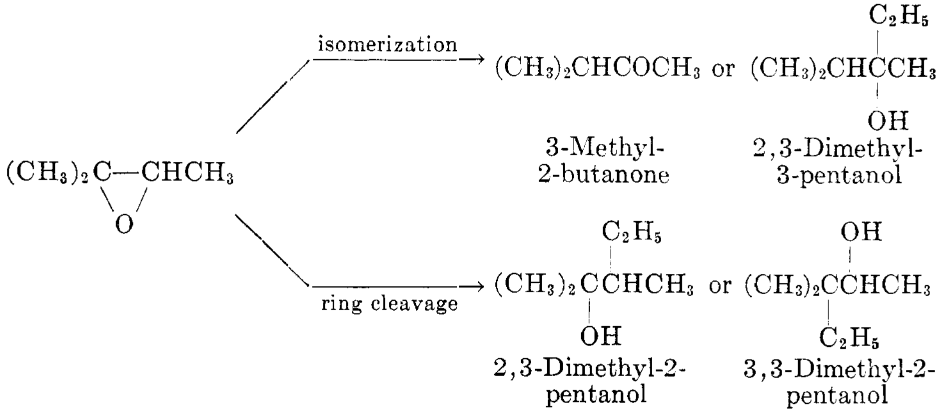
2,3-Dimethyl-2-butanol



$$(CH_3)_2C\underset{O}{—}CHCH_3 \rightarrow [(CH_3)_2CHCOCH_3] \xrightarrow{CH_3MgBr} (CH_3)_2CH\underset{OH}{C}(CH_3)_2 \qquad (b)$$

2,3-Dimethyl-2-butanol

In reviewing this work of Henry, Runge (174) stated that the ring is cleaved as in reaction (a). The fact that this was probably an instance of isomerization to a ketone, as in (b), was shown by Norton and Hass (156) when they obtained 2,3-dimethyl-3-pentanol from the oxide and ethylmagnesium bromide. Ring cleavage would have given 2,3-dimethyl-2-pentanol or 3,3-dimethyl-2-pentanol:



$$(CH_3)_2C\underset{O}{—}CHCH_3 \xrightarrow{\text{isomerization}} (CH_3)_2CHCOCH_3 \text{ or } (CH_3)_2CH\overset{C_2H_5}{\underset{OH}{C}}CH_3$$

3-Methyl-2-butanone; 2,3-Dimethyl-3-pentanol

$$(CH_3)_2C\underset{O}{—}CHCH_3 \xrightarrow[\text{ring cleavage}]{} (CH_3)_2\overset{C_2H_5}{\underset{OH}{C}}CHCH_3 \text{ or } (CH_3)_2\overset{OH}{\underset{C_2H_5}{C}}CHCH_3$$

2,3-Dimethyl-2-pentanol; 3,3-Dimethyl-2-pentanol

With diethylmagnesium the product was 2,3-dimethyl-2-pentanol, formed by ring cleavage, the secondary valence linkage breaking rather than the tertiary.

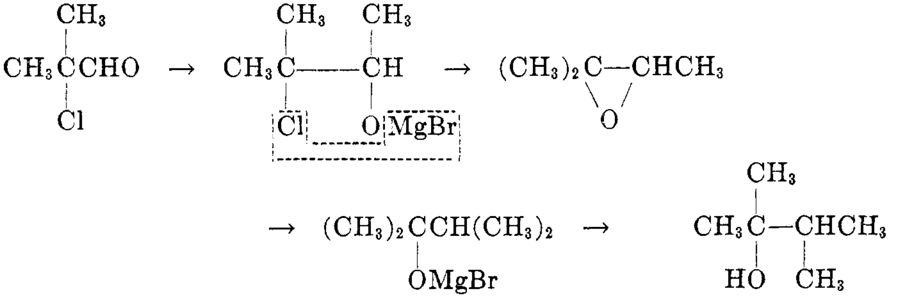
Henry (105) found that when ethyl α-chloroisobutyrate was treated with methylmagnesium bromide, pentamethylethanol or 2,3,3-trimethyl-2-butanol was formed:

$$(CH_3)_2CClCOOC_2H_5 \xrightarrow{CH_3MgBr} \underset{\text{2,3,3-Trimethyl-2-butanol}}{(CH_3)_3CC(CH_3)_2OH}$$

On this basis he expected that under the same conditions α-chloroisobutyraldehyde would give pinacolyl alcohol:

$$(CH_3)_2CClCHO \xrightarrow{CH_3MgBr} \underset{\text{Pinacolyl alcohol}}{(CH_3)_3CCH(CH_3)OH}$$

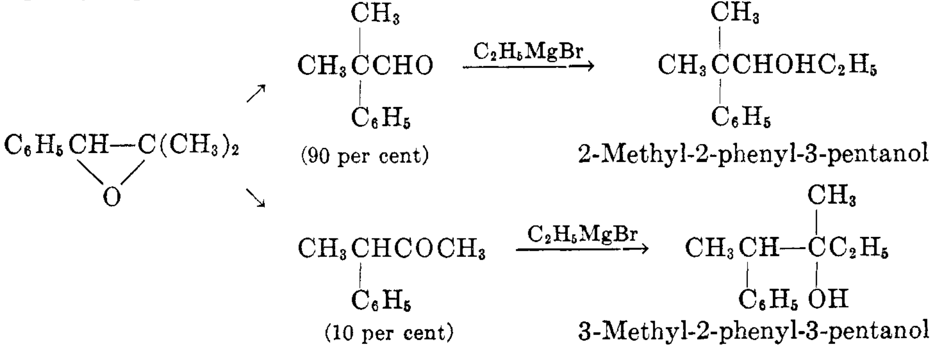
Instead, he obtained (106, 112) 2,3-dimethyl-2-butanol. This was explained by the following scheme:



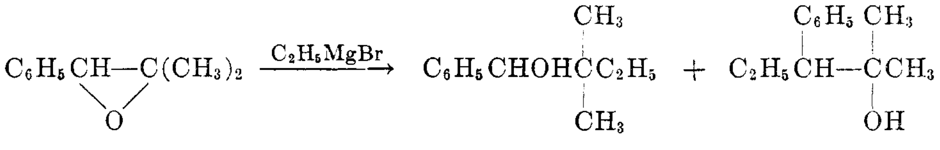
Here the oxide postulated as the intermediate is represented as going through a ring cleavage in its transformation to the tertiary alcohol. Actually, as shown by Norton and Hass (156), isomeric change to the ketone is more feasible.

When 2-chloro-2-methyl-3-butanol is allowed to react with methylmagnesium bromide the main product of the reaction is 2,3-dimethyl-2-butanol (65 per cent); pinacolyl alcohol is present in small amounts owing to ring cleavage of the oxide (112).

Poctivas and Tchoubar (159) found that upon heating 2,3-epoxy-2-methyl-3-phenylpropane in ether with magnesium bromide it is converted into 2-methyl-2-phenylpropanal (90 per cent) and 2-phenyl-3-butanone (10 per cent). With ethylmagnesium bromide these would be expected to give principally the secondary alcohol, 2-methyl-2-phenyl-3-pentanol, and some tertiary alcohol, 3-methyl-2-phenyl-3-pentanol:



Actually, it was found that reaction of the oxide and ethylmagnesium bromide gives 2,2-dimethyl-1-phenyl-1-butanol and 2-methyl-3-phenyl-2-pentanol in equal quantities. These could not be formed other than by rupture of the epoxy ring in the two possible directions:



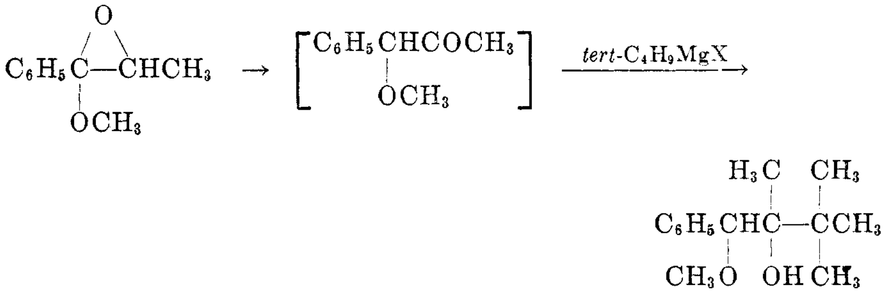
2,2-Dimethyl-1-phenyl-1-butanol 2-Methyl-3-phenyl-2-pentanol

It was concluded, on the basis of the equilibrium in the Grignard reagent, that the velocity of reaction with ethylmagnesium bromide or diethylmagnesium and the oxide was greater than that with magnesium bromide, since the latter would be expected to bring about rearrangement, as observed when the oxide reacted alone with magnesium bromide.

Stevens (193a) has recently reported on the reactions of a new class of epoxides with Grignard reagents: namely, epoxy ethers. It was found that 1-methoxy-1-phenyl-1,2-propylene oxide reacts with phenylmagnesium bromide to give 1-methoxy-1,1-diphenyl-2-propanol. An analogous product was obtained with methylmagnesium halide. However, with *tert*-butylmagnesium halide the product

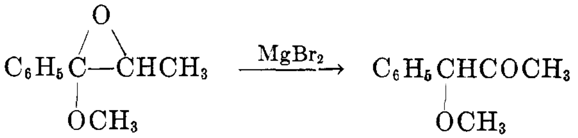
R = CH_3 or C_6H_5.

formed is that resulting from initial rearrangement of the epoxy ether to an epoxy ketone: namely, 1-methoxy-2,3,3-trimethyl-1-phenyl-2-butanol. In each



1-Methoxy-2,3,3-trimethyl-1-phenyl-2-butanol

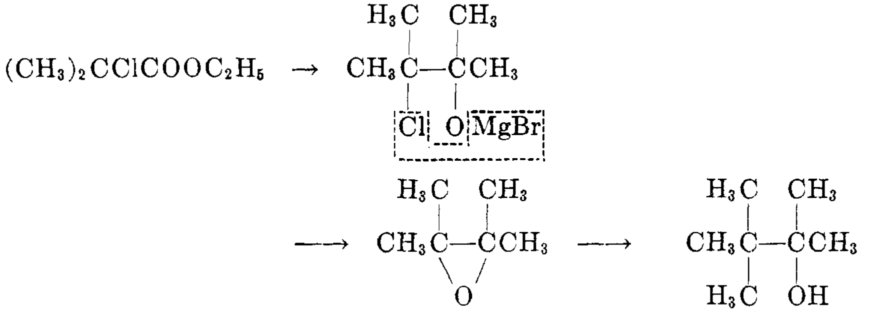
experiment the structure of the product was proved by independent synthesis. To substantiate the course of the last reaction, it was found that the epoxy ether rearranges to a ketone when treated with magnesium bromide alone.



These experiments are significant, in that they point up the necessity for consideration of both electronic and structural factors in predicting the course of the reaction. In the transition-state complex resonance into the phenyl ring favors opening of the oxirane ring adjacent to the phenyl ring. With the bulky *tert*-butyl group, this electronic consideration is subordinate to the steric factor, and rearrangement to the ketone takes place prior to addition.[4]

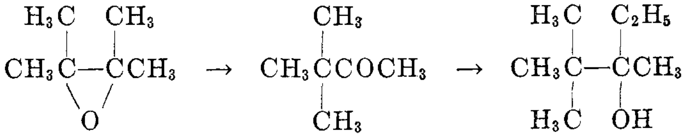
C. 1,1,2,2-TETRASUBSTITUTED ETHYLENE OXIDES (SEE TABLE 6)

Henry (112) found that 2,3,3-trimethyl-2-butanol was produced by the action of methylmagnesium bromide on 2,3-epoxy-2,3-dimethylbutane and also by the action of the methyl Grignard reagent on pinacolone, $(CH_3)_3CCOCH_3$, or on 2-chloro-1,1,2-trimethylpropanol, $(CH_3)_2CClC(CH_3)_2OH$. On the basis of these reactions he explained the formation of the same alcohol from ethyl α-chloroisobutyrate and methylmagnesium bromide (105) as due to the fact that the group $(CH_3)_2CCl$, which in α-chloroisobutyraldehyde is not attacked by the methylmagnesium bromide, is also present in the ester, as follows:



2,3,3-Trimethyl-2-butanol

Here again, with the symmetrical epoxy compound it is not possible to say whether ring cleavage or isomerization occurs, since, with methylmagnesium bromide, the same product would result in either case. However, Norton and Hass (156) obtained 2,2,3-trimethyl-3-pentanol from the oxide and ethylmagnesium bromide. This could only result from isomerization, since ring cleavage would give 2,3,3-trimethyl-2-pentanol:



---

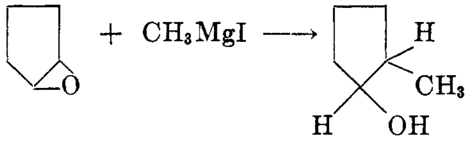
[4] *Note added in proof:* Temnikova and Kropacheva (235), however, claim that the same oxide with phenylmagnesium bromide gives 1,2-diphenyl-1,2-propanediol as the product.

In this instance the rearrangement involves a methyl group. The product expected from ring cleavage was obtained from the oxide and diethylmagnesium.

IV. Cyclic Epoxy Compounds

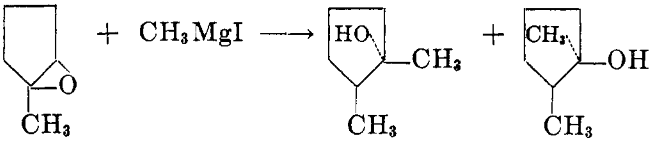
A. ALICYCLIC EPOXIDES (SEE TABLE 7)

In 1899 Meiser (150) found that cyclopentene oxide and magnesium chloride give a heavy voluminous precipitate, similar to that formed by ethylene oxide under the same conditions (228). Godchot and Bedos (88) reported that cyclopentene oxide and methylmagnesium iodide give *cis*-2-methylcyclopentanol. The phenylurethans and allophanates of this *cis* compound and the *trans* isomer obtained by reduction of 2-methylcyclopentanone with sodium and moist ether had melting points which were so similar that differentiation was actually not feasible. Recently, Turner (213) reported that cyclopentene oxide and methylmagnesium iodide give cyclopentene iodohydrin after standing overnight at room temperature, while refluxing with methyllithium gives *trans*-2-methylcyclopentanol. It was pointed out that the claim of Godchot and Bedos that the methyl Grignard reagent gave the *cis* compound was probably in error and that their product was actually the *trans* isomer.



trans-2-Methylcyclopentanol

Chavanne and de Vogel (37) reported that 1,2-epoxy-1-methylcyclopentane with excess methylmagnesium iodide gives a mixture of *cis*- and *trans*-1,2-dimethylcyclopentanols. When an equivalent quantity of the Grignard reagent is used, the product is dehydrated to the olefin.



The reactions with 1,2-epoxycyclohexane were not so simple. It was early reported (81) that 1,2-epoxycyclohexane reacts with methylmagnesium iodide to give a methylcyclohexanol which is not identical with the product of Sabatier and Mailhe (176) made by reduction of *o*-cresol. The difference was explained as being due to stereoisomerism. Similarly, phenylmagnesium bromide (11, 12, 15) was reported to give 2-phenylcyclohexanol as well as the bromohydrin, 2-bro-

TABLE 7

Reaction of cyclic epoxides with Grignard reagents

A. Alicyclic epoxides

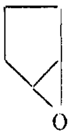
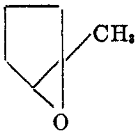
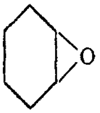
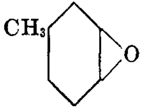
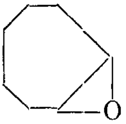
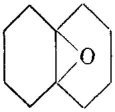
OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS	REFERENCE
			per cent		
Cyclopentene oxide.. 	Methylmagnesium iodide	*cis*-2-Methylcyclopentanol	—	Distill ether	(88)
		2-Iodocyclopentanol	—	Let stand overnight at room temperature	(213)
1,2-Epoxy-1-methylcyclopentane 	Methylmagnesium iodide	*cis*- and *trans*-1,2-dimethylcyclopentanols	—	Distill ether and heat	(37)
Cyclohexene oxide.. 	Methylmagnesium iodide	1-Cyclopentylethanol*	—	Distill ether	(11, 81)
		1-Cyclopentylethanol*	63	Distill ether and heat	(86)
		2-Iodocyclohexanol	—	Decompose without heat	(86)
		1-Cyclopentylethanol	—	Distill ether and heat	(90)
	Dimethylmagnesium	*trans*-2-Methylcyclohexanol	—	Distill ether and heat	(10)

TABLE 7—*Continued*

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS	REFERENCE
			per cent		
	Diethylmagnesium	*trans*-2-Ethylcyclohexanol	42	Distill ether and heat	(10)
	Benzylmagnesium chloride	2-Benzylcyclohexanol	50	Reflux	(44)
		2-Chlorocyclohexanol	20		
	2-Phenylethylmagnesium bromide	1-Cyclopentyl-3-phenyl-1-propanol*	91.5	Distill ether	(72, 172)
	Cyclohexylmagnesium bromide	Cyclohexylcyclopentylmethanol*	27	Distill ether and heat	(16)
	Cyclohexylmagnesium chloride	Cyclohexylcyclopentylmethanol*	—	Distill ether and heat	(13)
		Cyclohexylcyclopentylmethanol	—	—	(218)
	Phenylmagnesium bromide	Cyclopentylphenylmethanol*	—	Distill ether	(11, 12)
		2-Bromocyclohexanol Cyclopentylphenylmethanol*	37†	Decompose without heating	(15)
		Cyclopentylphenylmethanol*	12†	Distill ether and heat	(15)
		2-Bromocyclohexanol	—	Decompose without heating	(44)

TABLE 7—*Concluded*

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS	REFERENCE
			per cent		
		Cyclopentylphenylmethanol	—	Distill ether	(44)
		Cyclopentylphenylmethanol	—	Reflux in anisole	(44)
	5-Bromo-2-methoxyphenyllithium	2-(5-Bromo-2-methoxyphenyl)cyclohexanol	<4.5†	Reflux in ether	(7)
1,2-Epoxy-4-methylcyclohexane....... 	Methylmagnesium iodide	Dimethylcyclohexanol‡	"Very satisfactory"	Distill ether	(82, 83)
		2,5-Dimethylcyclohexanol‡	64	Distill ether and heat	(87)
	Isopropylmagnesium bromide	2-Isopropyl-4-methylcyclohexanol‡	—	Distill ether	(14, 17)
Cycloheptene oxide.. 	Methylmagnesium iodide	1-Methylcycloheptanol	—	—	(14)
	Phenylmagnesium bromide	Cyclohexylphenylmethanol	—	—	(93)
9,10-Epoxyoctalin... 	Methylmagnesium iodide	—	—	—	(39)

---

* Erroneously reported by the author as substituted cyclohexanol.

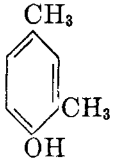
† Calculated from author's data.

‡ Reported by author as substituted methylcyclohexanol, although probably substituted methylcyclopentanol.

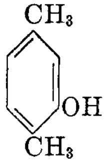
mocyclohexanol, while cyclohexylmagnesium chloride (13) and bromide (16) were reported to give 2-cyclohexylcyclohexanol. It was shown (86) that the halohydrin is the only product if the reaction mixture is worked up without heating, but that upon heating the substituted cyclohexanol is obtained.

The reaction of methylmagnesium iodide with 2-chlorocyclohexanol was reported (86) to give a 50 per cent yield of a mixture of alcohols. Two phenylurethans were obtained, one corresponding to that prepared from the hydrogenated *o*-cresol and the other to that derived from the reaction of cyclohexene oxide with the methyl Grignard reagent. In all these cases, discrepancies were found in boiling points and analyses of products and melting points of derivatives as compared with those previously reported by different syntheses. The authors attributed these anomalies to the existence of geometric isomers and to the fact that the derivatives reported previously were impure.

A similar situation existed with 1,2-epoxy-4-methylcyclohexane. Thus, methylcyclohexene oxide with methylmagnesium iodide (82, 83, 87) was reported to give isomeric 2,5- and 2,4-dimethylcyclohexanols. However, oxidation of the products with chromium trioxide in acetic acid gave one compound whose semicarbazone melted at 122°C., while the semicarbazones obtained by oxidation of the alcohols derived from hydrogenation of the xylenols



and

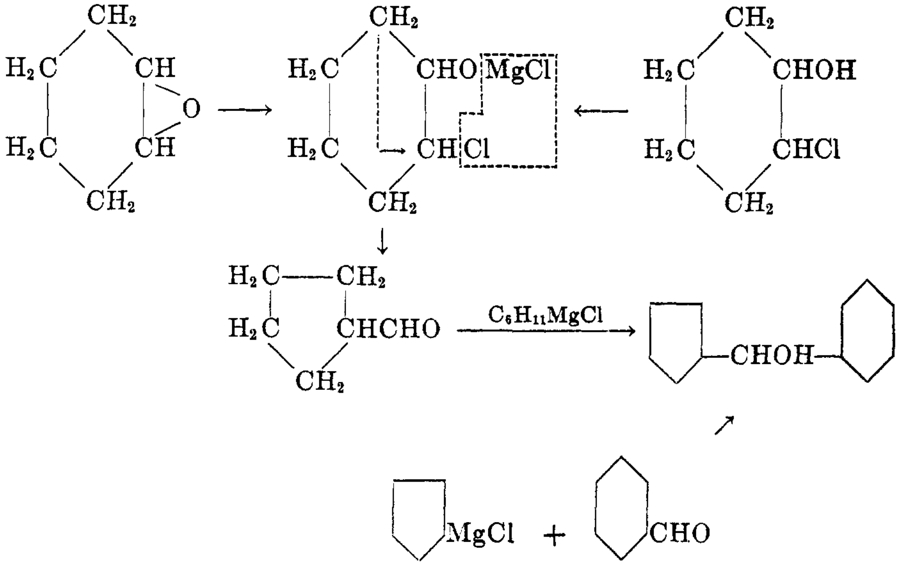


had melting points of 190° and 155°C., respectively.

