The Chemistry of the Carbonyl Group
Edited by Saul Patai

CHAPTER 15

Rearrangements involving the carbonyl group

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I. INTRODUCTION 761
II. ACID- AND BASE-CATALYZED REARRANGEMENTS 762
A. The Pinacol Rearrangements 762
B. The Semipinacolic Rearrangements 767
C. The Rearrangements of Aldehydes, Ketones, α-Ketols and Related Compounds (Acid-catalyzed) 771
D. The Dienone–Phenol, Quinamine and Some Related Rearrangements 775
E. The α-Ketol and Related Rearrangements (Base-catalyzed) 778
F. The Benzilic Acid and Related Rearrangements 783
G. Generalizations Concerning Certain Ketogenic Rearrangements 788
H. The Favorsky and Related Rearrangements 790
I. Ring–Chain Tautomerism 794
III. THERMAL REARRANGEMENTS 797
IV. OXIDATIVE REARRANGEMENTS 801
V. PHOTOCHEMICAL REARRANGEMENTS 808
VI. REFERENCES 815

I. INTRODUCTION

The term 'molecular rearrangement' has been so widely used that it cannot be exactly defined. In order that a 'rearrangement' be included in this chapter we decided that there should be no change in the total number of carbons as the molecule in question changes into product, but one or more carbons in that molecule should

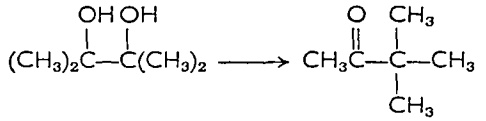
change position during reaction. We considered a carbonyl function to be involved in a rearrangement if it had been destroyed and/or formed during reaction. We have not hesitated, however, to discuss material excluded by these criteria when we thought it advisable or necessary. The Willgerodt reaction has been included, for example, because it has often been called a rearrangement.

Only rearrangements associated with aldehydes and ketones are discussed; reactions of carbonyl derivatives, of carboxylic acids and of esters and amides, in general, are excluded. These limitations seemed necessary to keep the chapter to a reasonable size and do at least a minimum of justice to the rearrangements discussed.

II. ACID- AND BASE-CATALYZED REARRANGEMENTS

A. *The Pinacol Rearrangements*

Fittig recorded the first example of the rearrangement of an α-glycol to a ketone[1]. Pinacol (**1**), obtained by the dimerization of

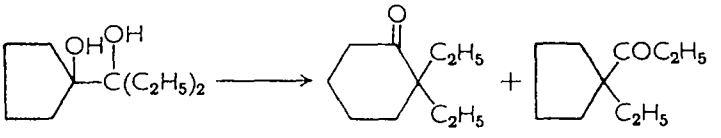


(**1**) (**2**)

acetone, yielded pinacolone (**2**) upon treatment with cold concentrated sulfuric acid. The reaction is general for α-glycols, and several reviews have appeared which adequately summarize the early[2-4] and recent[5] literature. Each of the two adjacent carbons bearing the hydroxyl groups can be primary, secondary, or tertiary, and each can be part of the same or different ring systems. Thus ethylene glycol (**3**) itself, as well as each of the compounds **4** to **8** obtained

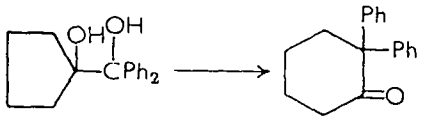
CH_2OHCH_2OH	$PhCHOHCH_2OH$	$PhCHOHCHOHPh$
(**3**)	(**4**)	(**5**)
Ph_2COHCH_2OH	$Ph_2COHCHOHPh$	$Ph_2COHCOHPh_2$
(**6**)	(**7**)	(**8**)

by successive phenyl substitution of the hydrogens of ethylene glycol, will undergo the pinacol rearrangement when treated with a

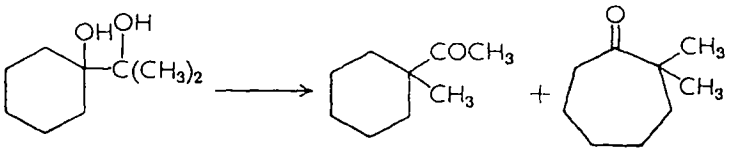


(**9**) (**10**) (**11**)

variety of acids. Compounds obtained through successive alkyl substitution also rearrange, as do the cyclic structures **9**, **12** and **14**[6]. Consequently, unusual ketones can often be synthesized through