As in the case of the cyclohexane halohydrin, 2-chloro-5-methylcyclohexanol with the methyl Grignard reagent gives (84, 87) a mixture of alcohols whose derivatives corresponded to those of the products obtained from the oxide. The authors did not realize at this time that they were victims of cyclic reasoning. Although the products from the oxide and the Grignard reagent were not completely identified, and in fact were dissimilar from those with which they were supposedly identical, the proof of structure of the alcohols derived from the halohydrin was that they were the same as those obtained from the oxide.

Isopropylmagnesium bromide and the methylcyclohexene oxide were reported (14, 17) to give an analogous cyclohexanol, while 2-chloro-5-methylcyclohexanol and the isopropyl Grignard reagent were reported (14, 17) to give a mixture of stereoisomeric isopropylmethylcyclohexanols analogous to those obtained with the methyl Grignard reagent.

In 1928 Vavon and Mitchovitch (218) found that cyclohexylmagnesium chloride and 1,2-epoxycyclohexane, as well as 2-chlorocyclohexanol, give, not 2-cyclohexylcyclohexanol as reported by Bedos (13, 16), but cyclohexylcyclopentylmethanol, identical with the product from cyclopentylmagnesium chloride and hexahydrobenzaldehyde. The contraction of the six-to a five-membered ring occurring through cyclopentylformaldehyde was postulated as follows:

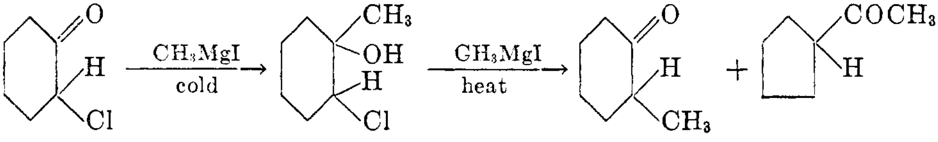


Almost simultaneously Godchot and Bedos (90), in 1928, reported that the product of the reaction of methylmagnesium iodide and cyclohexene oxide, or 2-chlorocyclohexanol, originally reported as 2-methylcyclohexanol (81, 86), was actually 1-cyclopentylethanol.

Fulton and Robinson originally reported in 1933 (72) that they had obtained, as a product from cyclohexene oxide and 2-phenylethylmagnesium bromide by distilling the ether, the result of direct addition: namely, 2-(2-phenylethyl)-cyclohexanol. However, they repeated their work in 1936 (172) and found that actually their product was 1-cyclopentyl-3-phenyl-1-propanol by transition from the six- to the five-membered ring through cyclopentylformaldehyde. Further, Bedos reported (18) that the action of magnesium bromide etherate on cyclohexene oxide, in which the ether was replaced by benzene or toluene and followed by decomposition with water, gives a 34 per cent yield of cyclopentylformaldehyde. Under the same conditions only a trace of aldehyde results when 2-chlorocyclohexanol is used, unless it is first treated with ethylmagnesium bromide, in which case a 40 per cent yield of cyclopentylformaldehyde results. Addition of methylmagnesium iodide to the adduct from the oxide, or chlorohydrin, and magnesium bromide gives a 40 per cent yield of 1-cyclopentylethanol. Thus the facile transition from a six- to a five-membered ring was established. The same rearrangement was reported by Clemo and Ormston (40).

A similar ring contraction of the oxide to cyclopentylformaldehyde was observed in the vapor phase over thorium oxide (20) and by the action of silver nitrate on 2-iodocyclohexanol (205). Another such rearrangement was observed in the reaction of 2-chlorocyclohexanone with the Grignard reagent. Vavon reported that this chloroketone with methyl (220), ethyl (219), and butyl (217)

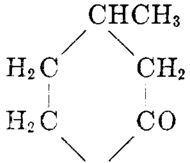
Grignard reagents gives upon heating and hydrolysis a mixture of the alkyl-substituted cyclohexanone and the alkyl cyclopentyl ketone. Similarly, 2-chlorocyclohexanone and methylmagnesium iodide in the cold give 2-chloro-1-methylcyclohexanol. Upon heating this product with methylmagnesium iodide a mixture of 2-methylcyclohexanone and acetylcyclopentane is obtained (208, 211). Analogous results are obtained with ethylmagnesium bromide.



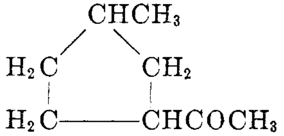
2-Methylcyclohexanone

Acetylcyclopentane

On the basis of these reactions it is possible to explain the results obtained by Godchot and Bedos with 1,2-epoxy-4-methylcyclohexane and with 2-chloro-5-methylcyclohexanol. Thus, the 4-methylcyclohexene oxide and methylmagnesium iodide give a mixture of alcohols whose allophanates have melting points of 157°C. and 125°C. However, oxidation of the two alcohols gives the same ketone, the semicarbazone of which melts at 122°C. The chlorohydrin and the Grignard reagent give the same results. The alcohols were postulated as stereoisomeric dimethylcyclohexanols, although Sabatier and Maihle (177) reported that oxidation of the dimethylcyclohexanol obtained by reduction of 2,5-xylenol gave a ketone, the semicarbazone of which melted at 155°C. At the same time, Godchot and Bedos (85) reported that 2-chloro-5-methylcyclohexanone reacted with methylmagnesium iodide to yield two 2,5-dimethylcyclohexanones, the semicarbazones of which melted at 155°C. and 122°C., and that the latter ketone was identical with that obtained by oxidation of the dimethylcyclohexanols obtained from the chlorohydrins. Tiffeneau and Tchoubar (208) repeated the reaction with the chloroketone and obtained two ketones, identified as 2,5-dimethylcyclohexanone and 1-acetyl-3-methylcyclopentane.



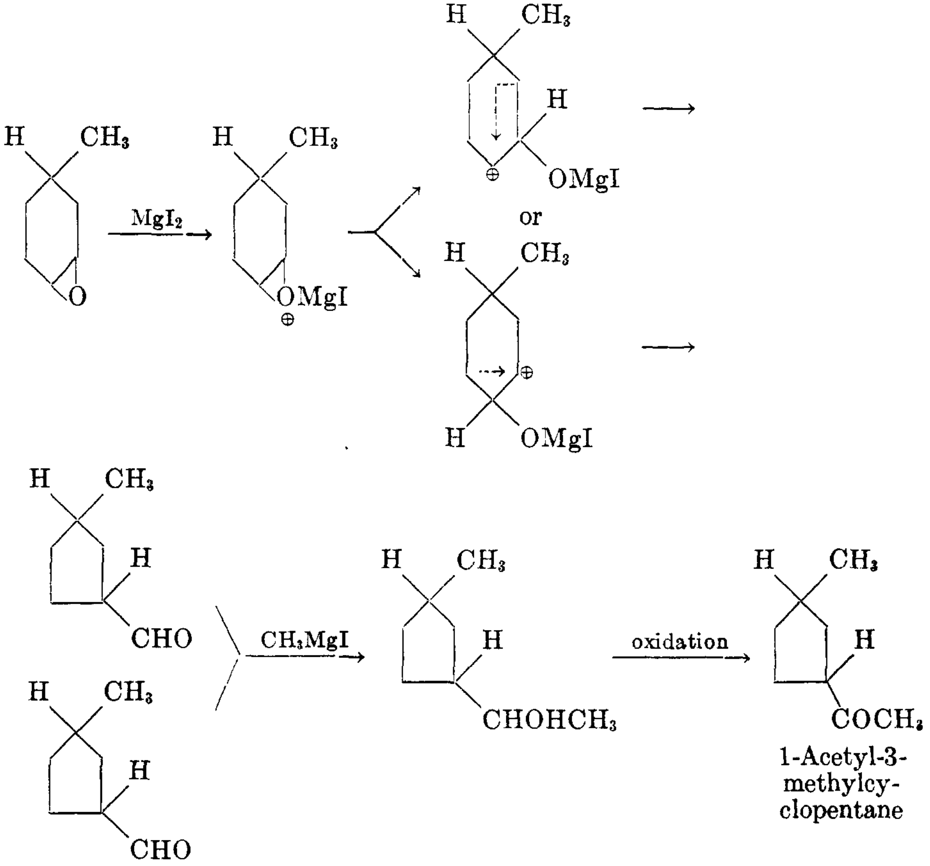
2,5-Dimethylcyclohexanone
(semicarbazone melts at 160°C.)



1-Acetyl-3-methylcyclopentane
(semicarbazone melts at 132°C.)

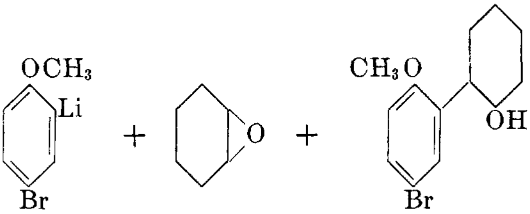
These products are the same as those reported by Godchot and Bedos, who obtained melting points of 155°C. and 122°C. It is therefore seen that the above cyclohexanone, the melting point of the semicarbazone of which has been reported as 155°C. (Sabatier), 155°C. (Godchot and Bedos), and 160°C. (Tiffeneau and Tchoubar), is analogous to the alkyl-substituted cyclohexanone obtained from 2-chlorocyclohexanone and the Grignard reagent. At the same time, 1-acetyl-3-

methylcyclopentane, the melting point of the semicarbazone of which has been reported as 132°C. (Tiffeneau and Tchoubar) and 122°C. (Godchot and Bedos), is the same as the product formed upon oxidation of the carbinols obtained from the Grignard reaction with 4-methylcyclohexene oxide and the corresponding chlorohydrin. The two alcohols obtained from the latter reactions are probably *cis–trans* isomers, since on oxidation they yield the same ketone. They may arise as follows:



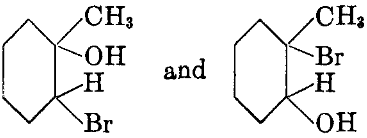
A similarly depicted intermediate would lead to a series of 2-methylcyclopentyl derivatives. This structure has not yet been ruled out.

As with acyclic oxides, cyclohexene oxide was found to react with diethylmagnesium without rearrangement to give *trans*-2-methyl- and -2-ethylcyclohexanols (10). This confirmed earlier findings that the presence of the halide was necessary for molecular rearrangement. Cook, Hewett, and Lawrence (44) gave additional results to establish the necessity for magnesium halide in the rearrangement reaction. Phenylmagnesium bromide and cyclohexene oxide, in the cold, on decomposition with water gave 2-bromocyclohexanol. The reaction with heating on the water bath was violent and was attended with rearrangement to cyclopentylphenylmethanol. The arrangement was avoided by using phenyllithium instead of phenylmagnesium bromide, the product being 2-phenylcyclohexanol. Similarly, 1-naphthyllithium gave 2-(1-naphthyl)cyclohexanol. However, an unexpected reaction was observed with one lithium compound. In an attempt to prepare 2-(4-methoxyphenyl)cyclohexanol by the reaction between the lithium derivative of *p*-bromoanisole and cyclohexene oxide a bromine-containing product was obtained (7). On the basis of previous work (79), which had established that *p*-anisyllithium can metalate *p*-bromoanisole ortho to the methoxy group, the product was assigned the structure 2-(5-bromo-2-methoxyphenyl)cyclohexanol.



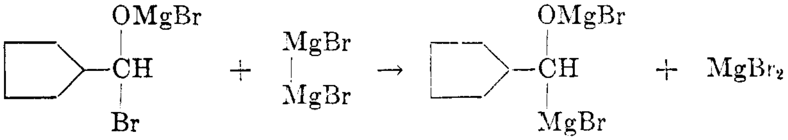
Benzylmagnesium chloride with 2-chlorocyclohexanol undergoes rearrangement to 1-cyclopentyl-2-phenylethanol. However, with cyclohexene oxide, even with heating, no rearrangement occurs and the product is 2-benzylcyclohexanol. Apparently dibenzylmagnesium is more reactive than benzylmagnesium chloride towards cyclohexene oxide. Some of the latter, however, does react, as indicated by the recovery (20 per cent) of 2-chlorocyclohexanol.

The influence of the magnesium halide in this series was further pointed up by the work of Tiffeneau and Tchoubar (209, 211). Cyclohexene oxide and magnesium bromide or iodide etherate, reacting in the cold, give after hydrolysis *trans*-2-halocyclohexanol. Upon heating, cyclopentylformaldehyde is formed. 1-Methylcyclohexene oxide with magnesium bromide etherate in the cold gives two isomeric *trans*-bromohydrins:

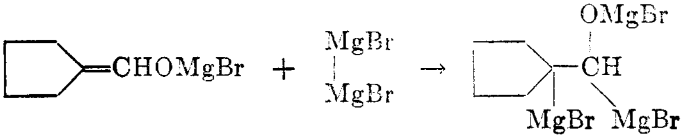


The first compound is stable and the second is unstable. If the bromohydrins are not isolated but the reaction mixture heated in the usual way by removal of ether, the first (stable) compound is dehydrohalogenated to acetylcyclopentane while the second (unstable) compound gives 1-methylcyclopentylformaldehyde and some 2-methylcyclohexanone.

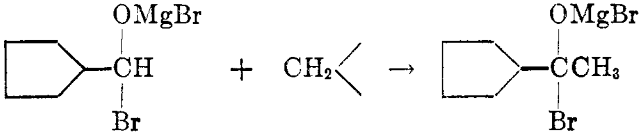
A new case of contraction of a six- to a five-membered ring by means of magnesium bromide etherate has recently been reported (19). Cyclohexene oxide and a mixture of methylmagnesium bromide and magnesium bromide etherate give a mixture of acetylcyclopentane and cyclopentylmethanol. With ethylmagnesium bromide and the etherate the products were propionylcyclopentane and cyclopentylmethanol. The author invoked magnesium subbromide and the methylene and ethylidene radicals to explain the results.



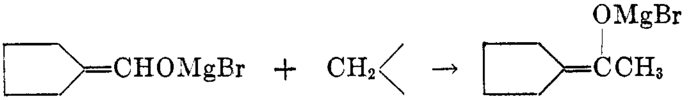
or



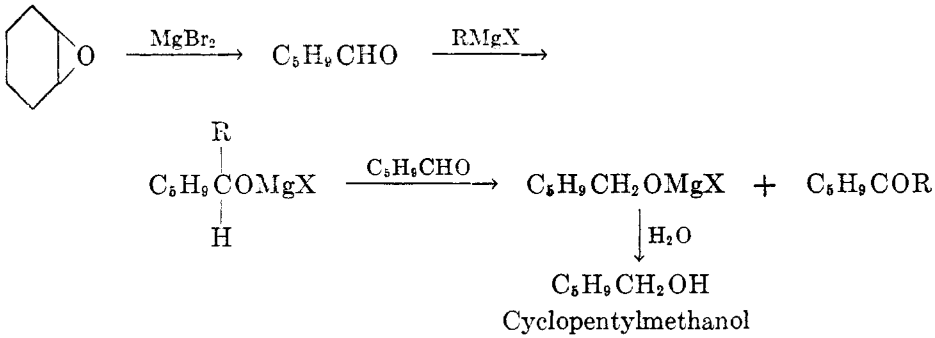
and



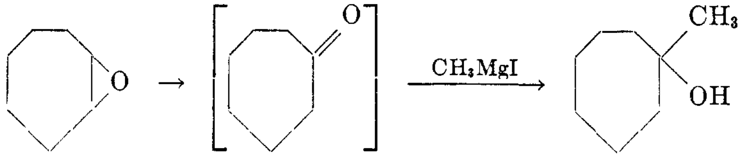
or



A more reasonable mechanism would involve isomerization of cyclohexene oxide to cyclopentylformaldehyde, followed by addition of the Grignard reagent. In accord with the known fact that secondary halomagnesium alkoxides may be oxidized to ketones by the addition of an aldehyde (32), the alkoxide is then oxidized by unreacted aldehyde.

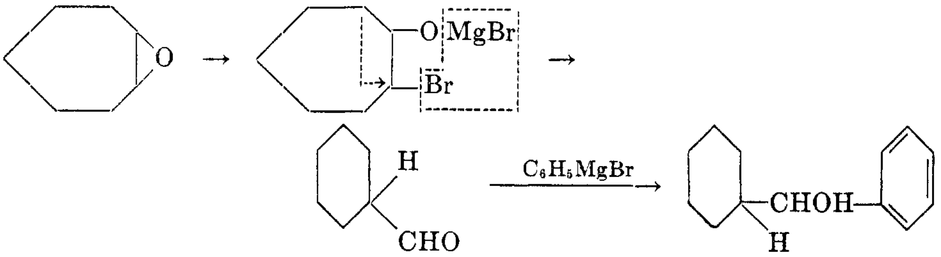


Godchot and Bedos (89) reported that cycloheptene oxide behaves differently from analogous five- and six-membered ring compounds with methylmagnesium iodide. The product obtained, 1-methylcycloheptanol, indicated isomerization to the ketone, suberone, followed by normal Grignard addition and was said to be the same as the alcohol prepared by Wallach from methylmagnesium iodide and suberone itself.



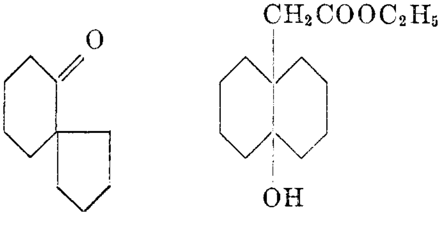
Cycloheptene oxide   Suberone   1-Methylcycloheptanol

However, with phenylmagnesium bromide cycloheptene oxide gives the same alcohol as that formed from cyclohexylmagnesium chloride and benzaldehyde (93), indicating ring contraction to cyclohexylformaldehyde.

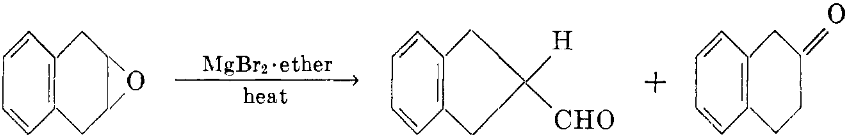


Ring contraction of cycloheptene oxide to cyclohexylformaldehyde by magnesium bromide was reported by Bedos (18). With 2-chlorocycloheptanol, ring contraction also occurs in reaction with both methyl and phenyl Grignard reagents. Thus, methylmagnesium iodide gives 1-cyclohexylethanol (90, 91, 92) and phenylmagnesium bromide gives cyclohexylphenylcarbinol (90) and ethylidenecyclohexane. The report that cycloheptene oxide reacts with methylmagnesium iodide to give 1-methylcycloheptanol (89) is therefore probably in error. It was reported one year before the authors learned that ring contraction attended the reaction of oxides and halohydrins with Grignard reagents (90). Furthermore, they had compared only the boiling point of their alcohol with that obtained unequivocally by Wallach (222).

The reaction of 9,10-epoxyoctalin with methylmagnesium iodide has been reported, but the reaction mixture was not separated (39). However, at the same time this oxide was subjected to the Reformatsky reaction, using zinc and ethyl bromoacetate. By this procedure a mixture of a rearranged product and the expected addition product is produced. Since such rearrangements are also characteristic of the Grignard reaction, analogous products might be expected to have formed from the reaction with methylmagnesium halide.

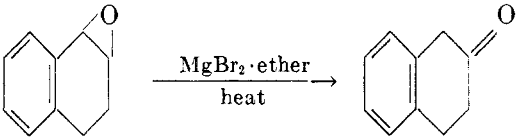


The isomerizations observed with other cyclic epoxides in the presence of magnesium bromide etherate are of interest, although Grignard reactions with these oxides have not been reported. Thus, Tchoubar (199) observed the isomerization of 1,4-dihydronaphthalene oxide to 2-indanaldehyde and β-tetralone,



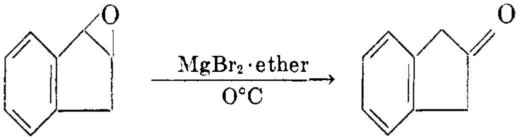
2-Indanaldehyde (major product) β-Tetralone

while 3,4-dihydronaphthalene oxide rearranges only to one product, β-tetralone.



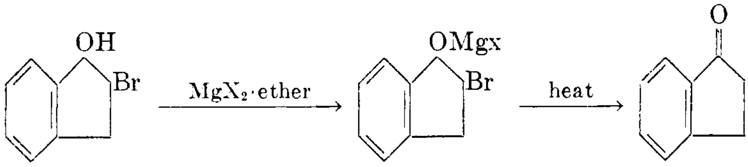
β-Tetralone

On the other hand, treating indene oxide with the etherate at 0°C. yields 2-indanone,



2-Indanone

while treatment of the bromohydrin or iodohydrin with the etherate, followed by heating, yields 1-indanone:



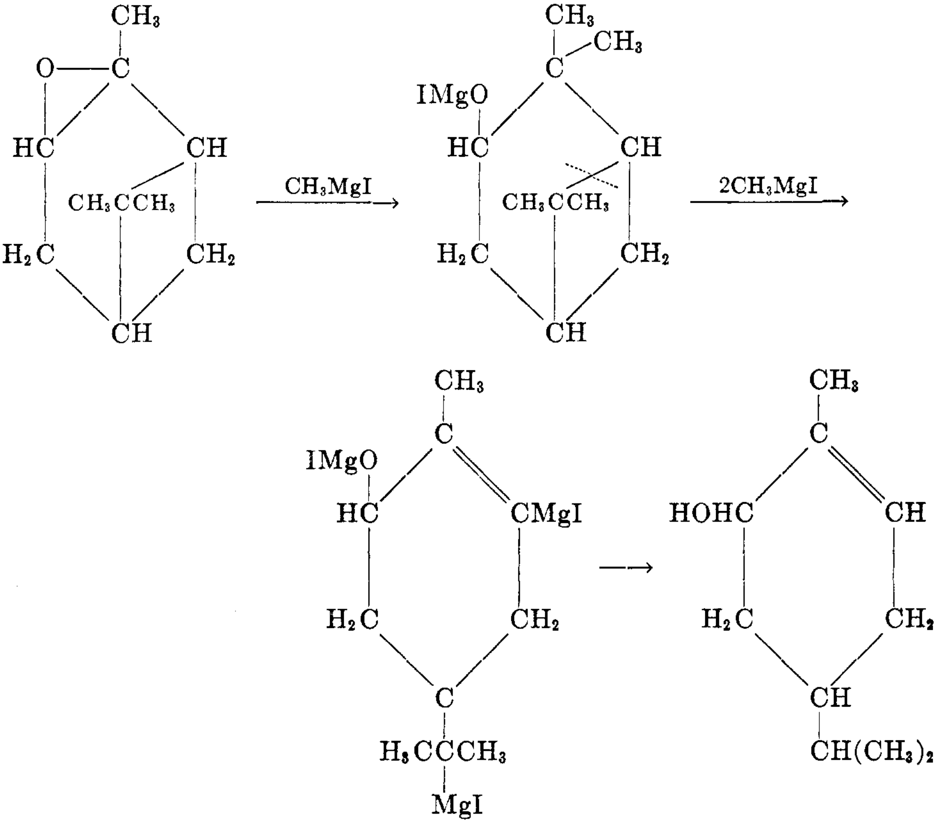
1-Indanone

A more complete discussion of these rearrangements has been given by Winstein and Henderson (227).

B. TERPENE EPOXIDES (SEE TABLE 8)

In the reaction with Grignard reagents oxides in the terpene series behave similarly to other oxides in that rearrangements occur when magnesium halide is present. The reaction of α-pinene oxide with methyl, ethyl, and isopropyl

Grignard reagents was reported by Prilezhaev and Vershuk (163) to proceed in a complicated manner, producing unsaturated alcohols. With methylmagnesium iodide, 1-menthen-6-ol was supposedly produced according to the following scheme:



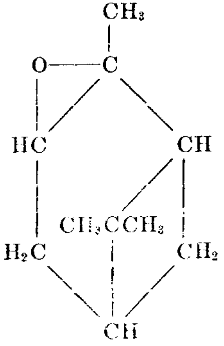
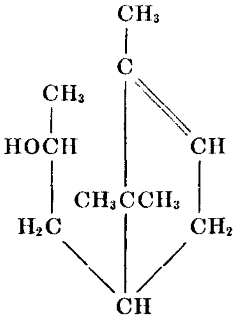
1-Menthen-6-ol

With the ethyl and isopropyl Grignard reagents it was postulated that the aliphatic group of the Grignard reagent displaces the methyl group of the oxide as methane and forms the unsaturated alcohol. The gaseous products which were evolved were not analyzed but were assumed to consist mainly of methane. In the case of the isobutyl Grignard reagent, although the product appeared to be unsaturated as indicated by its oxidation by permanganate and the addition of two atoms of bromine, the analytical data were interpreted as representing a saturated normal reaction product. This inconsistency was explained by nonhomogeneity of the product and the participation of the *gem*-dimethylcyclobutane bridge in the reactions, indicating unsaturation. With the phenyl Grignard reagent, no gas was evolved; the product only slowly oxidized permanganate and the analysis indicated a saturated alcohol. The reaction with the isobutyl and phenyl Grignard reagents was assumed, therefore, to proceed normally and

TABLE 8

Reaction of cyclic epoxides with Grignard reagents

B. Terpene epoxides

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS	REFERENCE
			per cent		
α-Pinene oxide............. 	Methylmagnesium iodide	 Methylcampholenol	82* †	Stir	(163)
			70	Replace ether with benzene; reflux at 70°C. for 6 hr.	(170)
	Ethylmagnesium iodide	Ethylcampholenol†	—	Stir	(163)
	C_2H_5MgX	Ethylcampholenol	70	Replace ether with benzene; reflux at 70°C. for 6 hr.	(170)
	C_3H_7MgX	*n*-Propylcampholenol	70	Replace ether with benzene; reflux at 70°C. for 6 hr.	(170)
	Isopropylmagnesium chloride	Isopropylcampholenol†	—	Stir	(163)

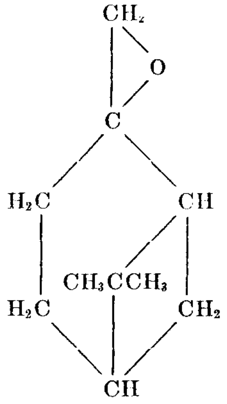
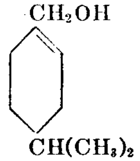
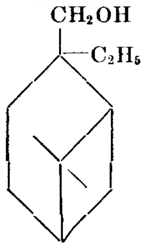
	n-C_4H_9MgX	n-Butylcampholenol	70	Replace ether with benzene; reflux at 70°C. for 6 hr.	(170)
	Isobutylmagnesium bromide	Isobutylcampholenol†	26*	Stir	(163)
	i-C_4H_9MgX	Isobutylcampholenol	70	Replace ether with benzene; reflux at 70°C. for 6 hr.	(170)
	Phenylmagnesium bromide	Phenylcampholenol†	—	Stir	(163)
		Phenylcampholenol	31*	Warm 1/2 hr. on water bath	(3, 5)
	C_6H_5MgX	Phenylcampholenol	70	Replace ether with benzene; reflux at 70°C. for 6 hr.	(170)
β-Pinene oxide 	Methylmagnesium iodide	1-Menthen-7-ol 	—	Stir	(162)

TABLE 8—*Concluded*

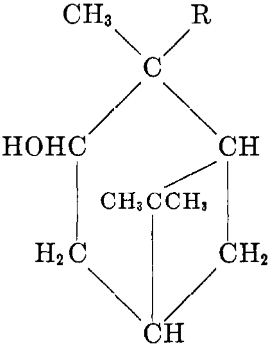
OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS	REFERENCE
			per cent		
	Ethylmagnesium bromide	1-Menthen-7-ol	—	Stir	(162)
		1-Ethyldihydromyrtenol 	—		

---

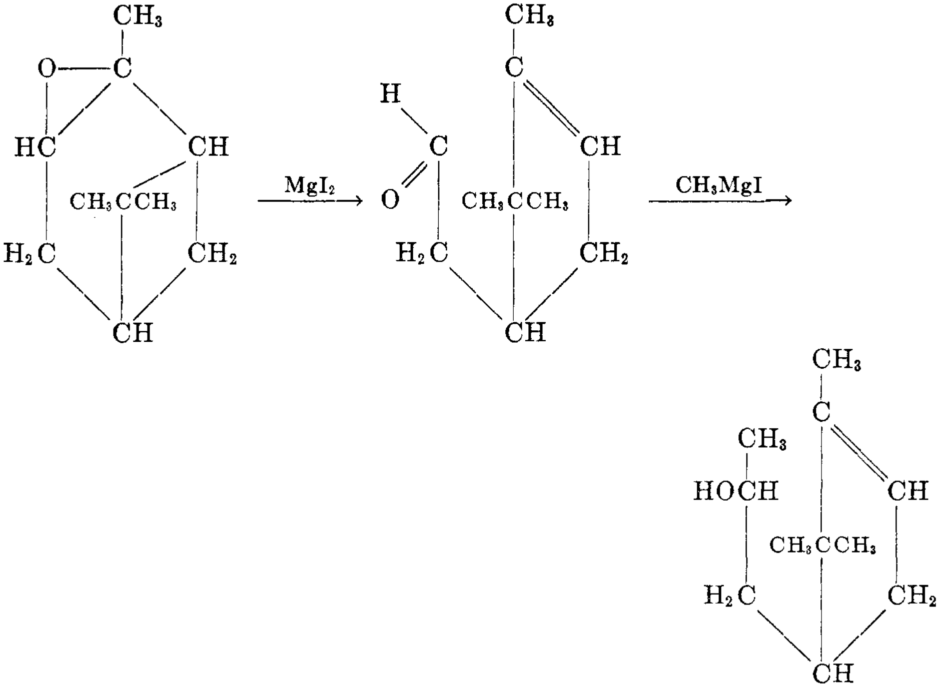
* Calculated from author's data.

† Product erroneously considered as 1-menthen-6-ol or its homolog.

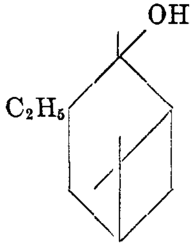
the products were assigned the following structure:



The reported isomerization of α-pinene oxide in the Reformatsky reaction and under the influence of zinc bromide to campholenic aldehyde (2) led to a reinvestigation of the reaction of the oxide and the Grignard reagent. Ritter and Russell (170) found that campholenic aldehyde, prepared by isomerization of the oxide with zinc bromide, reacts with methylmagnesium iodide to yield methylcampholenol identical with the product obtained directly from α-pinene oxide by action of the same reagent. A series of carbinols was obtained from α-pinene oxide and the ethyl, *n*-propyl, *n*-butyl, isobutyl, and phenyl Grignard reagents. The structures of the alcohols were not demonstrated, but by analogy with methylcampholenol they were considered homologs of methylcampholenol. The reaction of the oxide and the Grignard reagent was said, therefore, to proceed as follows:

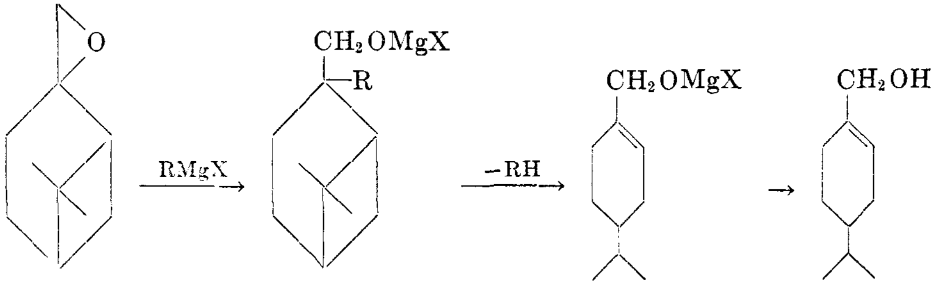


In an independent study of the reaction between α-pinene oxide and phenylmagnesium bromide Arbusov (3, 5) obtained results that indicated initial isomerization to campholenic aldehyde and so confirmed the findings of Ritter and Russell. However, α-pinene oxide and diethylzinc gave an alcohol, $C_{12}H_{22}O$, which differed from that obtained by Ritter and Russell (170) and by Prilezhaev and Vershuk (163) from α-pinene oxide and ethylmagnesium bromide. By analogy with other dialkyl compounds, it may be surmised that this alcohol is that resulting from simple ring cleavage:



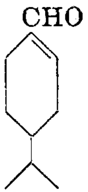
Phenyllithium failed to react with α-pinene oxide even when heated to 70°C.

The behavior of β-pinene oxide with the Grignard reagent has been investigated by Prilezhaev and Prokopchuk (162). They reported the synthesis of the same alcohol, 1-menthen-7-ol, from both methyl and ethyl Grignard reagents, with the evolution of a gas which was not identified but was assumed to correspond to the Grignard reagent involved. The mechanism advanced was as follows:



1-Menthen-7-ol

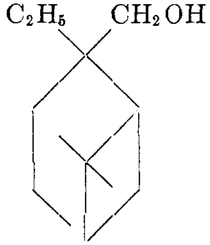
In the reaction with methylmagnesium iodide the product was not homogeneous and the alcohol was isolated by saponification of its acetate. The remainder of the reaction product was not considered, but the isolated alcohol, which was oxidized by permanganate and added bromine in the cold, was oxidized to an aldehyde with a "chromium salt." On the basis of the density, refractive index, and analysis of the aldehyde and melting point of the semicarbazone and its analysis, the structure assigned was that of phellandral.



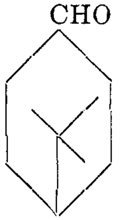
Phellandral

Actually, there is sufficient variation in the physical properties of the carbonyl compound obtained from those given for phellandral to raise a doubt as to their identity. Thus the aldehyde obtained by Prilezhaev and Prokopchuk had the following physical constants: b.p. 122–125°C./32 mm., $d^{20} = 0.9760$, $n_D^{20} = 1.4830$, while phellandral (168) has the following physical constants: b.p. 89°C./5 mm., $d^{20} = 0.9412$, $n_D^{20} = 1.4912$. The semicarbazones melted at 201° and 204°C., respectively.

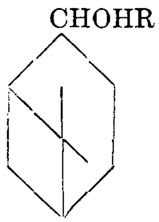
The reaction of β-pinene oxide and ethylmagnesium bromide gave an alcohol which was assumed to be identical with that obtained from the methyl Grignard reagent on the basis of analytical data, physical properties, and reaction with permanganate and bromine. In addition to this alcohol the reaction with the ethyl Grignard reagent gave an alcohol supposedly formed by normal addition and assigned the following structure:



The structures are all open to doubt in view of the fact that β-pinene oxide upon distillation with pumice (60), or upon refluxing with zinc chloride or bromide in benzene (4), isomerizes to dihydromyrtenal:



The same result is observed in the Reformatsky reaction with β-pinene oxide (4). The alcohols probably have the structure derived from dihydromyrtenal (186):



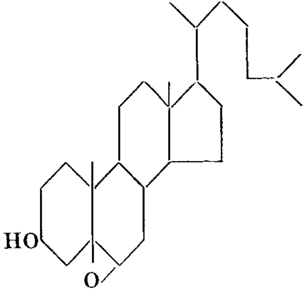
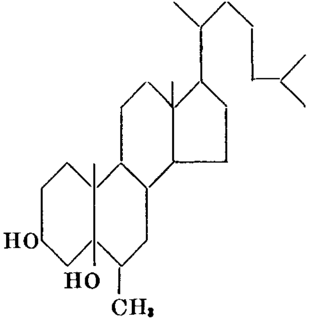
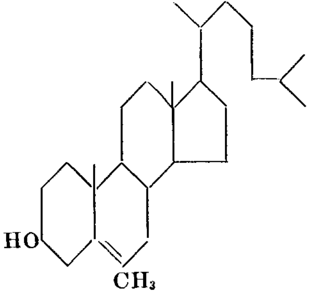
C. STEROL EPOXIDES (SEE TABLE 9)

Ushakov and Madaeva (214) reported that although dimethylmagnesium and methyllithium did not react with α-epoxycholesterol, heating in benzene for

TABLE 9

Reaction of cyclic epoxides with Grignard reagents

C. Sterol epoxides

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS	REFERENCE
			per cent		
α-Epoxycholesterol............... 	Methylmagnesium iodide	6-Methyl-3,5-cholestanediol 	60	Reflux 5 hr. at 78°C. in benzene	(214)
		6-Methylcholesterol 	—	Reflux 7 hr. at 78°C. in benzene	(214)

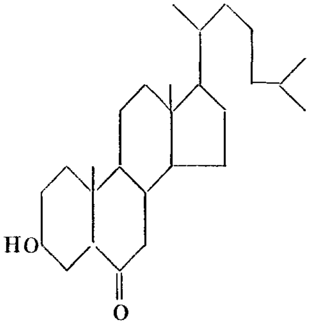
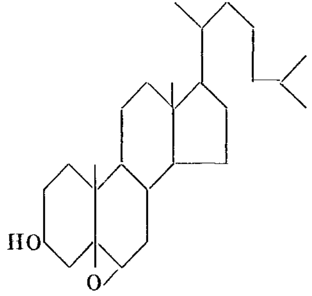
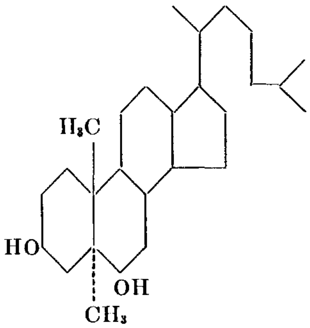
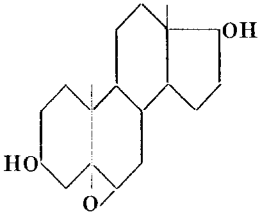
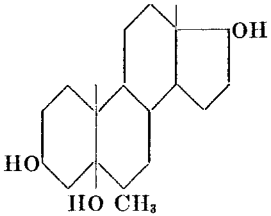
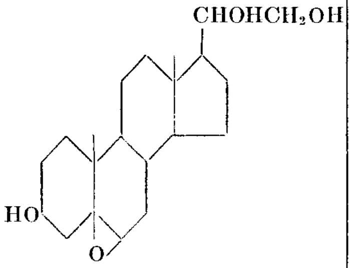
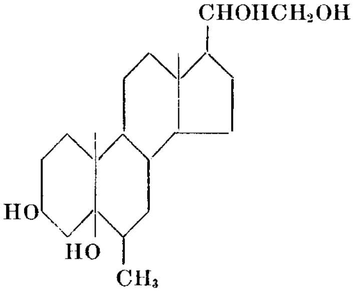
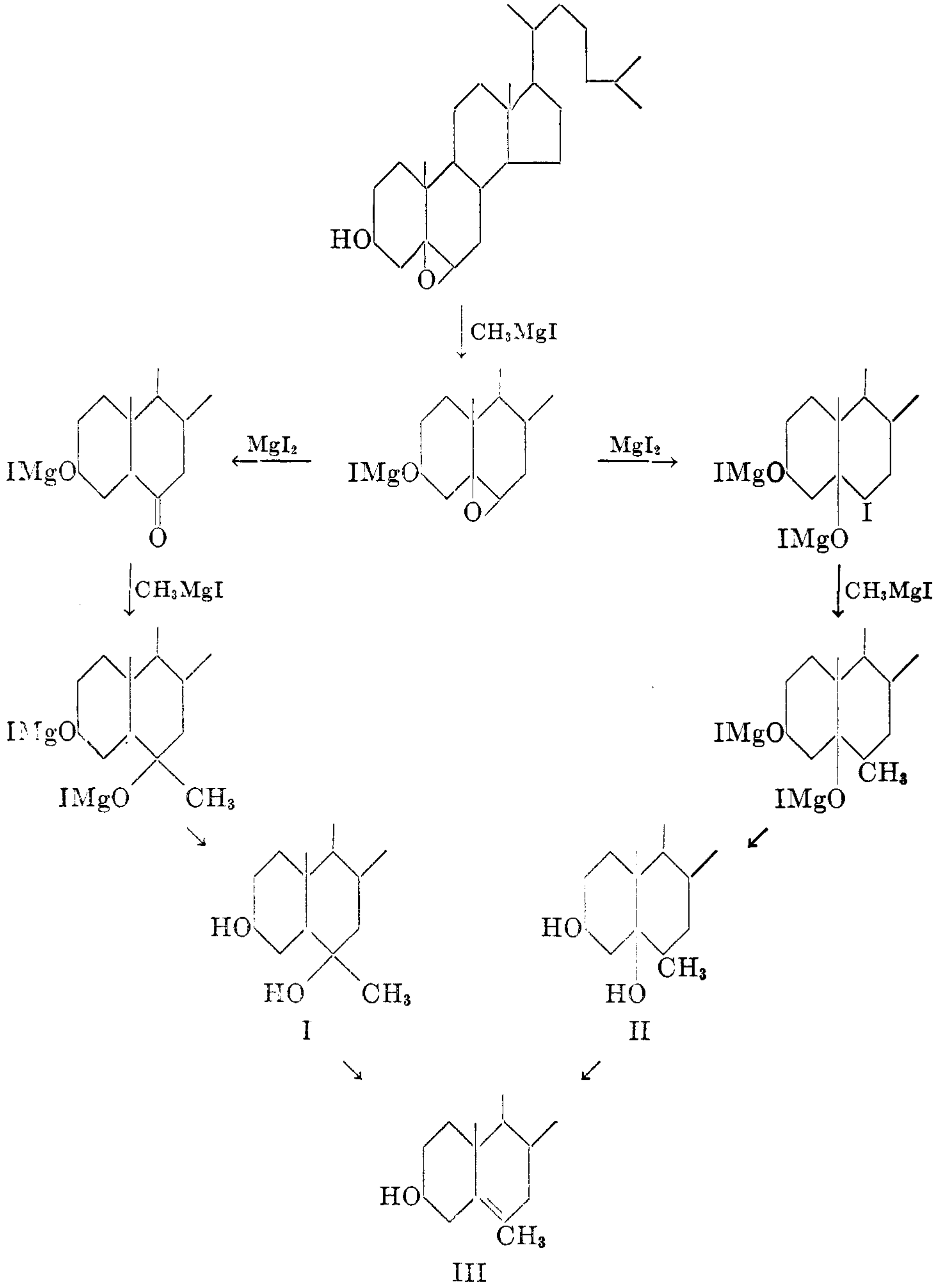
	Phenylmagnesium bromide	6-Keto-3-cholestanol 	—	Reflux at 70°C. in benzene	(38)
β-Epoxycholesterol................ 	Methylmagnesium iodide		—	—	(213a)

TABLE 9—*Concluded*

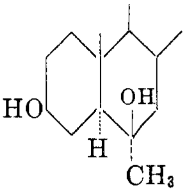
OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS	REFERENCE
			per cent		
5,6-Epoxyandrostane-3,17-diol .... 	Methylmagnesium iodide	6-Methylandrostane-3,5,17-triol 	—	Reflux at 78°C. in benzene for 3 hr.	(145)
5,6-Epoxypregnane-3(β),20,21-triol .... 	Methylmagnesium bromide	6-Methylpregnane-3(β), 5,20,21-tetraol 	53*	Reflux at 130°C. for 3¼ hr.	(58)

* Calculated from author's data.