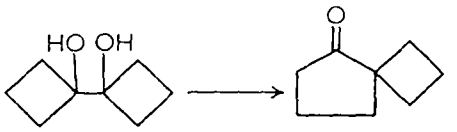


(**12**) (**13**)



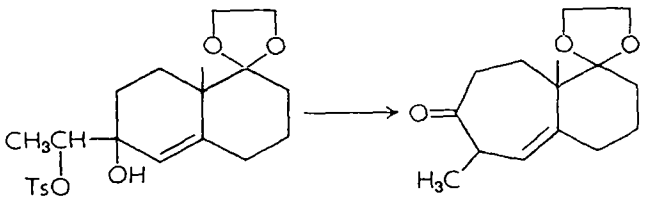
(**14**) (**15**) (**16**)

pinacol rearrangement of the appropriate α-glycol. For example, Vogel[7] prepared the spiroketone **18** through rearrangement of the α-glycol **17**, and Corey and coworkers[8] used a modified pinacol



(**17**) (**18**)

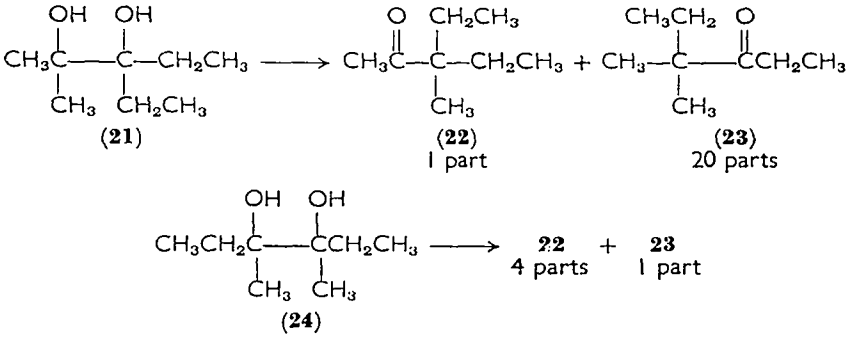
rearrangement of **19** (semipinacolic rearrangement, according to Bennett and Chapman[2]) to prepare the ketone **20**, a key intermediate in the total synthesis of longifoline[8].



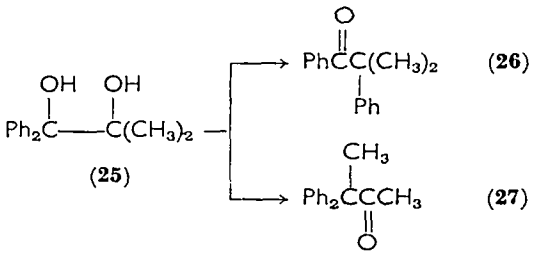
(**19**) (**20**)

Although the pinacol rearrangement is ordinarily a high-yield reaction, glycols whose four substituents are not all the same can yield more than one product. Further, the relative yields of the products can be varied by changing the concentration of acid, or even

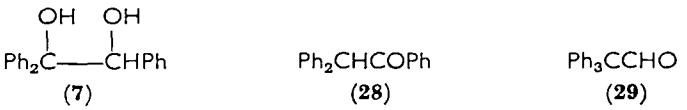
by changing the acid used to effect the rearrangement. Thus, the related α-glycols **21** and **24**, in cold concentrated sulfuric acid, both yield mixtures in different proportions of the same two ketones (**22** and **23**)[9]. The effect of different acidic media in bringing about



the rearrangement of the same α-glycol is illustrated in the rearrangement of **25**, whereby the action of cold concentrated sulfuric acid affords the ketone **27**, although a trace of sulfuric acid in acetic acid produces the ketone **26**[5].