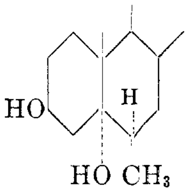
5 hr. with methylmagnesium iodide gave a 60 per cent yield of a sterol diol. If the reaction is continued for 7 hr. the product is 6-methylcholesterol, formed by dehydration of the alcohol. The diol contains one tertiary hydroxyl group as a result of the Grignard reaction. The reaction can proceed by two distinct paths:



The possible isomerization of the oxide to the ketone, leading to the diol I, was investigated (215). Benzene and ether solutions of the oxide were heated with magnesium iodide. No carbonyl compound, as shown by failure to obtain a semicarbazone, was obtained in either case; the only reaction product formed was cholesterol, probably produced by the reducing action of the hydrogen iodide formed in the reaction. When magnesium bromide was used, neither cholesterol nor a carbonyl compound was formed, but an unsaturated crystalline material, $C_{27}H_{44}O$, was isolated in 25 per cent yield. This compound "appeared to be a double compound." Treatment of α-epoxycholesterol with dilute sulfuric acid led to hydration of the epoxy group but no isomerization. Therefore it was concluded that α-epoxycholesterol does not tend to isomerize to a carbonyl compound, and thus the product from the Grignard reaction must be 6-methyl-3,5-cholestanediol (II), formed by normal cleavage of the oxirane ring. Notwithstanding this inability to isomerize the oxide to a ketone, the Fiesers (63) maintain that structure II is unlikely because a *cis*-elimination would be required for the establishment of the 5,6-double bond in III. They choose structure IV—the structure considered and discarded by Ushakov and Madaeva—as more likely and able to account for the properties noted and the dehydration to III.[5]

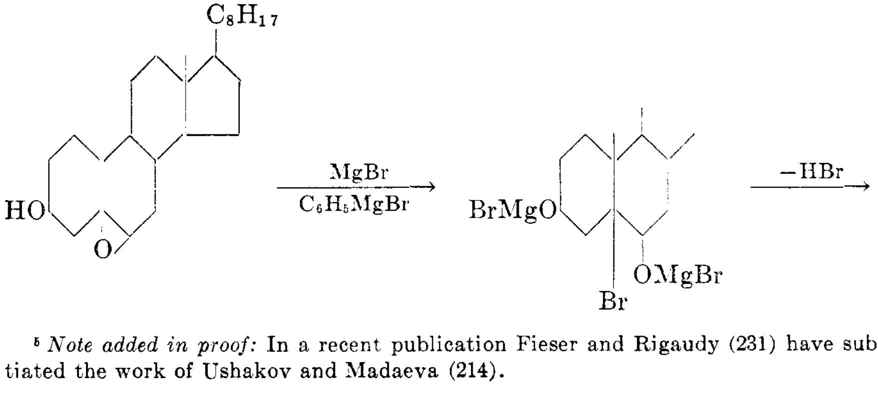


IV



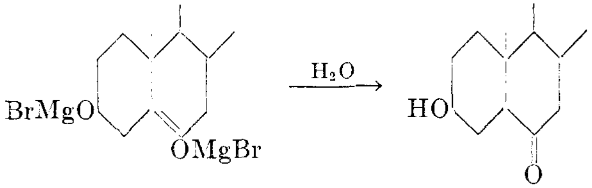
V

In line with this, Chinaeva and Ushakov (38) found that when phenylmagnesium bromide and α-epoxycholesterol are heated in benzene at 70°C. and the resulting tar is treated with benzoyl chloride and then with semicarbazide hydrochloride in chloroform, the product is a semicarbazone benzoate from which 6-keto-3-cholestanol is obtained. This reacts with phenylmagnesium bromide to give 6-phenyl-3,6-cholestanediol. The scheme proposed is as follows:



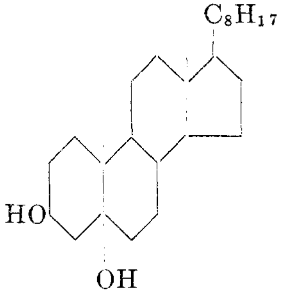
---

[5] *Note added in proof:* In a recent publication Fieser and Rigaudy (231) have substantiated the work of Ushakov and Madaeva (214).

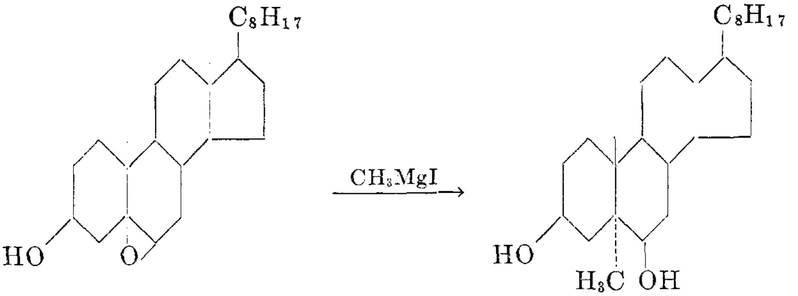


VI

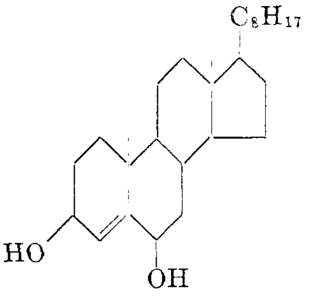
The formation of VI explains why the ketone can be isolated in spite of the large excess of Grignard reagent used. The action of phenyllithium on the oxide is to reduce it to 3,5-cholestanediol:



Urushibara and Chuman (213a) report that β-cholesteryl oxide with methylmagnesium iodide produces 5(α)-methyl-3(β),6(β)-cholestanediol, a product which gives a diacetate, a dibenzoate, and a diketone, 5(α)-methyl-3,6-cholestanedione.



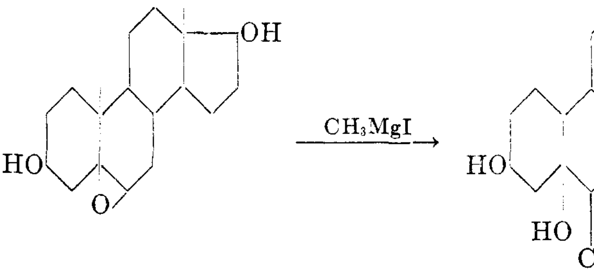
β-Cholesteryl oxide 5(α)-Methyl-3(β),6(β)-cholestanediol



Δ^4-3(β),6(β)-Cholestenediol

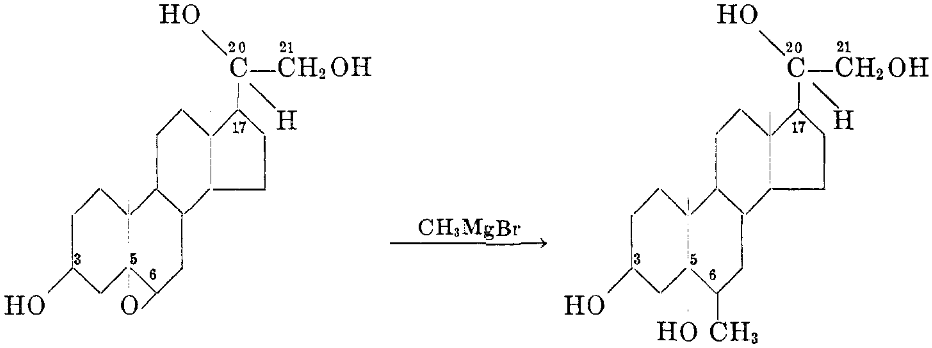
Chuman (230) reported that with α-cholesteryl oxide methylmagnesium iodide gave 6(α)-methyl-3(β),5(α)-cholestanediol and also a small quantity of Δ^4-3(β),6(β)-cholestenediol (see page 503).

The oxide of $\Delta^{5,6}$-androstene-3,17-diol was reported (145) to give 6-methylandrostane-3,5,17-triol after boiling in benzene for 3 hr. with methylmagnesium iodide:



The structure of the product, indicating ring cleavage, was not proved but simply assigned on the basis of the earlier work with cholesterol α-oxide and the methyl Grignard reagent (214).

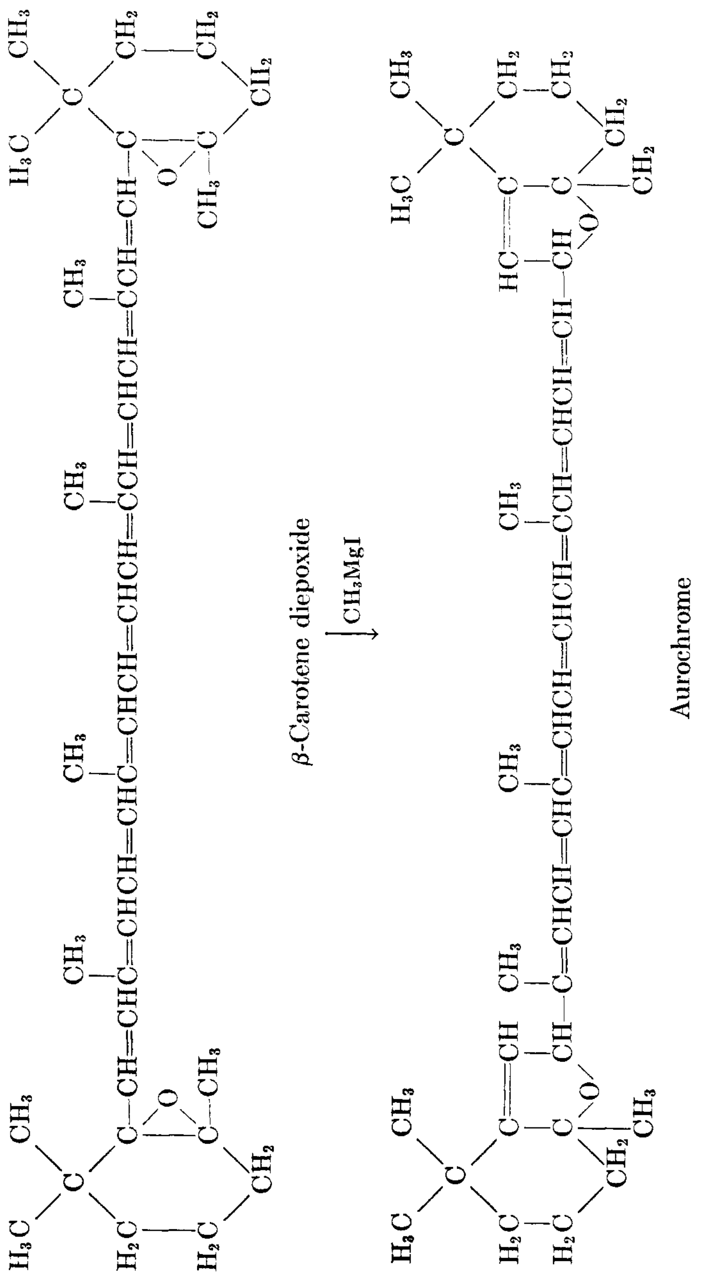
Ehrenstein (58) allowed pregnane-$\Delta^{5,6}$-oxide-3(β),20,21-triol to react with methylmagnesium bromide in anisole at 130°C. for 3 hr. and obtained 6-methylpregnane-3(β),5,20,21-tetraol:



The product was assigned the indicated structure in preference to the isomeric product arising through rearrangement to a ketone, owing to the fact that the characteristic ultraviolet absorption spectrum of an α,β-unsaturated ketone was obtained after chromic acid oxidation of the hydroxy group in the 3-position to the ketone, followed by dehydration by dry hydrogen chloride to the 4-pregnene compound.

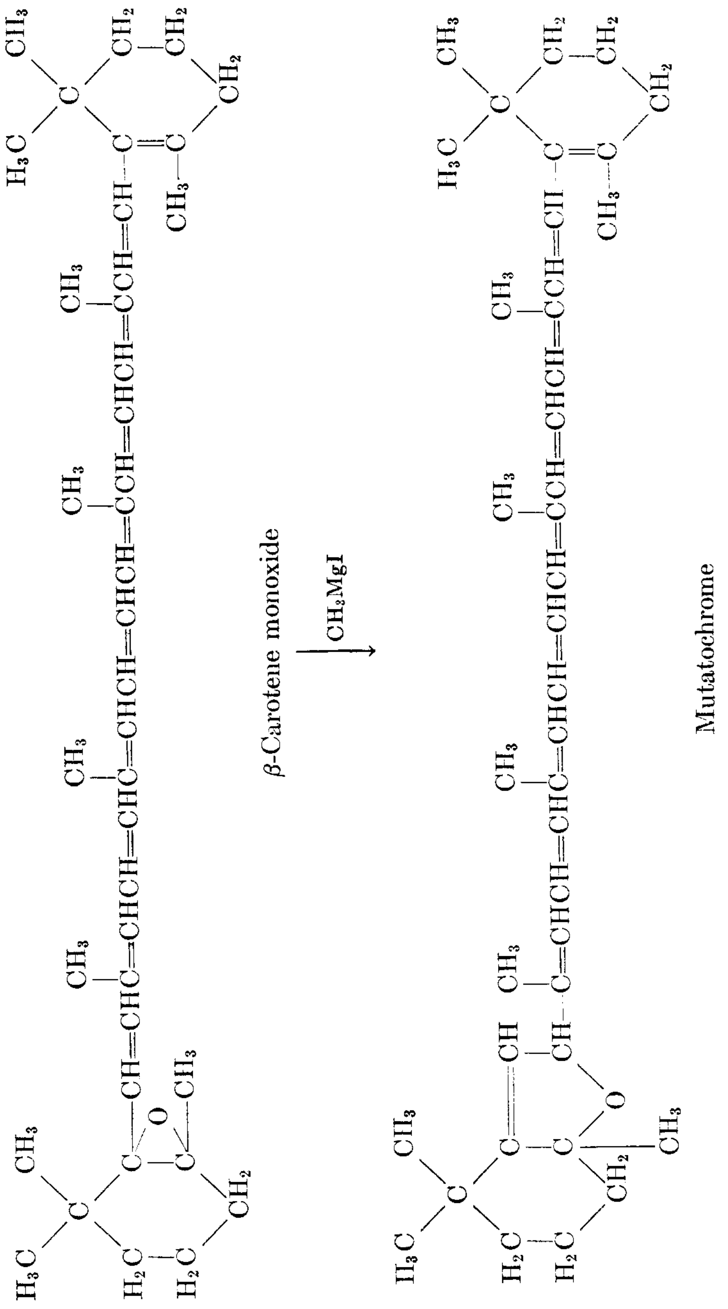
D. CAROTENE EPOXIDES

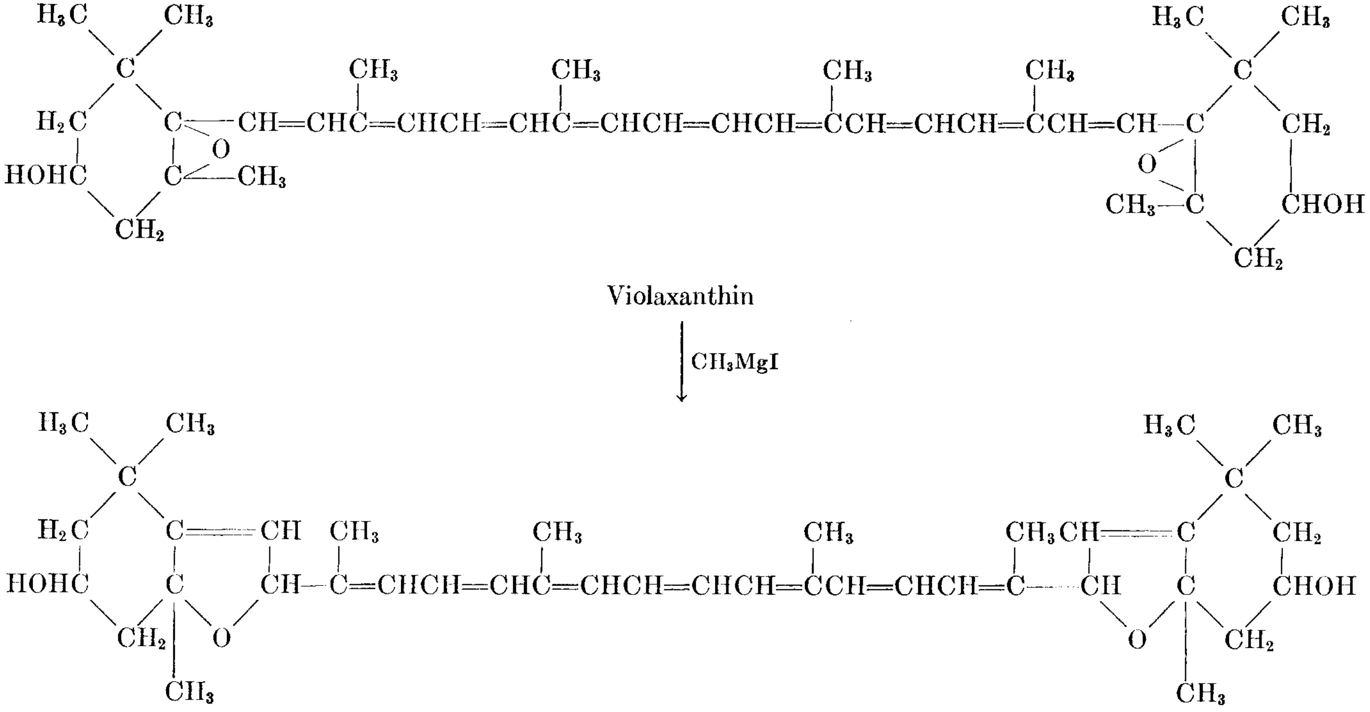
An unusual reaction was observed by Karrer, Jucker, and Steinlin (126). It was found that β-carotene diepoxide and methylmagnesium iodide, after warming and hydrolysis, gave aurochrome (see page 505).



β-Carotene diepoxide

Aurochrome

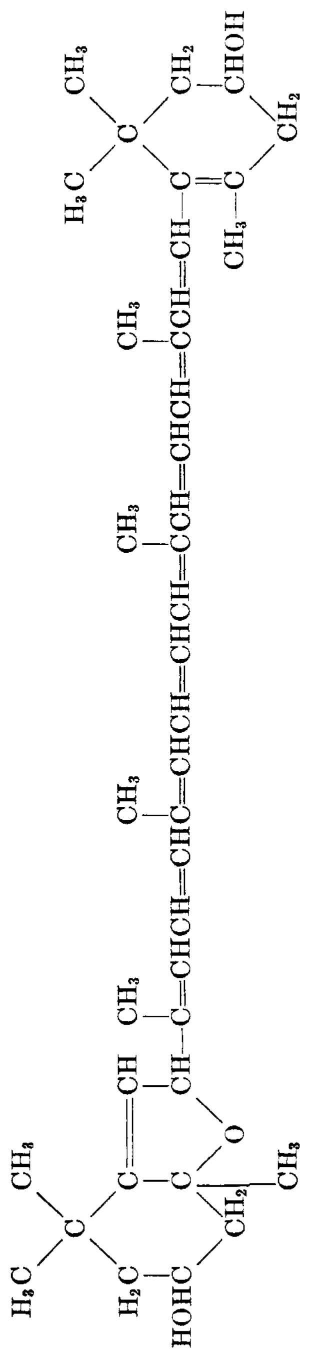

β-Carotene monoxide
CH$_3$MgI
Mutatochrome



Violaxanthin

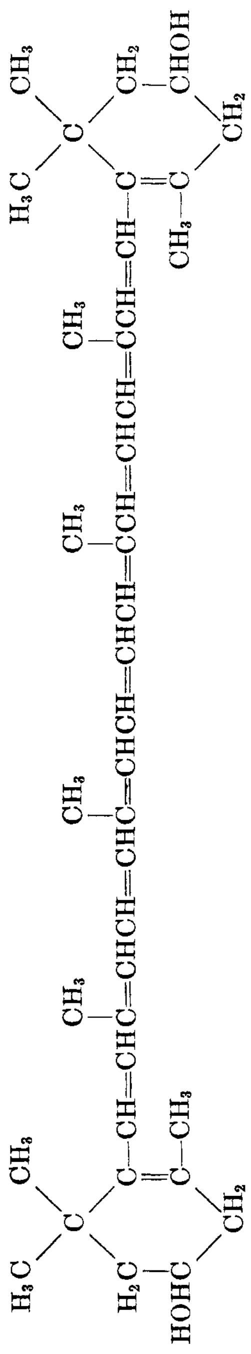
Auroxanthin

and traces of



Mutatoxanthin

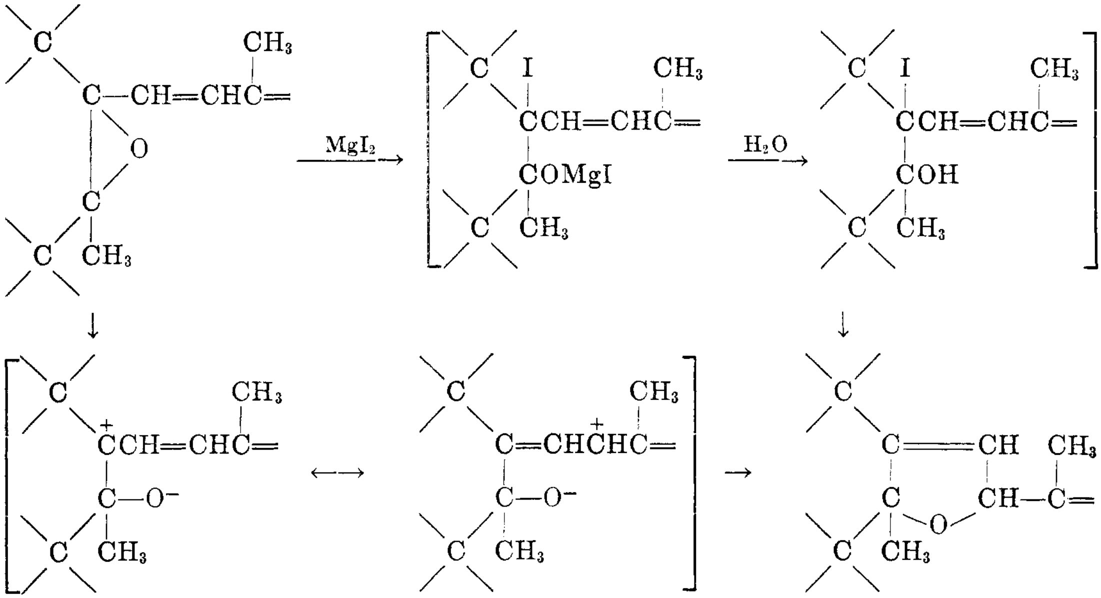
and



Zeaxanthin

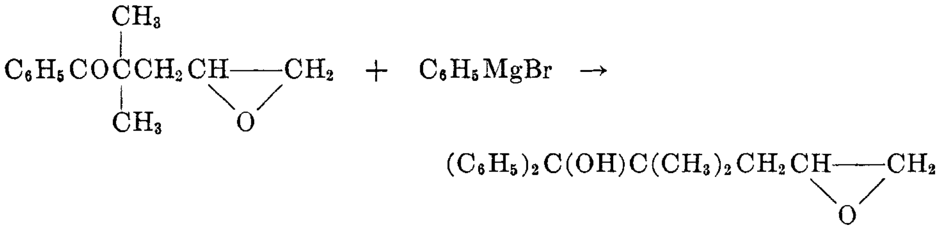
Similarly, β-carotene monoepoxide gave mutatochrome and violaxanthin gave auroxanthin along with traces of mutatoxanthin and zeaxanthin (see pages 506–508).

Thus, the effect of alkylmagnesium salts upon carotene oxides is to cause a rearrangement into furanoic oxides, analogous to the rearrangement observed with a chloroform solution of hydrogen chloride. Two mechanisms were suggested, the first requiring the addition of magnesium iodide to the oxirane ring, followed by splitting out of hydrogen iodide and rearrangement, and the second involving cleavage of the ring under the influence of the polar Grignard reagent, followed by an allylic shift and ring closure to a five-membered ring. The latter appears more feasible, in view of the identical change brought about with hydrogen chloride.



V. EPOXY KETONES, ESTERS, AND CARBINOLS (SEE TABLE 10)

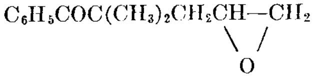
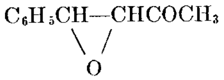
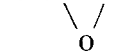
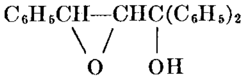
Haller and Ramart-Lucas (102) found that in an epoxy ketone in which the carbonyl group is not directly attached to the oxirane ring, the carbonyl group alone is attacked by a Grignard reagent despite the hindrance to the reaction created by a branched chain:



$$C_6H_5CO\overset{CH_3}{\underset{CH_3}{C}}CH_2\underbrace{CH\text{——}CH_2}_{O} + C_6H_5MgBr \rightarrow (C_6H_5)_2C(OH)C(CH_3)_2CH_2\underbrace{CH\text{——}CH_2}_{O}$$

TABLE 10

Reaction of epoxy ketones, esters, and carbinols with the Grignard reagent

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS	REFERENCE
			per cent		
1,2-Epoxy-4,4-dimethyl-5-phenyl-5-pentanone  $C_6H_5COC(CH_3)_2CH_2CH—CH_2$ (O)	Phenylmagnesium bromide	1,2-Epoxy-4,4-dimethyl-5,5-diphenyl-5-pentanol	—	Reflux 6–7 hr.	(102)
Benzalacetone oxide  $C_6H_5CH—CHCOCH_3$ (O)	Mesitylmagnesium bromide	Acetylmesitylene $2,4,6\text{-}(CH_3)_3C_6H_2COCH_3$	—	Stir at room temperature	(141)
Benzalacetophenone oxide  $C_6H_5CH—CHCOC_6H_5$ (O)	Ethylmagnesium bromide	3-Phenyl-3-pentanol	66	Stir at room temperature	(141)
	Phenylmagnesium bromide	Triphenylmethanol	70	Stir at room temperature	(141)
		1,2-Epoxy-1,3,3-triphenyl-3-propanol  $C_6H_5CH—CHC(C_6H_5)_2$ (O) (OH)	49*	Stir at −10°C.; decompose immediately	(141)
			45*	(1:1) inverse addition at −10°C.; decompose immediately	(141)

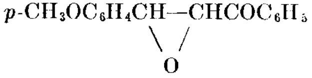
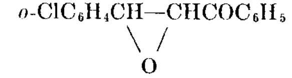
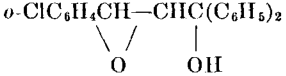
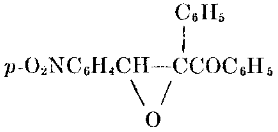
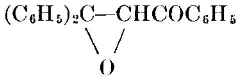
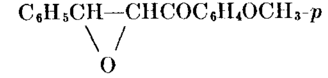
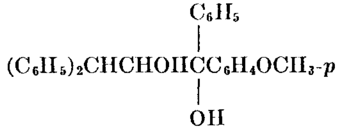
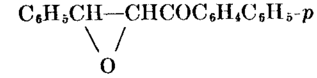
		Benzophenone	—	(1:1) inverse addition at −10°C.; let stand overnight at room temperature	(141)
	Phenylmagnesium bromide + Mg + $MgBr_2$	Benzopinacol	25*	Let stand at room temperature	(8)
Anisalacetophenone oxide  $p\text{-}CH_3OC_6H_4\underset{\diagdown O \diagup}{CH\text{—}CH}COC_6H_5$	Phenylmagnesium bromide	Triphenylmethanol	—	Stir at room temperature	(141)
o-Chlorobenzalacetophenone oxide  $o\text{-}ClC_6H_4\underset{\diagdown O \diagup}{CH\text{—}CH}COC_6H_5$	Phenylmagnesium bromide	1-(*o*-Chlorophenyl)-1,2-epoxy-3,3-diphenyl-3-propanol  $o\text{-}ClC_6H_4\underset{\diagdown O \diagup}{CH\text{—}CH}\underset{OH}{C}(C_6H_5)_2$	69*	Stir at −15°C.	(140)
α-Phenyl-*p*-nitrobenzalacetophenone oxide  $p\text{-}O_2NC_6H_4\underset{\diagdown O \diagup}{CH\text{—}\overset{C_6H_5}{C}}COC_6H_5$	Phenylmagnesium bromide	Triphenylmethanol	—	Stir at room temperature	(141)
1-Benzoyl-2,2-diphenylethylene oxide  $(C_6H_5)_2\underset{\diagdown O \diagup}{C\text{—}CH}COC_6H_5$	Ethylmagnesium iodide	3-Phenyl-3-pentanol Diphenylacetaldehyde	— —	Stir at room temperature	(141)

TABLE 10—*Continued*

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS	REFERENCE
			per cent		
	Phenylmagnesium bromide	Triphenylmethanol Diphenylacetaldehyde	— —	Stir at room temperature	(141)
Benzal *p*-methoxyacetophenone oxide  $C_6H_5CH\text{—}CHCOC_6H_4OCH_3\text{-}p$ (epoxide O)	Phenylmagnesium bromide	1-(*p*-Anisyl)-1,3,3-triphenyl-1,2-propanediol†  $(C_6H_5)_2CHCHOH\overset{C_6H_5}{\overset{\vert}{\underset{\underset{OH}{\vert}}{C}}}C_6H_4OCH_3\text{-}p$	37*	"Usual"	(22)
			99*	(1:1) inverse addition; stir at −15°C.	(24)
			97*	Excess Grignard reagent; reflux	(24)
Benzal *p*-phenylacetophenone oxide  $C_6H_5CH\text{—}CHCOC_6H_4C_6H_5\text{-}p$	Phenylmagnesium bromide	4,4′-Diphenylbenzopinacol 3-Biphenylyl-1,2,3-triphenyl-1,3-propanediol‡	—	"Usual"	(22)
		4-Phenylbenzophenone	60	(1:1); let stand at room temperature	(8)
		4-Phenyltriphenylmethanol	51	Excess Grignard reagent; let stand at room temperature	(8)

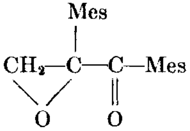
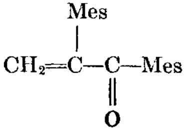
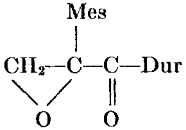
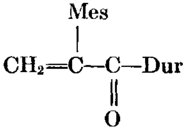
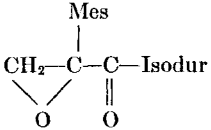
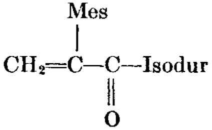
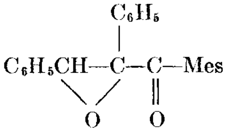
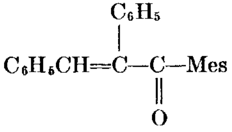
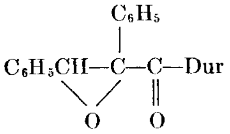
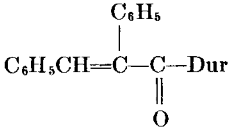
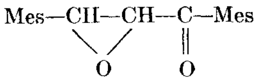
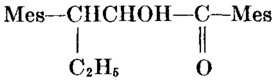
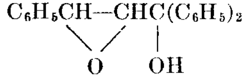
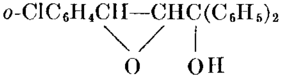
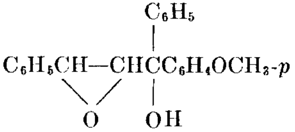
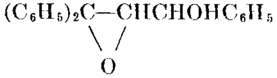
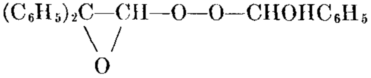
	Phenylmagnesium bromide + Mg + $MgBr_2$	4,4′-Diphenylbenzopinacol	45	Let stand at room temperature	(8)
Oxido mesityl α-mesitylvinyl ketone 	Methylmagnesium iodide	Mesityl α-mesitylvinyl ketone  $\mathrm{CH_2{=}\overset{\overset{Mes}{\mid}}{C}{-}\underset{\underset{O}{\Vert}}{C}{-}Mes}$	Quantitative	Reflux	(73)
	Ethylmagnesium bromide		—	Reflux	(73)
	Phenylmagnesium bromide		—	Reflux	(73)
Oxido duryl α-mesitylvinyl ketone 	RMgX	Duryl-α-mesitylvinyl ketone  $\mathrm{CH_2{=}\overset{\overset{Mes}{\mid}}{C}{-}\underset{\underset{O}{\Vert}}{C}{-}Dur}$	—	Reflux	(73)
Oxido isoduryl α-mesitylvinyl ketone 	RMgX	Isoduryl α-mesitylvinyl ketone  $\mathrm{CH_2{=}\overset{\overset{Mes}{\mid}}{C}{-}\underset{\underset{O}{\Vert}}{C}{-}Isodur}$	—	Reflux	(73)

TABLE 10—*Concluded*

OXIDE	GRIGNARD REAGENT	PRODUCT	YIELD	CONDITIONS	REFERENCE
			per cent		
Oxido α,β-diphenylvinyl mesityl ketone 	Ethylmagnesium bromide	α,β-Diphenylvinyl mesityl ketone  $C_6H_5CH{=}C(C_6H_5)-C(=O)-Mes$	—	Reflux	(73)
Oxido α,β-diphenylvinyl duryl ketone 	Ethylmagnesium bromide	α,β-Diphenylvinyl duryl ketone  $C_6H_5CH{=}C(C_6H_5)-C(=O)-Dur$	—	Reflux	(73)
Oxido mesityl β-mesitylvinyl ketone 	Ethylmagnesium bromide	1-Hydroxy-2-mesitylbutyl mesityl ketone  $Mes-CH(C_2H_5)CHOH-C(=O)-Mes$	—	Reflux	(73)
Ethyl dimethylglycidate 	Phenylmagnesium bromide	Triphenylmethanol	—	Stir at room temperature	(141)
Ethyl diphenylglycidate 	Phenylmagnesium bromide	Triphenylmethanol Diphenylacetaldehyde	— —	Stir at room temperature	(141)

2,3-Epoxy-1,1,3-triphenyl-1-propanol  $C_6H_5\underbrace{CH{-}CH}_{O}\underset{OH}{C}(C_6H_5)_2$	Phenylmagnesium bromide	Triphenylmethanol	—	Stir at room temperature	(141)
3-(*o*-Chlorophenyl)-2,3-epoxy-1,1-diphenyl-1-propanol  $o\text{-}ClC_6H_4\underbrace{CH{-}CH}_{O}\underset{OH}{C}(C_6H_5)_2$	Ethylmagnesium bromide	1,1-Diphenyl-1-propanol	—	Let stand at room temperature	(140)
1-(*p*-Anisyl)-2,3-epoxy-1,3-diphenyl-1-propanol  $C_6H_5\underbrace{CH{-}CH}_{O}\overset{C_6H_5}{\underset{OH}{C}}C_6H_4OCH_3\text{-}p$	Phenylmagnesium bromide	1-(*p*-Anisyl)-1,3,3-triphenyl-1,2-propanediol	40*	Reflux	(24)
2,3-Epoxy-1,3,3-triphenyl-1-propanol  $(C_6H_5)_2\underbrace{C{-}CH}_{O}CHOHC_6H_5$	Methylmagnesium iodide	Benzaldehyde Diphenylacetaldehyde 1,3,3-Triphenylpropan-1-ol-2-one $(C_6H_5)_2CHCOCHOHC_6H_5$	—	Inverse addition; reflux	(141)
	Phenylmagnesium bromide	Diphenylacetaldehyde Benzohydrol	—	Stir at room temperature	(141)
 $(C_6H_5)_2\underbrace{C{-}CH}_{O}{-}O{-}O{-}CHOHC_6H_5$	Methylmagnesium iodide	1,1-Diphenyl-1,2-propanediol 1-Phenylethanol	—	Stir at room temperature	(141)

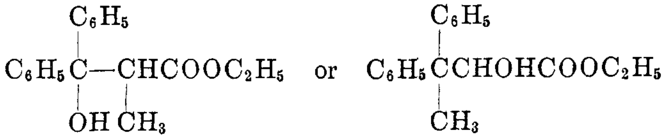
---

* Calculated from author's data.

† Author erroneously assumed isomeric structure.

‡ Product probably has isomeric structure.

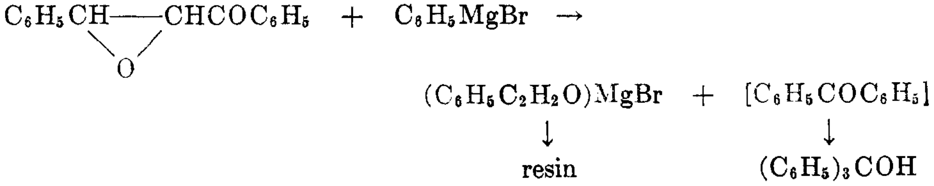
Bardon and Ramart (9) prepared diphenylglycidic ester by the condensation of benzophenone and ethyl chloroacetate. With methylmagnesium iodide the glycidic ester gave an ester alcohol, postulated as either



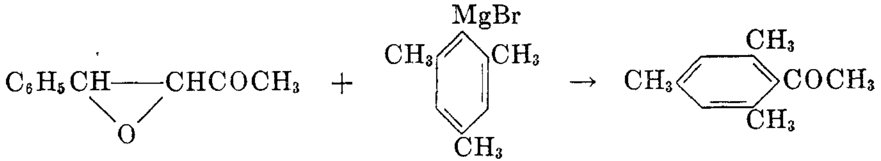
$$C_6H_5\underset{OH}{\overset{C_6H_5}{C}}-\underset{CH_3}{C}HCOOC_2H_5 \quad \text{or} \quad C_6H_5\underset{CH_3}{\overset{C_6H_5}{C}}CHOHCOOC_2H_5$$

With phenylmagnesium bromide the products were an ester alcohol, m.p. 130°C., and another product, m.p. 203–205°C., neither of which was identified.

Kohler, Richtmyer, and Hester (141), working with the oxides of benzalacetophenone, found that when organomagnesium compounds react with α-epoxy ketones, only the carbonyl group is attacked. Operating at a low temperature, immediate decomposition yields the epoxy carbinol; at higher temperatures the intermediate products decompose into magnesium derivatives of aldehydes and into ketones which may be transformed into tertiary alcohols.

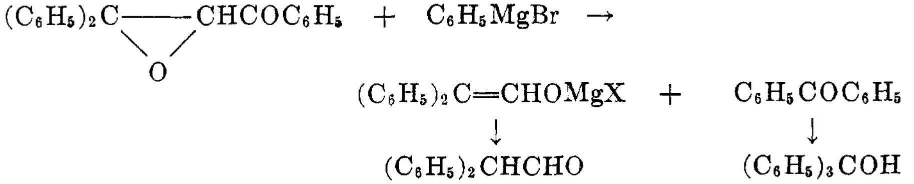


Thus the epoxy ketone is cleaved between the carbonyl and epoxy groups. The oxides of anisalacetophenone and α-phenyl-*p*-nitrobenzalacetophenone also gave triphenylmethanol and a resin. The formation of acetylmesitylene from the reaction of the oxide of benzalacetone and mesitylmagnesium bromide established the ketone as one of the primary cleavage products:



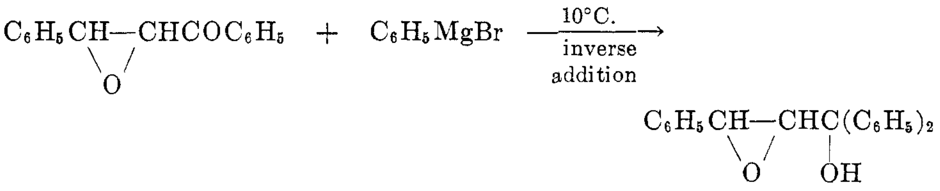
Acetylmesitylene or
2,4,6-trimethylacetophenone

The nature of the second cleavage product was established in the reaction of 1-benzoyl-2,2-diphenylethylene oxide and phenylmagnesium bromide. Two products were formed, triphenylmethanol and diphenylacetaldehyde. With the ethyl Grignard reagent the second product was also diphenylacetaldehyde.



Diphenylacetaldehyde Triphenylmethanol

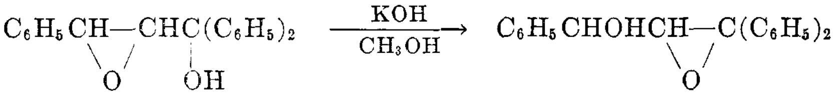
If equivalent amounts of benzalacetophenone oxide and phenylmagnesium bromide react at $-10°C.$ and the mixture is immediately decomposed, the product is the epoxy carbinol, 1,2-epoxy-1,3,3-triphenyl-3-propanol, called an oxanol:



$$\underset{\diagdown\, O\, \diagup}{C_6H_5CH{-}CH}COC_6H_5 + C_6H_5MgBr \xrightarrow[\text{inverse addition}]{10°C.} \underset{\diagdown\, O\, \diagup}{C_6H_5CH{-}CH}\underset{|\atop OH}{C}(C_6H_5)_2$$

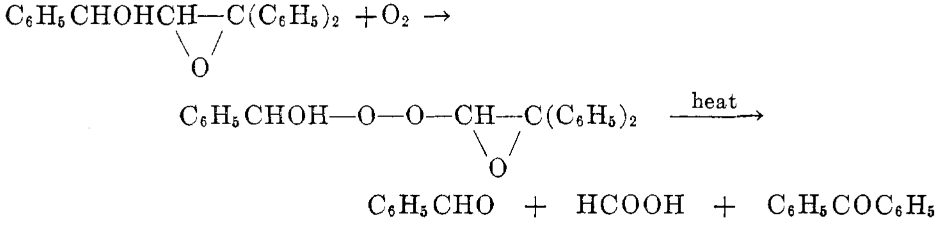
If the reaction mixture stands overnight at room temperature before decomposition, only benzophenone and a resin are obtained. Excess phenyl Grignard reagent does not react with the epoxy carbinol at $-10°C.$, but at room temperature triphenylmethanol and a resin are the final products.