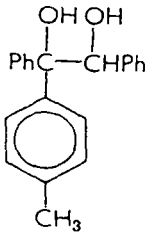


α-Glycols which are less than tetra-substituted can produce aldehydes as well as ketones. The relative yield of aldehyde and ketone is dependent upon temperature, and upon the strength and dilution of the acid used to effect the rearrangement. Ordinarily, lower temperatures and weaker acids favor aldehyde formation, for the aldehydes themselves are irreversibly converted into ketones under more drastic conditions. For example, in cold concentrated sulfuric acid, triphenylethylene glycol (**7**) is converted quantitatively

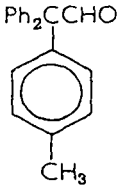


into benzhydryl phenyl ketone (**28**), whereas the action of 40% aqueous sulfuric acid affords mostly triphenylacetaldehyde (**29**)[10,11].

Similarly, either *threo-* or *erythro*-1,2-diphenyl-1-*p*-tolylethylene glycol (**30**) yields a mixture of two isomeric ketones in concentrated



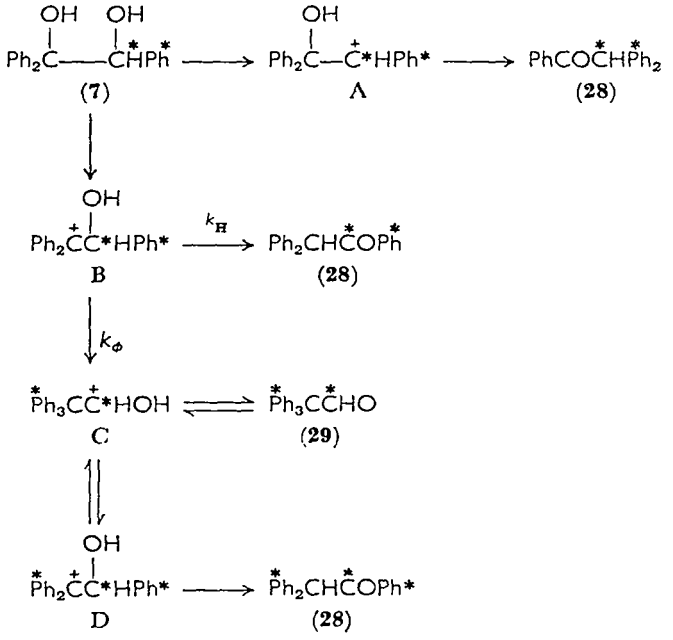
(**30**)



(**31**)

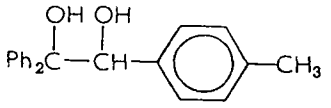
sulfuric acid at 0°c[12]. When the same glycol (**30**) is allowed to dissolve slowly in 98% formic acid at room temperature, diphenyl-*p*-tolylacetaldehyde (**31**) is the major product[12]. Phenyldi-*p*-tolylacetaldehyde[13] and diphenyl-*o*-tolylacetaldehyde[14] have been prepared by analogous rearrangements, in formic acid, of the appropriate glycols.

Considerable mechanistic information concerning the pinacol rearrangement is summarized in two papers[11,12]. In the first paper[11] ^{14}C-double-labeling experiments established the several pathways for rearrangement of triphenylethylene glycol (**7**) (Scheme 1) in a



SCHEME 1.

variety of acidic media. It was possible to calculate how much each path contributed to product formation and, in addition, to determine the migratory rate ratio k_ϕ/k_H for each medium. Removal of the secondary hydroxyl group was of insignificant importance under any



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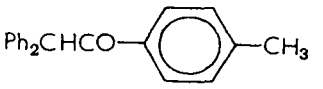

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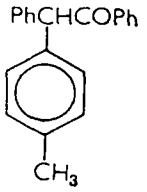
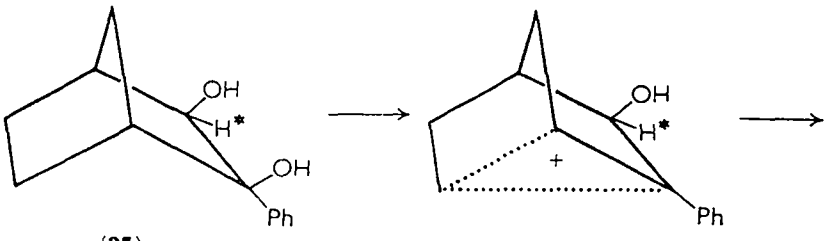


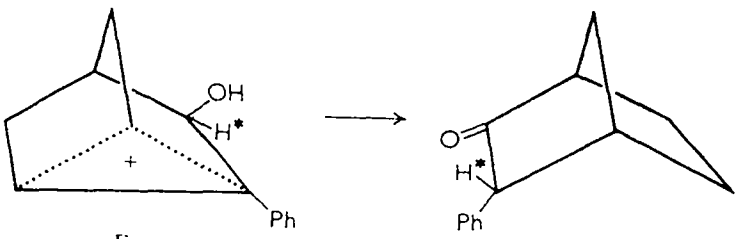
(34)

of the conditions studied. In the second paper[12] 1,1-diphenyl-2-*p*-tolylethylene glycol (**32**) was shown to suffer loss of its *secondary* hydroxyl group in cold concentrated sulfuric acid to the extent of 23% to yield the ketone **34**. Loss of the tertiary hydroxyl group of **32** (77%) led to a mixture of ketones **33** and **34**. The mechanism of the conversion of diphenyl-*p*-tolylacetaldehyde (**31**) into the two ketones **33** and **34** was also established[5,12].

In a very recent study Collins and coworkers[15] subjected 2-phenyl-2,3-*cis-exo*-norbornanediol (**35**) to rearrangement in cold concentrated sulfuric acid. The product, 3-*endo*-phenylnorbornanone (**36**), was shown to have been formed with intramolecular migration of the hydrogen at $C_{(3)}$ (shown with asterisk), and with inversion of



(35) E



F (36)

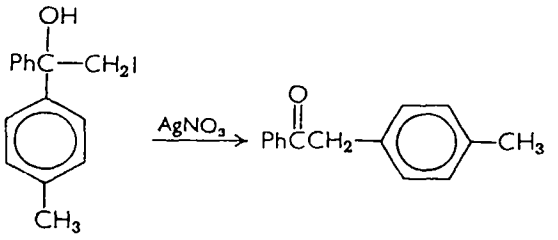
configuration. Experiments with a ^{14}C-label in the 2-position of **35** showed that the phenyl group in **36** was still attached to the original carbon. Although it is difficult to understand why the tertiary benzyl-type carbonium ion should prefer a bridged rather than an open structure, the results are best explained through the formation of the nonclassical ion E which rearranges to F by an intramolecular (6–1) migration of hydrogen.

Migratory aptitudes in the pinacol rearrangement have received exhaustive study[3–5], and it is clear that those groups which are the better electron donors are also better able to migrate to an adjacent carbonium center. Thus the usual order *p*-methoxyphenyl > *p*-tolyl > phenyl > *p*-nitrophenyl, etc., is maintained in the pinacol and also in the aldehyde–ketone rearrangement[12–14], in spite of the belief once held[3,4] that migratory aptitudes during the latter reaction were 'reversed'.

The early studies of Bachmann, Bailar, and others upon the migratory aptitudes of substituted phenyl groups in symmetrically substituted glycols are of considerable mechanistic importance, but have been reviewed so completely and so frequently[3–5] that they will not be discussed further in this chapter.

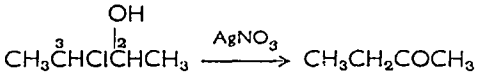
B. The Semipinacolic Rearrangements

The terms 'semipinacol' and 'semipinacolic change' were first applied by Tiffeneau[16] and later used by Bennett and Chapman[2] to signify rearrangement through secondary hydroxyl removal from an α-glycol containing both secondary and tertiary hydroxyl groups. Thus that fraction (23%) of the rearrangement[12] of 1,1-diphenyl-2-*p*-tolylethylene glycol (**32**) which yields ketone **34** through secondary hydroxyl loss followed by phenyl migration is a semipinacolic rearrangement. Unless the single alkyl or aryl substituent adjacent to the *s*-hydroxyl is strongly electron-donating, the semipinacolic rearrangement cannot usually compete with tertiary hydroxyl loss. Further, the semipinacolic rearrangement of an α-glycol often cannot be recognized without the use of an isotopic tracer. In the event that secondary hydroxyl is replaced with a better leaving group, such as halogen, amino, or *p*-toluenesulfonyl (compare with the conversion[8] **19** → **20**), then the semipinacolic reaction can be forced to take place at the expense of, and to the exclusion of, tertiary hydroxyl removal. Tiffeneau[17], for example, reported that the sole product resulting from treatment of 2-iodo-1-phenyl-1-*p*-tolylethanol (**37**) with silver nitrate was α-*p*-tolylacetophenone (**38**). Similarly, Alexander and Dittmer[18]