The epoxy carbinol isomerizes, under the influence of methanolic potassium hydroxide, to 1,2-epoxy-1,1,3-triphenyl-3-propanol:



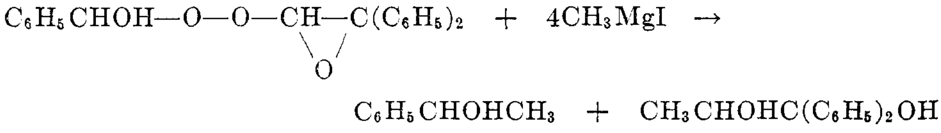
$$\underset{\diagdown\, O\, \diagup}{C_6H_5CH{-}CH}\underset{|\atop OH}{C}(C_6H_5)_2 \xrightarrow[CH_3OH]{KOH} C_6H_5CHOH\underset{\diagdown\, O\, \diagup}{CH{-}C}(C_6H_5)_2$$

This reacts with the phenyl Grignard reagent to give diphenylacetaldehyde and benzhydrol and with methylmagnesium iodide to give benzaldehyde, diphenylacetaldehyde, and a product postulated as $C_6H_5CHOHCOCH(C_6H_5)_2$. Autoxidation of the isomeric epoxy carbinol gives a peroxide whose formula was advanced on the basis of its thermal decomposition and reaction with methylmagnesium iodide.



$$C_6H_5CHOH\underset{\diagdown\, O\, \diagup}{CH{-}C}(C_6H_5)_2 + O_2 \rightarrow$$
$$C_6H_5CHOH{-}O{-}O{-}\underset{\diagdown\, O\, \diagup}{CH{-}C}(C_6H_5)_2 \xrightarrow{\text{heat}}$$
$$C_6H_5CHO + HCOOH + C_6H_5COC_6H_5$$

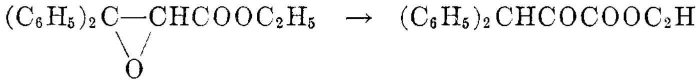
The peroxide reacts with four moles of methyl Grignard reagent to give methyldiphenylglycol and methylphenylcarbinol.



$$C_6H_5CHOH{-}O{-}O{-}\underset{\diagdown\, O\, \diagup}{CH{-}C}(C_6H_5)_2 + 4CH_3MgI \rightarrow$$
$$C_6H_5CHOHCH_3 + CH_3CHOHC(C_6H_5)_2OH$$

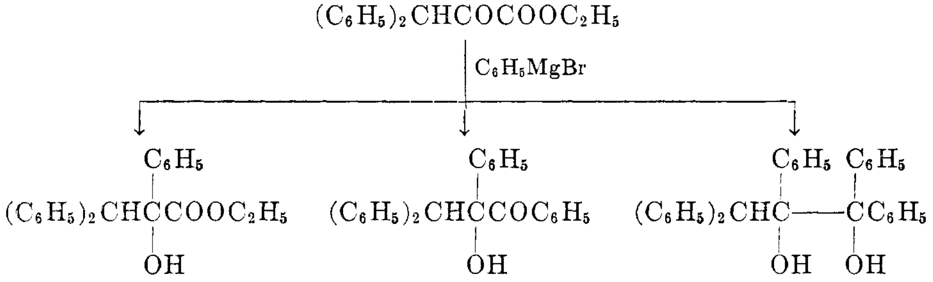
Methylphenylcarbinol Methyldiphenylglycol

These results are at variance with the work of Bardon and Ramart (9). Initial attempts to repeat their work with diphenylglycidic ester indicated that in its preparation the glycidic ester, which is the primary product, rearranges to the ketonic ester during distillation (141).



$$(C_6H_5)_2\underbrace{C\text{—}CH}_{O}COOC_2H_5 \rightarrow (C_6H_5)_2CHCOCOOC_2H_5$$

That this was the product used by Bardon and Ramart in their reaction with the Grignard reagent was indicated by the fact that under varying conditions the ketonic ester and excess phenylmagnesium bromide gave the hydroxy ester (A), the hydroxy ketone (B), and the glycol (C):



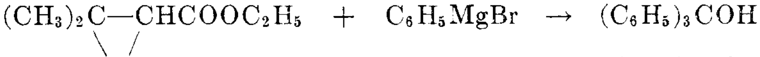
$$(C_6H_5)_2CHCOCOOC_2H_5 \xrightarrow{C_6H_5MgBr} (C_6H_5)_2CH\overset{C_6H_5}{\underset{OH}{C}}COOC_2H_5,\quad (C_6H_5)_2CH\overset{C_6H_5}{\underset{OH}{C}}COC_6H_5,\quad (C_6H_5)_2CH\overset{C_6H_5}{\underset{OH}{C}}\text{——}\overset{C_6H_5}{\underset{OH}{C}}C_6H_5$$

A (m.p. 118°C.)

B (m.p. 123°C.)

C (m.p. 190°C.)

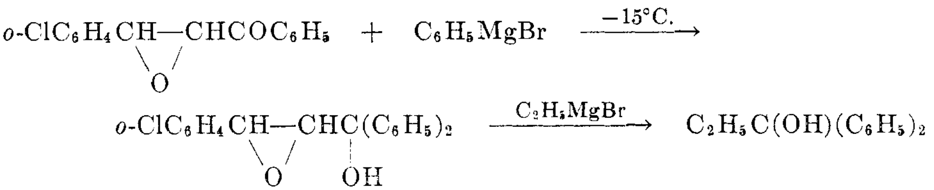
When the crude reaction mixture from the synthesis of the glycidic ester—a mixture of the glycidic ester, benzophenone, and ethyl chloroacetate—was treated with excess phenylmagnesium bromide the products were the same as those obtained with the epoxy ketones, i.e., triphenylmethanol and diphenylacetaldehyde. Therefore the epoxy ester does not give products of the type described by Bardon and Ramart but is cleaved like the epoxy ketones. In a similar manner the aliphatic glycidic ester reacts with phenylmagnesium bromide to give triphenylmethanol:



$$(CH_3)_2\underbrace{C\text{—}CH}_{O}COOC_2H_5 + C_6H_5MgBr \rightarrow (C_6H_5)_3COH$$

Triphenylmethanol

o-Chlorobenzalacetophenone oxide was prepared by Kohler and Bickel (140). From phenylmagnesium bromide at −15°C. the expected oxanol was obtained, which reacted with the ethyl Grignard reagent to give diphenylethylcarbinol:

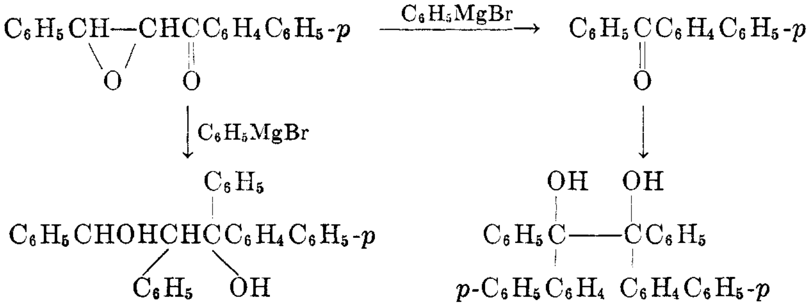


$$o\text{-}ClC_6H_4\underbrace{CH\text{—}CH}_{O}COC_6H_5 + C_6H_5MgBr \xrightarrow{-15°C.}$$

$$o\text{-}ClC_6H_4\underbrace{CH\text{—}CH}_{O}\underset{OH}{C}(C_6H_5)_2 \xrightarrow{C_2H_5MgBr} C_2H_5C(OH)(C_6H_5)_2$$

The oxanol and phenyllithium at −18°C. give a solid lithium compound which upon decomposition results in a quantitative recovery of the oxanol. However, if after the formation of the intermediate product at −18°C. the ethereal reaction mixture is refluxed for 30 min. before decomposition, the products are triphenylmethanol and a polymeric aldehyde. The oxanol and sodium in liquid ammonia give a resin which on steam distillation results in the isolation of benzophenone and a resin. Therefore it was concluded that cleavage is dependent on replacement of the hydrogen atom of the hydroxyl group with a metallic atom and decomposition of the metallic derivative.

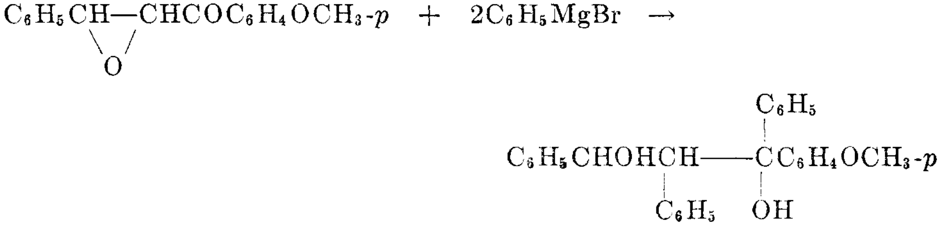
In reviewing the work of Kohler and his coworkers, Bergmann and Wolff (22) prepared benzal-*p*-phenylacetophenone oxide by the condensation of biphenyl and cinnamoyl chloride with aluminum chloride, followed by oxidation with alkaline hydrogen peroxide. The condensation gave a product melting at 165°C. and the oxidation gave two oxides, melting at 126°C. and 162°C. The isomer melting at 126°C. was allowed to react with phenylmagnesium bromide, yielding two products, a pinacol of phenyl biphenyl ketone (B) and the so-called normal reaction product (A):



A B

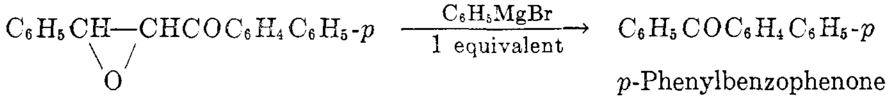
The formation of the pinacol was explained by the reducing action of finely divided magnesium, present from the preparation of the Grignard reagent. The structure of the 1,3-glycol (A) was assumed "in view of known reactions of ethylene oxide" in preference to the isomeric 2,3-glycol.

From benzal *p*-methoxyacetophenone oxide and the phenyl Grignard reagent, 1-(*p*-anisyl)-1,2,3-triphenyl-1,3-propanediol was obtained as the sole product:



Here again the structure of the product was assumed in preference to that of the isomeric glycol, which is actually more probable, as is shown later.

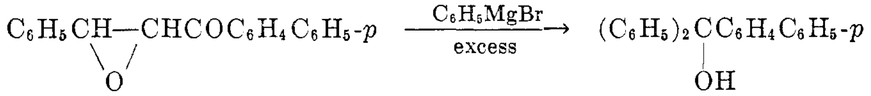
Bachmann and Wiselogle (8) repeated the work of Bergmann and Wolff and found several discrepancies. The condensation of biphenyl and cinnamoyl chloride with aluminum chloride did not yield the product previously reported, melting at 165°C., but a substance melting at 156°C. Oxidation gave one oxide, m.p. 136–137°C., instead of the two oxides reported by Bergmann. The oxide, benzal-*p*-phenylacetophenone oxide, gave with one equivalent of phenylmagnesium bromide a 60 per cent yield of *p*-phenylbenzophenone



$$C_6H_5\underset{\diagdown O \diagup}{CH—CH}COC_6H_4C_6H_5\text{-}p \xrightarrow[\text{1 equivalent}]{C_6H_5MgBr} C_6H_5COC_6H_4C_6H_5\text{-}p$$

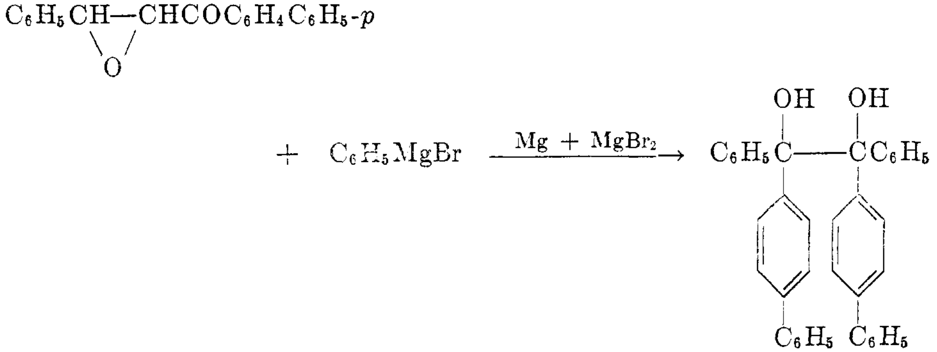
p-Phenylbenzophenone

while with excess Grignard reagent a 51 per cent yield of *p*-phenyltriphenylmethanol was obtained:



$$C_6H_5\underset{\diagdown O \diagup}{CH—CH}COC_6H_4C_6H_5\text{-}p \xrightarrow[\text{excess}]{C_6H_5MgBr} (C_6H_5)_2\underset{OH}{C}C_6H_4C_6H_5\text{-}p$$

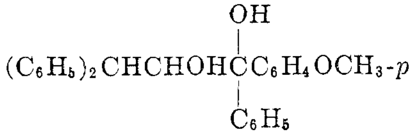
Addition of magnesium and magnesium bromide to a mixture of the oxide and phenylmagnesium bromide gave a 45 per cent yield of 4,4′-diphenylbenzopinacol:



4,4′-Diphenyl-benzopinacol

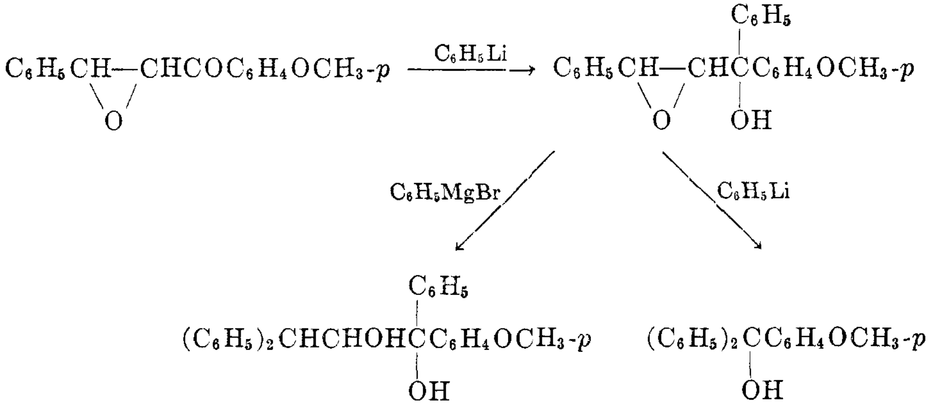
In a similar manner benzalacetophenone oxide gives benzopinacol.

Bickel (24) also repeated the work of Bergmann and Wolff and found that benzal-*p*-methoxyacetophenone oxide and one equivalent of phenylmagnesium bromide at −15°C. gave 1-(*p*-anisyl)-1,3,3-triphenyl-1,2-propanediol,



$$(C_6H_5)_2CHCHOH\overset{OH}{\underset{C_6H_5}{C}}C_6H_4OCH_3\text{-}p$$

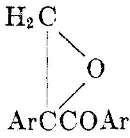
which was shown to be Bergmann's product rather than the isomer previously reported. Refluxing with excess Grignard reagent gave the same results. The oxide with phenyllithium in ether at −15°C. gave the oxanol, 1-(*p*-anisyl)-2,3-epoxy-1,3-diphenyl-1-propanol. This reacted with phenylmagnesium bromide to give the *vic*-glycol above and with phenyllithium to give diphenyl(*p*-anisyl)-carbinol and a resin:



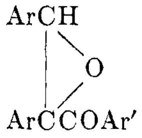
Similarly, benzalacetophenone oxide and phenyllithium give 2,3-epoxy-1,1,3-triphenyl-1-propanol and *o*-chlorobenzalacetophenone oxide gives the 3-(*o*-chlorophenyl) analog, identical with the compounds obtained by Kohler, Richtmyer, and Hester (141) and by Kohler and Bickel (140) with phenylmagnesium bromide. The difference in the reaction of benzalacetophenone oxide and the *p*-methoxy compound with phenylmagnesium bromide was explained as due to activation of the oxirane ring by the anisyl group. Simultaneous addition to the carbonyl group and to the oxide ring produces a magnesium derivative having no tendency to undergo cleavage.

In an elegant piece of work Gaertner (74) has been able to resolve the controversy between Bergmann and Bachmann. Pointing out that the pinacol derived from *p*-phenylbenzophenone may exist in meso- and *d*,*l*-forms, he proceeded to separate two pinacols from the reaction, one melting at 190°C. and the other at 207°C. He associated the compound of Bergmann and Wolff (m.p. 181°C.) with that melting at 190°C. and the compound of Bachmann and Wiselogle (m.p. 198°C.) with the higher-melting form. By means of ultraviolet absorption spectra Gaertner further assigned the meso-configuration to the high-melting form and the *d*,*l*-configuration to the low-melting form.

Fuson *et al.* (73) investigated the action of Grignard reagents upon epoxy ketones derived from highly hindered *α*,*β*-unsaturated ketones and found that they acted as reducing agents. It was found that *α*-epoxy ketones of the type

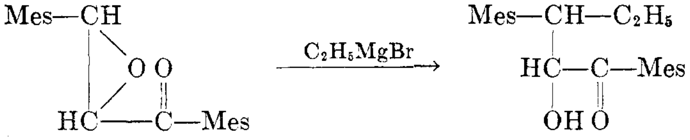


and

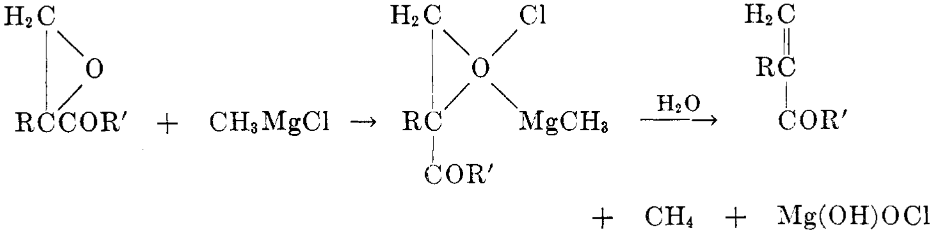


in which Ar′ is a mesityl, duryl, or isoduryl radical, undergo loss of oxygen in the presence of Grignard reagents, forming the corresponding α,β-unsaturated ketones. One mole of hydrocarbon derived from the Grignard reagent is evolved for each mole of epoxy ketone during reduction. Thus, oxido mesityl α-mesitylvinyl ketone under the influence of methyl, ethyl, and phenyl Grignard reagents forms the corresponding unsaturated mesityl α-mesitylvinyl ketone:

Similarly, the epoxy derivatives of duryl α-mesitylvinyl ketone, isoduryl α-mesitylvinyl ketone, α,β-diphenylvinyl mesityl ketone, and α,β-diphenylvinyl duryl ketone revert to the unsaturated ketone. However, oxido mesitylacetomesitylene (or oxido mesityl β-mesitylvinyl ketone) undergoes normal addition with ethylmagnesium bromide, although the structure of the product was not proven.

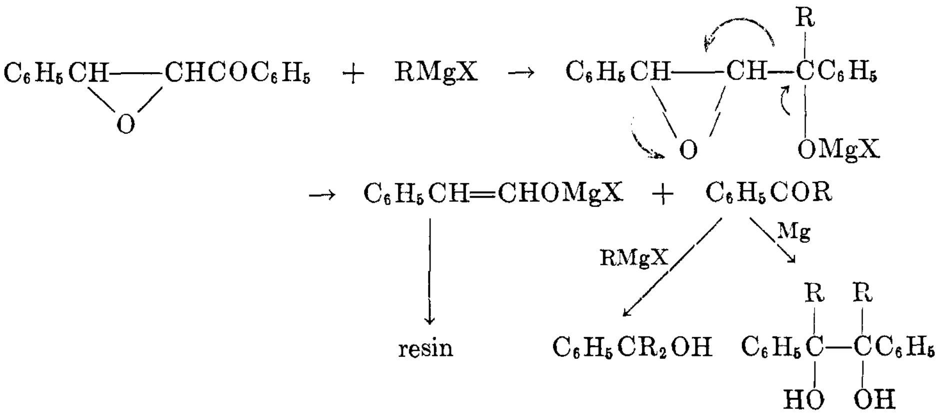


Karrer, Jucker, and Steinlin (126) proposed the following mechanism:



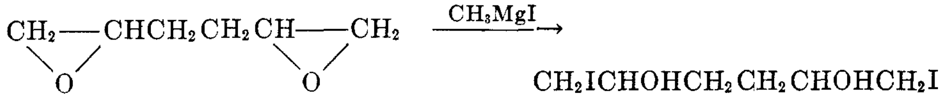
However, the cleavage of the Grignard reagent at the magnesium–halogen bond is difficult to conceive.