(37) (38)

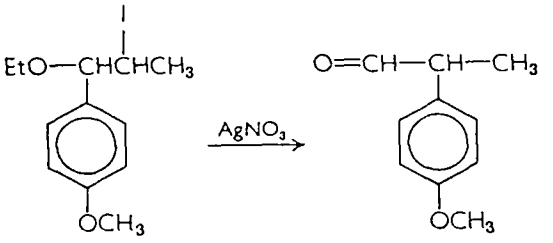
prepared methyl ethyl ketone (**40**) by the action of aqueous silver



(39) (40)

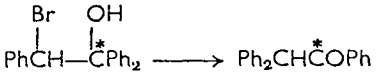
nitrate upon either of the diastereomers of structure **39**. The reaction can be formulated as proceeding with loss of chloride ion followed by a 1,2-shift of hydrogen from the 2-position to the carbonium center ($C_{(3)}$) so obtained.

Tiffeneau[19] prepared the aldehyde **42** by the action of silver nitrate on the iodohydrin **41**, a reaction which requires migration of the *p*-methoxyphenyl group to the carbon originally inhabited by the iodine atom.



(41) (42)

The action of mercuric ion upon an aqueous dioxane solution of 2-bromo-1,1,2-triphenylethanol (**43**) to yield benzhydryl phenyl ketone (**28**) was studied by Lane and Walters[20]. The same reaction

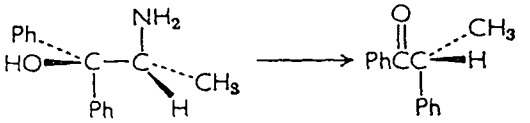


(43) (28a)

was investigated by Collins and Bonner[21] using ^{14}C to trace the course of the rearrangements. The tracer result is shown with the asterisks in the two formulae **43** and **28a**, and confirms that a

rearrangement of the carbon–carbon bonds has taken place; that is, a phenyl adjacent to the 1-position has shifted by means of a carbonium ion process to the carbon originally attached to bromine.

Another 'leaving group' often employed in semipinacolic rearrangements is the amino group. In an early study Luce[22] prepared 1-(α-naphthyl)acetophenone by the action of sodium nitrite in acid medium upon 2-amino-1-(α-naphthyl)-1-phenylethanol. One such reaction which has become a classic because of its mechanistic

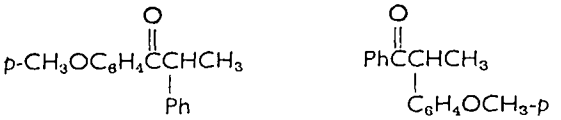


(+)-(**44**) (−)-(**45**)

importance is the deamination, originally studied by McKenzie, Roger and Wills[23], of (+)-2-amino-1,1-diphenypropanol (**44**) to yield (−)-α-phenylpropiophenone (**45**). The stereochemical study of McKenzie and coworkers[23], when combined with the configurational relationship later proved by Bernstein and Whitmore[24], was used for many years[3,4] as evidence that a Walden inversion takes place at the migration terminus during Wagner–Meerwein-type rearrangements which are accompanied by aryl or alkyl migration.