It can be said in conclusion that epoxy ketones and keto esters react first at the ketone group. At low temperatures and with an equivalent of the Grignard reagent, the oxanol or the hydroxy ester may be isolated. Under more vigorous conditions and in the presence of excess Grignard reagent these compounds undergo facile cleavage to ketones, which may react further to give a tertiary alcohol or with each other (in the presence of magnesium and magnesium bromide) to give pinacols. A likely mechanism for the latter reaction is the following:

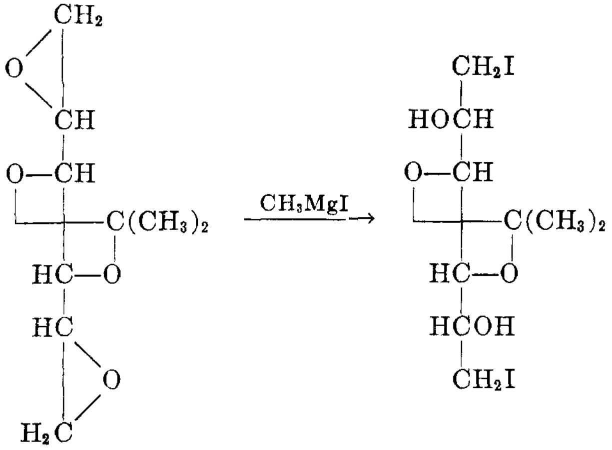


VI. Diepoxides

The reaction of only two diepoxides with Grignard reagents has thus far been carried out. Further study should prove of great interest. Thus, 1,2,5,6-diepoxyhexane gives 2,5-dihydroxy-1,6-diiodohexane (225) and 3,4-isopropylidene-1,2,5,6-dianhydromannitol gives 1,6-diiodo-3,4-isopropylidene-1,6-deoxymannitol.



2,5-Dihydroxy-1,6-diiodohexane



VII. Trimethylene Oxide

The only trimethylene oxide which has been subjected to the Grignard reaction is trimethylene oxide itself (see table 11). It reacts with both Grignard

TABLE 11

Trimethylene oxide

GRIGNARD REAGENT	PRODUCT	YIELD	REFERENCE
		per cent	
Anhydrous magnesium bromide	3-Bromo-1-propanol	54[e]	(183)
Ethylmagnesium bromide	1-Pentanol	30[a]	(23)
	3-Bromo-1-propanol	34	
	3-Bromo-1-propanol	38[b]	
n-Propylmagnesium bromide	1-Hexanol	11.5[c]	(53)
Isopropylmagnesium bromide	4-Methyl-1-pentanol	28[e]	(183)
	3-Bromo-1-propanol	12	
tert-Butylmagnesium chloride	4,4-Dimethyl-1-pentanol (?)		(183)
	3-Chloro-1-propanol	37[e]	
n-Butyllithium	1-Heptanol	28[d]	(183)
Cyclohexylmagnesium bromide	3-Cyclohexyl-1-propanol	28[e]	(183)
	3-Bromo-1-propanol	40	
Benzylmagnesium chloride	4-Phenyl-1-butanol	83[d]	(183)
9-Fluorenyllithium	3-(9-Fluorenyl)-1-propanol	44[d]	(183)
Phenylmagnesium bromide	3-Phenyl-1-propanol	84[d]	(183)
	3-Bromo-1-propanol	4	
Phenyllithium	3-Phenyl-1-propanol	85[d]	(183)
1-Naphthylmagnesium bromide	3-(1-Naphthyl)-1-propanol	80[d]	(183)
2-Naphthylmagnesium bromide	3-(2-Naphthyl)-1-propanol	60[d]	(183)

(a) The trimethylene oxide is added to the Grignard solution and allowed to stand overnight. After adding benzene, distilling the ether, and refluxing, the mixture is decomposed and worked up in the usual manner.

(b) The procedure is the same as in (a), except that the ether is not distilled.

(c) After adding the oxide the ether is distilled, whereupon a sudden reaction occurs; then the mixture is hydrolyzed in the usual manner.

(d) The oxide is added to the Grignard solution and refluxed 1 hr. Benzene is now added, the ether is distilled, and the mixture is refluxed 4 hr., followed by hydrolysis with ammonium chloride solution.

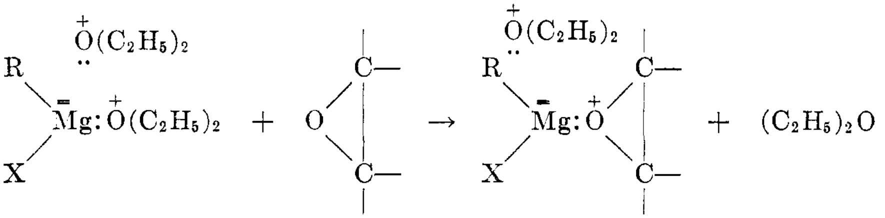
(e) A modification of (d) in which the reaction mixture is allowed to stand overnight and then is refluxed only 2 hr. after the benzene is added.

reagents and organolithium derivatives with simple opening of the ring to produce a primary alcohol in which the hydrocarbon chain has been lengthened by three carbon atoms. Some 1,3-halohydrin accompanies the reaction, but no rearrangements have been observed. The only extensive work in this field has been reported by Searles (183).

VIII. Mechanism

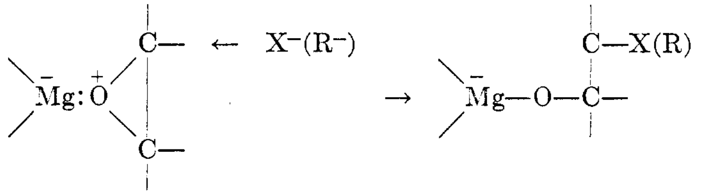
The mechanism of the reaction of Grignard reagents with epoxy compounds has not been unequivocally elucidated. Both products resulting from simple opening of the ring (the halohydrin and the new alcohol) and products which may be written as resulting from the rearrangement of the oxide to a carbonyl group are known. Further, there is the report that the order of addition of the reactants changes the course of the reaction (133). Although these facts can be rationalized, chemical evidence for their substantiation is for the most part unavailable. It is the purpose of this section to interpret the observed results and to suggest, where possible, evidence that could be gathered.

The Grignard reagent in solution is known to exist as a solvate with ether; the first step in the reaction with an epoxy compound would probably be displacement of one of the ether groups by the oxide:



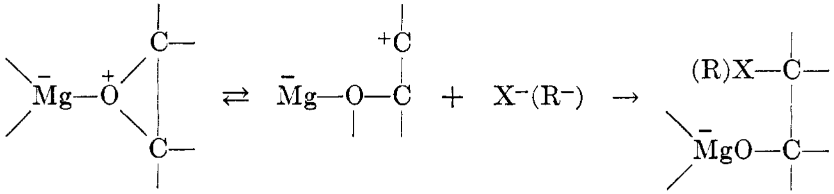
(1)

Ordinary ring opening, then, can be considered as taking place by nucleophilic attack of X^- or R^- (the equation shows only the coördinated magnesium atom):



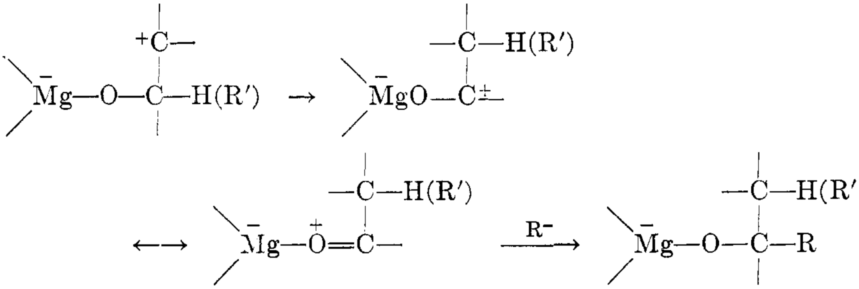
(2)

or by prior opening of the ring, followed by addition of the negative fragment:



(3)

The ionic intermediate conceivably may rearrange in a 1,2-shift to give a carbonyl structure, which subsequently could react with the R^- group.

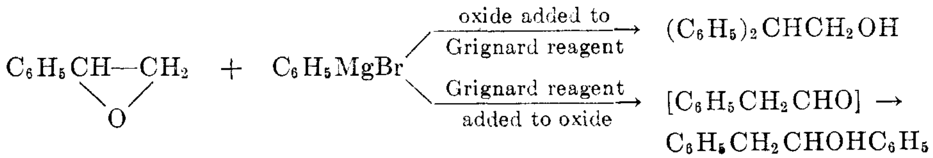

(4)

The reaction represented by equation 2 takes place at room temperature as well as at elevated temperatures. Early workers, and also later ones, have reported that at room temperatures only the halohydrin forms, while at reflux temperature, or if the ether is displaced with a higher-boiling inert solvent, the desired alcohol is formed. Norton and Hass (156) showed, however, that if the reaction mixture were held long enough at the lower temperatures the alcohol is formed. Apparently the first product is the adduct of the oxide with magnesium bromide (117), which subsequently reacts with the dialkylmagnesium remaining in solution. Kinetic data for the reactions at various temperatures would help accurate selection of reaction conditions as well as make possible the prediction of reaction products, but such data are not available.

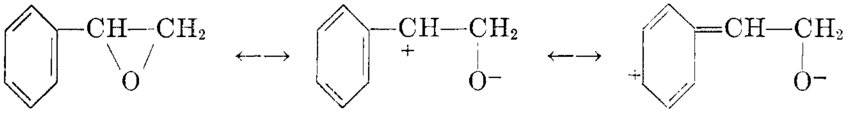
With respect to the ease of carrying out the reaction, the reactivity of the Grignard reagent and/or the oxide is important. It is known that benzyl Grignards, diorganomagnesiums, and organolithiums react smoothly with most oxides without heating. Also, oxides adjacent to double bonds, such as styrene oxide and butadiene monoxide, react with aryl or alkyl Grignard reagents without heating. However, no quantitative data relating these activities are available.

It is not known specifically whether the nucleophilic opening is accompanied with inversion. In the only example employing an optically active oxide, *d*-1,2-epoxypropane was treated with isopropyl- (144), *n*-propyl-, and phenylmagnesium bromides (143) to give optically active alcohols without evidence of inversion. Only alcohols corresponding to opening of the ring at the 1-position were obtained. In the case of *n*-propylmagnesium bromide, the alcohol recovered had a value for $[\alpha]_D^{25}$ of $-1.75°$. In a previous paper (142) it has been shown that pure *d*-methylbutylcarbinol has a value for $[\alpha]_D^{24}$ of $+6.3°$. It therefore appears that some racemization of the oxide had occurred during the course of the reaction. A further examination of this type of reaction should prove fruitful.

An interesting observation is that of Kharasch and Clapp (133) in which the order of addition of reagents appears to determine the nature of the products when styrene oxide reacts with an arylmagnesium bromide. Some of the isomeric alcohol is formed in each case. The results are capable of rationalization if it is

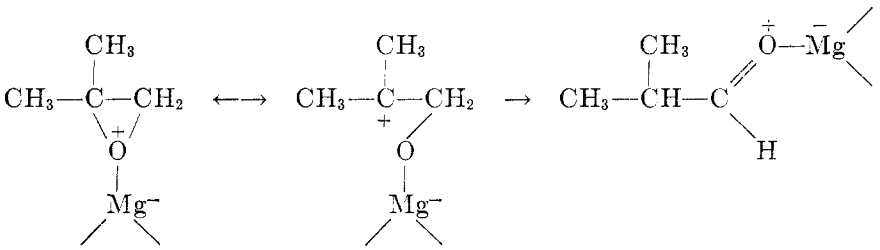


accepted that the presence of magnesium halide is responsible for the rearrangement reaction. Thus, in the presence of a large excess of Grignard reagent the reaction of the oxide with reactive diarylmagnesium would lead to ordinary ring opening before rearrangement could set in. With the oxide in excess the concentration of free diarylmagnesium would always be very small and the magnesium halide would be able to rearrange the oxide prior to addition of R^-. This, then, is not in disagreement with the work of Golumbic and Cottle (94), who found that with styrene oxide methylmagnesium iodide gives 1-phenyl-2-propanol, while dimethylmagnesium gives 2-phenyl-1-propanol. The fact that the alkyl (or aryl) group enters the ring adjacent to the phenyl ring indicates that in this instance electronic effects overshadow the expected steric effect of the bulky phenyl group, structures such as

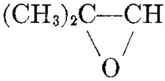


tending to direct a carbanion to the α-position.

The ability to predict to what extent normal reaction will take precedence over reaction accompanied by rearrangement is not on a sound basis; there is a paucity of experiments carried out with material balances included. Even ethylene oxide can give rise to some rearranged product (46). It seems, in general, that if a more stable carbonium ion can be formed, then rearrangement will take place. For example, 1,2-epoxy-2-methylpropane is observed to form only rearranged products.



A steric factor is also evident, since it is observed that propylene oxide opens only by attack at the terminal position with benzyl, *n*-alkyl, and isopropyl Grignard reagents, but that the rearrangement product is obtained with a *tert*-butyl Grignard reagent.

The rearrangement reaction is entirely avoided by employing diorganomagnesiums or organolithium compounds. This is somewhat unexpected, since in both classes the metal is still a Lewis acid. A further point of interest is that in unsymmetrical alkyl oxides and either of these reagents, the hydrocarbon residue attaches to the least substituted position, despite the fact that the carbonium ion is most stabilized at the more highly hindered position. Thus,  $(CH_3)_2C{-}CH_2$ (epoxide, $\diagdown O \diagup$) reacts with R_2Mg to yield $(CH_3)_2C(OH)CH_2R$ and not $(CH_3)_2CRCH_2OH$. With dialkylmagnesium it appears that resonance through a conjugated unsaturated bond can direct the carbanion to the more hindered position (*vide supra*). However, this is not so when phenyllithium is used with propylene oxide, styrene oxide, and 1,1-diphenylethylene oxide. In each instance the only products isolated correspond to opening of the ring at the less hindered C—O bond. It would be of interest to see whether organometallic compounds of still more electropositive elements, such as sodium or potassium, would react similarly.

Another unelucidated problem in this basic reaction is the influence of strong polar factors. In no set of experiments has an attempt been made to substitute a group such as the trifluoromethyl group into ethylene oxide with a view to studying the change in the course of the reaction. Substituting such a group into an already unsymmetrical oxide would also be of interest.

IX. REFERENCES

(1) ALTWEGG, J.: U. S. patent 1,315,619 (September 9, 1919); Chem. Abstracts **13,** 2883 (1919).
(2) ARBUSOV, B. A.: Ber. **68,** 1430 (1935).
(3) ARBUSOV, B. A.: J. Gen. Chem. (U.S.S.R.) **9,** 249 (1939); Chem. Abstracts **33,** 6279 (1939).
(4) ARBUSOV, B. A.: J. Gen. Chem. (U.S.S.R.) **9,** 255 (1939); Chem. Abstracts **33,** 6280 (1939).
(5) ARBUSOV, B. A.: Trans. Kirov Inst. Chem. Technol. Kazan **6,** 226 (1936); Chem. Zentr. **1937,** 4942.
(6) BACHMAN, G. B.: J. Am. Chem. Soc. **57,** 382 (1935).
(7) BACHMANN, W. E., FUJIMOTO, G. I., AND WICK, L. B.: J. Am. Chem. Soc. **72,** 1995 (1950).
(8) BACHMAN, W. E., AND WISELOGLE, F. Y.: J. Am. Chem. Soc. **56,** 1559 (1934).
(9) BARDON AND RAMART: Compt. rend. **183,** 214 (1926).
(10) BARTLETT, P. D., AND BERRY, C. M.: J. Am. Chem. Soc. **56,** 2683 (1934).
(11) BEDOS, P.: Bull. soc. chim. [4] **33,** 163 (1923).
(12) BEDOS, P.: Compt. rend. **177,** 111 (1923).
(13) BEDOS, P.: Compt. rend. **177,** 958 (1923).
(14) BEDOS, P.: Compt. rend. **181,** 117 (1925).
(15) BEDOS, P.: Bull. soc. chim. [4] **39,** 292 (1926).
(16) BEDOS, P.: Bull. soc. chim. [4] **39,** 473 (1926).
(17) BEDOS, P.: Bull. soc. chim. [4] **39,** 674 (1926).
(18) BEDOS, P.: Compt. rend. **189,** 255 (1929).
(19) BEDOS, P.: Compt. rend. **228,** 1441 (1949).
(20) BEDOS, P., AND RUYES, A.: Compt. rend. **188,** 962 (1929).
(21) BERGMANN, E., AND BLUM-BERGMANN, O.: J. Am. Chem. Soc. **58,** 1678 (1936).
(22) BERGMANN, E., AND WOLFF, H. A.: J. Am. Chem. Soc. **54,** 1644 (1932).
(23) BERMEJO, L., AND ARANDA, V. G.: Anales soc. españ. fís. y quím. **27,** 798 (1929).
(24) BICKEL, C. L.: J. Am. Chem. Soc. **59,** 325 (1937).
(25) BLAISE, E. E.: Compt. rend. **134,** 551 (1902).
(26) BOGERT, M. T., AND HAMANN, E. H.: Am. Perfumer Essent. Oil Rev. **25,** 19, 75 (1930); Chem. Abstracts **24,** 4008 (1930).
(27) BOGOMOLEZ, J.: Bull. soc. chim. [2] **34,** 330 (1880).
(28) BOGOMOLEZ, J.: Ann. **209,** 70 (1881).
(29) BOUSSET, R.: Bull. soc. chim. [5] **1,** 1305 (1934).
(30) BOUVEAULT, M. L.: Bull. soc. chim. [3] **31,** 1308 (1904).
(31) BOYD, D. R., AND VINEALL, G. J. C.: J. Chem. Soc. **1929,** 1622.

(32) Bradsher, C. K.: J. Am. Chem. Soc. **66,** 45 (1944).
(33) Butlerow, A.: Ber. **10,** 407 (1877).
(34) Butlerow, A., and Ossokin, M.: Ann. **145,** 257 (1868).
(35) Cason, J.: J. Am. Chem. Soc. **64,** 1106 (1942).
(36) Cason, J., and Winans, W. R.: J. Org. Chem. **15,** 139 (1950).
(37) Chavanne, G., and de Vogel, L.: Bull. soc. chim. Belg. **37,** 141 (1928).
(38) Chinaeva, A. D., and Ushakov, M. I.: J. Gen. Chem. (U.S.S.R.) **11,** 335 (1941).
(39) Clemo, G. R., and Ormston, J.: J. Chem. Soc. **1932,** 1778.
(40) Clemo, G. R., and Ormston, J.: J. Chem. Soc. **1933,** 362.
(41) Cohen, A., Cook, J. W., Hewett, C. L., and Girard, A.: J. Chem. Soc. **1934,** 653.
(42) Conant, J. B., and Kirner, W. R.: J. Am. Chem. Soc. **46,** 240 (1924).
(43) Cook, J. W., and Hewett, C. L.: J. Chem. Soc. **1933,** 1098.
(44) Cook, J. W., Hewett, C. L., and Lawrence, C. A.: J. Chem. Soc. **1936,** 71.
(45) Cottle, D. L.: Private communication.
(46) Cottle, D. L., and Hollyday, W. C., Jr.: J. Org. Chem. **12,** 510 (1947).
(47) Cottle, D. L., and Powell, L. S.: J. Am. Chem. Soc. **58,** 2267 (1936).
(48) Cristol, S. J., Douglass, J. R., and Meek, J. S.: J. Am. Chem. Soc. **73,** 816 (1951).
(49) Danehy, J. P., Vogt, R. R., and Nieuwland, J. A.: J. Am. Chem. Soc. **56,** 2790 (1934).
(50) Danehy, J. P., Vogt, R. R., and Nieuwland, J. A.: J. Am. Chem. Soc. **57,** 2327 (1935).
(51) Delaby, R.: Ann. chim. [9] **20,** 57 (1923).
(52) Delaby, R.: Compt. rend. **176,** 1153 (1923).
(53) Derick, C. G., and Bissell, D. W.: J. Am. Chem. Soc. **38,** 2478 (1916).
(54) Deux, Y.: Compt. rend. **207,** 920 (1938).
(55) Deux, Y.: Compt. rend. **211,** 441 (1940).
(56) Dice, J. R., Watkins, T. E., and Schuman, H. L.: J. Am. Chem. Soc. **72,** 1738 (1950).
(57) Dreger, E. E.: *Organic Syntheses*, Collective Volume I, 2nd edition, edited by H. Gilman and A. H. Blatt, p. 306. John Wiley and Sons, Inc., New York (1941).
(58) Ehrenstein, M.: J. Org. Chem. **8,** 83 (1943).
(59) Elderfield, R. C., Pitt, B. M., and Wempen, I.: J. Am. Chem. Soc. **72,** 1334 (1950).
(60) Faidutti, M.: Compt. rend. **189,** 854 (1929).
(61) Farbenfabriken vorm F. Bayer and Co. (Taub, Wingler, and Schulemann): German patent 423,544 (December 17, 1925); Chem. Zentr. **1926, I,** 3635.
(62) Faucounau, L.: Compt. rend. **199,** 605 (1934).
(63) Fieser, L. F., and Fieser, M.: *Natural Products Related to Phenanthrene*, 3rd edition, p. 224. Reinhold Publishing Corporation, New York (1949).
(64) Fourneau, E., and Poulenc Frères: French patent 350,248 (October 23, 1905).
(65) Fourneau, E., and Tiffeneau, M.: Bull. soc. chim. [3] **33,** 741 (1905).
(66) Fourneau, E., and Tiffeneau, M.: Bull. soc. chim. [4] **1,** 1227 (1907).
(67) Fourneau, E., and Tiffeneau, M.: Compt. rend. **145,** 435 (1907).
(68) Fourneau, E., and Tiffeneau, M.: Compt. rend. **145,** 437 (1907).
(69) Fourneau, E., Tréfouel, J., and Tréfouel, Mme.: Bull. soc. chim. [4] **43,** 454 (1928).
(70) Frank, R. L., Adams, C. E., Allen, R. E., Gander, R., and Smith, P. V.: J. Am. Chem. Soc. **68,** 1365 (1946).
(71) Freedman, R. F., and Becker, E. I.: J. Org. Chem. **16,** 1701 (1951).
(72) Fulton, J. D., and Robinson, R.: J. Chem. Soc. **1933,** 1463.
(73) Fuson, R. C., Byers, D. J., Sperati, C. A., Foster, R. E., and Warfield, P. F.: J. Org. Chem. **10,** 69 (1945).
(74) Gaertner, R.: J. Org. Chem. **15,** 1006 (1950).
(75) Gaylord, N. G., and Becker, E. I.: J. Org. Chem. **15,** 305 (1950).
(76) Gilman, H., and Abbott, R. K., Jr.: J. Org. Chem. **8,** 224 (1943).
(77) Gilman, H., and Fullhart, L.: J. Am. Chem. Soc. **71,** 1478 (1949).

(78) Gilman, H., and Kirby, J. E.: J. Am. Chem. Soc. **54,** 345 (1932).

(79) Gilman, H., Langham, W., and Moore, F. W.: J. Am. Chem. Soc. **62,** 2327 (1940).

(80) Gmitter, G. T., and Benton, F. L.: J. Am. Chem. Soc. **72,** 4586 (1950).

(81) Godchot, M., and Bedos, P.: Compt. rend. **174,** 461 (1922).

(82) Godchot, M., and Bedos, P.: Compt. rend. **175,** 1411 (1922).

(83) Godchot, M., and Bedos, P.: Bull. soc. chim. [4] **33,** 162 (1923).

(84) Godchot, M., and Bedos, P.: Compt. rend. **178,** 1184 (1924).

(85) Godchot, M., and Bedos, P.: Compt. rend. **178,** 1374 (1924).

(86) Godchot, M., and Bedos, P.: Bull. soc. chim. [4] **37,** 1451 (1925).

(87) Godchot, M., and Bedos, P.: Bull. soc. chim. [4] **37,** 1637 (1925).

(88) Godchot, M., and Bedos, P.: Compt. rend. **182,** 393 (1926).

(89) Godchot, M., and Bedos, P.: Compt. rend. **184,** 208 (1927).

(90) Godchot, M., and Bedos, P.: Bull. soc. chim. [4] **43,** 521 (1928).

(91) Godchot, M., and Cauquil, G.: Bull. soc. chim. [4] **43,** 520 (1928).

(92) Godchot, M., and Cauquil, G.: Compt. rend. **186,** 375 (1928).

(93) Godchot, M., and Cauquil, G.: Compt. rend. **186,** 955 (1928).

(94) Golumbic, G., and Cottle, D. L.: J. Am. Chem. Soc. **61,** 996 (1939).

(95) Grignard, V.: Bull. soc. chim. [3] **29,** 944 (1903).

(96) Grignard, V.: Compt. rend. **136,** 1260 (1903).

(97) Grignard, V.: Bull. soc. chim. [3] **33,** 918 (1905).

(98) Grignard, V.: Compt. rend. **141,** 44 (1905).

(99) Grignard, V.: French patent 348,957 (February 28, 1905).

(100) Grignard, V.: Ann. chim. [8] **10,** 23 (1907).

(101) Grignard, V.: Bull. soc. chim. [4] **1,** 247 (1907).

(102) Haller, A., and Ramart-Lucas: Compt. rend. **159,** 143 (1914).

(103) Hardegger, E., Redlich, D., and Gal, A.: Helv. Chim. Acta **28,** 628 (1945).

(104) Harlow, I. F., and Britton, E. C.: U. S. patent 1,591,125 (July 6, 1926); Chem. Abstracts **20,** 3171 (1926).

(105) Henry, L.: Compt. rend. **142,** 1023 (1906).

(106) Henry, L.: Compt. rend. **144,** 308 (1907).

(107) Henry, L. Compt. rend. **145,** 21 (1907).

(108) Henry, L.: Compt. rend. **145,** 154 (1907).

(109) Henry, L.: Compt. rend. **145,** 354 (1907).

(110) Henry, L.: Compt. rend. **145,** 406 (1907).

(111) Henry, L.: Compt. rend. **145,** 453 (1907).

(112) Henry, L.: Bull. acad. roy. Belg. **1907,** 162.

(113) Hess, K.: Ber. **46,** 3113 (1913).

(114) Hiers, G. S., and Adams, R.: J. Am. Chem. Soc. **48,** 1089 (1926).

(115) Hiers, G. S., and Adams, R.: J. Am. Chem. Soc. **48,** 2385 (1926).

(116) Homeyer, A. H., Whitmore, F. C., and Wallingford, V. H.: J. Am. Chem. Soc. **55,** 4209 (1933).

(117) Huston, R. C., and Agett, A. H.: J. Org. Chem. **6,** 123 (1941).

(118) Huston, R. C., and Bostwick, C. O.: J. Org. Chem. **13,** 331 (1948).

(119) Huston, R. C., and Brault, R. G.: J. Org. Chem. **15,** 1211 (1950).

(120) Huston, R. C., and Langham, C. C.: J. Org. Chem. **12,** 90 (1947).

(121) I. G. Farbenindustrie A.-G.: French patent 807,632 (October 19, 1936); Chem. Zentr. **1937, I,** 4022.

(122) Iotsitch, I.: J. Russ. Phys. Chem. Soc. **34,** 96 (1902); Bull. soc. chim. [3] **28,** 920 (1902).

(123) Iotsitch, I.: J. Russ. Phys. Chem. Soc. **35,** 554 (1903); Bull. soc. chim. [3] **32,** 740 (1904).

(124) Iotsitch, I.: J. Russ. Phys. Chem. Soc. **36,** 6 (1904); Bull. soc. chim. [3] **34,** 185 (1905).

(125) Iotsitch, I., Breitfus, V. L., Rudolf, K. I., Stasevitch, N. N., Elmanovitch, N. A., Kondirev, M. N., and Fomin, D. A.: J. Russ. Phys. Chem. Soc. **39,** 652 (1907); Bull. soc. chim. [4] **6,** 98 (1909).

(126) Karrer, P., Jucker, E., and Steinlin, K.: Helv. Chim. Acta **29,** 233 (1946).
(127) Kaschirsky, M.: Ber. **10,** 408 (1877).
(128) Kaschirsky, M.: Bull. soc. chim. [2] **28,** 350 (1877).
(129) Kayser, F.: Compt. rend. **196,** 1127 (1933).
(130) Kayser, F.: Compt. rend. **199,** 1424 (1934).
(131) Kayser, F.: Ann. chim. [11] **6,** 145 (1936).
(132) Khaletzkiĭ, A. M.: J. Gen. Chem. (U.S.S.R.) **6,** 1 (1936); Chem. Abstracts **30,** 4844 (1936).
(133) Kharasch, M. S., and Clapp, H. G.: J. Org. Chem. **3,** 355 (1938).
(134) Kharasch, M. S., and Nudenberg, W.: J. Org. Chem. **8,** 189 (1943).
(135) Kling, A.: Compt. rend. **137,** 756 (1903).
(136) Kling, A.: Bull. soc. chim. [3] **31,** 14 (1904).
(137) Kling, A.: Bull. soc. chim. [3] **31,** 16 (1904).
(138) Koelsch, C. F., and McElvain, S. M.: J. Am. Chem. Soc. **51,** 3390 (1929).
(139) Koelsch, C. F., and McElvain, S. M.: J. Am. Chem. Soc. **52,** 1164 (1930).
(140) Kohler, E. P., and Bickel, C. L.: J. Am. Chem. Soc. **57,** 1099 (1935).
(141) Kohler, E. P., Richtmyer, N. K., and Hester, W. R.: J. Am. Chem. Soc. **53,** 205 (1931).
(142) Levene, P. A., and Haller, H. L.: J. Biol. Chem. **79,** 475 (1928).
(143) Levene, P. A., and Walti, A.: J. Biol. Chem. **90,** 81 (1931).
(144) Levene, P. A., and Walti, A.: J. Biol. Chem. **94,** 367 (1931).
(145) Madaeva, O. S., Ushakov, M. I., and Kosheleva, N. F.: J. Gen. Chem. (U.S.S.R.) **10,** 213 (1940).
(146) Magrane, J. K., Jr., and Cottle, D. L.: J. Am. Chem. Soc. **64,** 484 (1942).
(147) Malinovksiĭ, M. S., and Konevichev, B. S.: J. Gen. Chem. (U.S.S.R.) **18,** 1833 (1948); Chem. Abstracts **43,** 3776 (1949).
(148) Malinovskiĭ, M. S., Volkova, E. E., and Morozova, N. M.: J. Gen. Chem. (U.S.S.R.) **19,** 114 (1949); Chem. Abstracts **43,** 6155 (1949).
(149) Meisenheimer, J.: Ann. **442,** 180 (1925).
(150) Meiser, W.: Ber. **32,** 2049 (1899).
(151) Mousseron, M., and Du, N. P.: Bull. soc. chim. France **1948,** 91.
(152) Natelson, S., and Gottfried, S. P.: J. Am. Chem. Soc. **61,** 1001 (1939).
(153) Newman, M. S.: J. Am. Chem. Soc. **62,** 2295 (1940).
(154) Newth, F. H., Richards, G. N., and Wiggins, L. F.: J. Chem. Soc. **1950,** 2356.
(155) Normant, H.: Compt. rend. **219,** 163 (1944).
(156) Norton, F. H., and Hass, H. B.: J. Am. Chem. Soc. **58,** 2147 (1936).
(157) Oddo, B., and Cambieri, F.: Gazz. chim. ital. **69,** 19 (1939); Chem. Abstracts **33,** 4239 (1939).
(157a) Pariselle, H.: Ann. chim. phys. [8] **24,** 376 (1911).
(158) Plate, A. F., Shafran, R. N., and Batuev, M. I.: J. Gen. Chem. (U.S.S.R.) **20,** 472 (1950); Chem. Abstracts **44,** 7785 (1950).
(159) Poctivas, M., and Tchoubar, B.: Compt. rend. **205,** 287 (1937).
(160) Poulenc Frères and Fourneau, E.: French patent 338,889 (June 23, 1903).
(161) Price, C. C., and Halpern, B. D.: J. Am. Chem. Soc. **73,** 818 (1951).
(162) Prilezhaev, N., and Prokopchuk, N.: J. Gen. Chem. (U.S.S.R.) **3,** 865 (1933); Chem. Abstracts **28,** 6133 (1934).
(163) Prilezhaev, N., and Vershuk, V.: J. Russ. Phys. Chem. Soc. **61,** 473 (1929); Chem. Abstracts **23,** 4463 (1929).
(164) Ribas, I.: Anales soc. españ. fís. y quím. **26,** 122 (1928).
(165) Ribas, I., and Tapia, E.: Anales soc. españ. fís. y quím. **28,** 636 (1930).
(166) Ribas, I., and Tapia, E.: Anales soc. españ. fís. y quím. **30,** 778 (1932).
(167) Ribas, I., and Tapia, E.: Anales soc. españ. fís. y quím. **30,** 944 (1932).
(168) Richter, V.: *The Chemistry of the Carbon Compounds,* Vol. II, revised by T. W. J. Taylor and A. F. Millidge, p. 229. Elsevier Publishing Company, Amsterdam, Holland (1938).

(169) RIEDEL CO., J. D.: German patent 183,361 (June 19, 1904).

(170) RITTER, J. J., AND RUSSELL, K. L.: J. Am. Chem. Soc. **58,** 291 (1936).

(171) ROBERTS, J. D., AND YOUNG, W. G.: J. Am. Chem. Soc. **67,** 148 (1945).

(172) ROBINSON, R.: J. Chem. Soc. **1936,** 80.

(173) ROTHMAN, L., AND BECKER, E. I.: Unpublished results.

(174) RUNGE, F.: *Organometallverbindungen*, p. 343. Lithoprinted by Edwards Brothers, Inc., Ann Arbor, Michigan (1945).

(175) RUZICKA, L., EHMANN, L., GOLDBERG, M. W., AND HOSLI, H.: Helv. Chim. Acta **16,** 833 (1933).

(176) SABATIER, P., AND MAILHE, A.: Compt. rend. **140,** 350 (1905).

(177) SABATIER, P., AND MAILHE, A.: Compt. rend. **142,** 554 (1906).

(178) SCHINZ, H., AND SIMON, H. L.: Helv. Chim. Acta **28,** 774 (1945).

(179) SCHLENK, W., AND SCHLENK, W., JR.: Ber. **62B,** 920 (1929).

(180) SCHLENK, W., JR.: Ber. **64B,** 734 (1931).

(181) SCHLUBACH, H. H., WOLF, V., JUSTUS, W., AND KÖHNCKE, C. A.: Ann. **568,** 141 (1950).

(182) SCHORIGIN, P., ISSAGULJANZ, W., GUSSEWA, A., OSSIPOWA, V., AND POLJAKOVA, A.: Ber. **64,** 2584 (1931).

(183) SEARLES, J.: J. Am. Chem. Soc. **73,** 124 (1951).

(184) SEMENIUK, F., AND JENKINS, G. L.: J. Am. Pharm. Assoc., Sci. Ed. **37,** 118 (1948).

(185) SHAREFKIN, J. G., AND RITTER, J. J.: J. Am. Chem. Soc. **63,** 1478 (1941).

(186) SIMONSEN, J.: *The Terpenes*, Vol. II, 2nd edition, p. 200. Cambridge University Press, London (1949).

(187) SMITH, H. A., AND FUZEK, J. F.: J. Am. Chem. Soc. **72,** 3454 (1950).

(188) SOBOTKA, H., AND STYNLER, F. E.: J. Am. Chem. Soc. **72,** 5139 (1950).

(189) SOCIÉTÉ CHIMIQUE DES USINES DU RHONE: British patent 122,630 (January 3, 1919); Chem. Abstracts **13,** 1715 (1919).

(190) SOMMER, L. H., VAN STRIEN, R. E., AND WHITMORE, F. C.: J. Am. Chem. Soc. **71,** 3056 (1949).

(191) SONDHEIMER, F.: J. Chem. Soc. **1950,** 877.

(192) SONTAG, D.: Ann. chim. [11] **1,** 359 (1934).

(193) STAHL, G. W., AND COTTLE, D. L.: J. Am. Chem. Soc. **65,** 1782 (1943).

(193a) STEVENS, C. L., AND PRATT, R.: Paper presented before the Organic Division at the 119th Meeting of the American Chemical Society, Cleveland, Ohio, April, 1951, Paper No. 51.

(194) STEVENS, P. G., AND McCOUBREY, J. A.: J. Am. Chem. Soc. **63,** 2847 (1941).

(195) STOLL, M., AND ROUVÉ, A.: Helv. Chim. Acta **21,** 1542 (1938).

(196) SWERN, D., BILLEN, G. N., AND KNIGHT, H. B.: J. Am. Chem. Soc. **71,** 1152 (1949).

(197) SZMANT, H. H., ANZENBERGER, J. F., AND HARTLE, R.: J. Am. Chem. Soc. **72,** 1419 (1950).

(198) TAPIA, E., AND HERNANDEZ, M. A.: Anales soc. españ. fís. y quím. **28,** 691 (1930).

(199) TCHOUBAR, B.: Compt. rend. **214,** 117 (1942).

(200) TIFFENEAU, M.: Bull. soc. chim. [3] **29,** 1156 (1903).

(201) TIFFENEAU, M.: Compt. rend. **140,** 1458 (1905).

(202) TIFFENEAU, M.: Ann. chim. [8] **10,** 145 (1907).

(203) TIFFENEAU, M.: Ann. chim. [8] **10,** 148, 192 (1907).

(204) TIFFENEAU, M.: Ann. chim. [8] **10,** 178, 192 (1907).

(205) TIFFENEAU, M.: Compt. rend. **159,** 771 (1914).

(206) TIFFENEAU, M., AND FOURNEAU, E.: Compt. rend. **146,** 697 (1908).

(207) TIFFENEAU, M., AND KURIAKI, P. K.: Compt. rend. **209,** 465 (1939).

(208) TIFFENEAU, M., AND TCHOUBAR, B.: Compt. rend. **198,** 941 (1934).

(209) TIFFENEAU, M., AND TCHOUBAR, B.: Compt. rend. **207,** 918 (1938).

(210) TIFFENEAU, M., WEILL, P., AND TCHOUBAR, B.: Compt. rend. **205,** 54 (1937).

(211) TIFFENEAU, M., WEILL, P., AND TCHOUBAR, B.: Compt. rend. **205,** 144 (1937).

(212) Truce, W. E., and Wise, J. T.: J. Am. Chem. Soc. **72**, 2300 (1950).
(213) Turner, R. B.: J. Am. Chem. Soc. **72**, 878 (1950).
(213a) Urushibara, Y., and Chuman, M.: Bull. Chem. Soc. Japan **22**, 69 (1949); Chem. Abstracts **44**, 1124c (1950).
(214) Ushakov, M. I., and Madaeva, O. S.: J. Gen. Chem. (U.S.S.R.) **9**, 436 (1939).
(215) Ushakov, M. I., and Madaeva, O. S.: J. Gen. Chem. (U.S.S.R.) **9**, 1690 (1939).
(216) Vaughan, T. H., Spahr, R. J., and Nieuwland, J. A.: J. Am. Chem. Soc. **55**, 4206 (1933).
(217) Vavon, G., and Guédon, A.: Bull. soc. chim. [4] **47**, 904 (1930).
(218) Vavon, G., and Mitchovitch, V. M.: Compt. rend. **186**, 702 (1928).
(219) Vavon, G., and Mitchovitch, V. M.: Bull. soc. chim. [4] **45**, 961 (1929).
(220) Vavon, G., and Perlin-Borrel: Bull. soc. chim. **51**, 994 (1932).
(221) Veibel, S., Lundgrist, F., Andersen, F., and Frederiksen, E.: Bull. soc. chim. France **6**, 990 (1939).
(222) Wallach, O.: Ann. **345**, 139 (1906).
(223) Wallis, E. S.: In *Organic Chemistry*, Vol. I, edited by H. Gilman, p. 1010. John Wiley and Sons, Inc., New York (1943).
(224) Whitmore, W. C., and Homeyer, A. H.: J. Am. Chem. Soc. **55**, 4194 (1933).
(225) Wiggins, L. F., and Wood, D. J. C.: J. Chem. Soc. **1950**, 1566.
(226) Winogradow, W.: Ann. **191**, 125 (1878).
(227) Winstein, S., and Henderson, R. B.: *Heterocyclic Compounds*, Vol. I, edited by R. C. Elderfield, p. 47. John Wiley and Sons, Inc., New York (1950).
(228) Wurtz, A.: Compt. rend. **50**, 1197 (1860).

References added in proof

(229) Beeby, M. H., and Mann, F. G.: J. Chem. Soc. **1951**, 411.
(230) Chuman, M.: J. Chem. Soc. Japan, Pure Chem. Sect. **70**, 253 (1949); Chem. Abstracts **45**, 6651a (1951).
(231) Fieser, L. F., and Rigaudy, J.: J. Am. Chem. Soc. **73**, 4660 (1951).
(232) Golse, R.: Ann. chim. **3**, 527 (1948).
(233) Heilbron, I. M., and Jones, E. R. H.: U. S. patent 2,525,672 (October 10, 1950).
(234) Huston, R. C., and Tiefenthal, H. E.: J. Org. Chem. **16**, 673 (1951).
(235) Temnikova, T. I., and Kropacheva, E. N.: Zhur. Obshcheĭ Khim. (U.S.S.R.) **21**, 183 (1951); Chem. Abstracts **45**, 7046a (1951).

General references

Bodforss, S.: *Die Aethylenoxyde*. Enke, Stuttgart, Germany (1920).
Courtot, C.: *Le magnesium en chimie organique*. Rigot et Cie, Nancy, France (1926).
Dubien, M.: Rev. gén. sci. **37**, 366 (1926).
Hapworth, H.: J. Soc. Chem. Ind. **41**, 7 (1922).
Runge, F.: *Organometallverbindungen*, lithoprinted by Edwards Brothers, Inc., Ann Arbor, Michigan (1945).
Schlenk, W.: In Houben-Weyl's *Methoden der organischen Chemie*, 2nd edition, Vol. IV, p. 781. Georg Thieme, Leipzig (1924).
Schmidt, J.: "*Die organische Magnesiumverbindungen und ihre Anwendung zu Synthesen*," Sammlung chem. chem.-tech. Vorträge **10**, 138 (1905); **13**, 432 (1908).
West, C., and Gilman, H.: *Organomagnesium Compounds in Synthetic Chemistry. A Bibliography of the Grignard Reagent. 1900–1921.* National Research Council, Reprint and Circular Series, No. 24, Washington, D. C. (1922).
Wren, H.: *Organometallic Compounds of Zinc and Magnesium*. D. Van Nostrand Company, Inc., New York (1913).