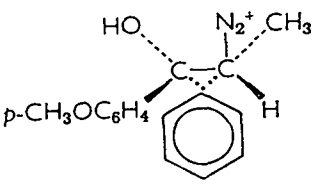
(**46**) (**47**)

Curtin and coworkers[25–29] carried out an extensive mechanistic investigation of the ketone-forming deamination of several amino alcohols. Of particular interest are their results for compounds **46** and **47**, which are closely related to the classic example[23,24] of 2-amino-1,1-diphenyl-1-propanol (**44**). Curtin showed that upon deamination of such amino alcohols as **46** the phenyl undergoes predominant migration (90%) to yield the ketone **48**, whereas the amino alcohol **47** undergoes deamination to produce predominantly (again about

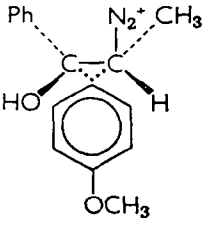


(**48**) (**49**)

90%) the ketone **49**. These and similar experiments were used by Curtin to state the '*cis* effect' in which **46**, for example, yields ketone **48** in greater amount because the transition state G, for



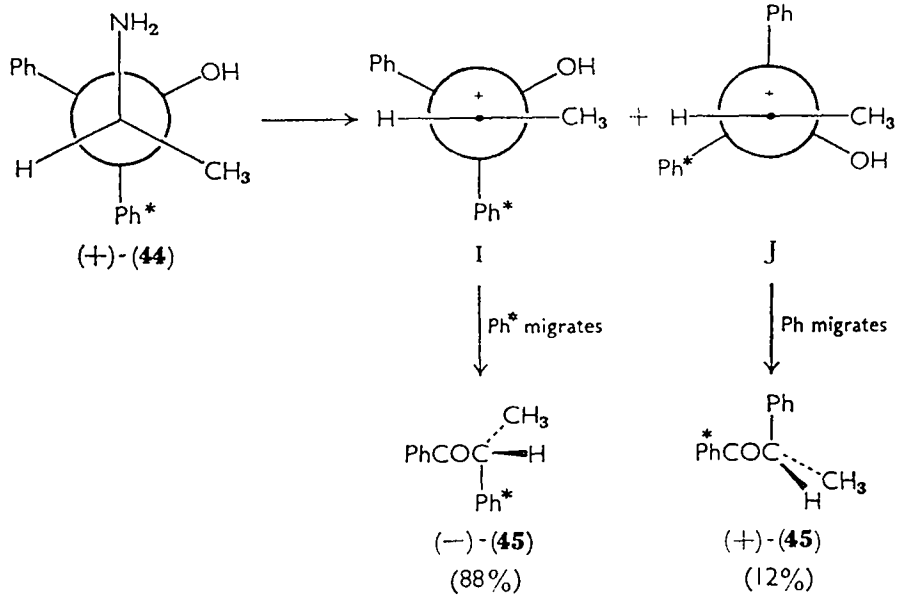
G



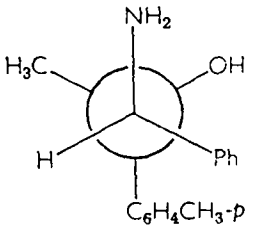
H

formation of ketone **48** places the two large bulky groups (methyl and anisyl) *trans* to each other. When, conversely, the anisyl group of **46** migrates, the methyl and phenyl must eclipse each other in the *cis* configuration to yield the transition state H. Since H is less favorable than G, the amino alcohol **46** reacts preferentially through G to form ketone **48**.

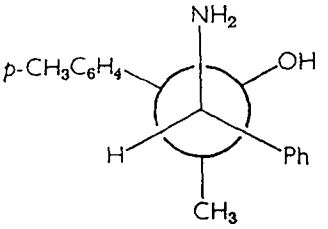
Collins and coworkers[30-33] studied several ketone-forming deaminations, combining stereochemical experiments with radioactive tracer techniques. Optically active 2-amino-1,1-diphenyl-1-propanol (e.g. (+)-**44**)[30] was subjected to deamination conditions, and the product was resolved. Oxidative degradation followed by radio-



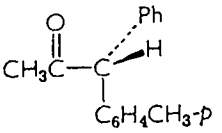
activity assay of the degradation products was used to demonstrate that *both* labeled and unlabeled phenyl groups undergo 1,2-shift through the *trans* transition state arising from ions I and J, respectively. The *cis* transition state similar to H, therefore, cannot be involved in the deamination of (+)-**44** (nor, by implication, during deaminations of **46**, **47** and other 2-amino-1,1-diarylpropanols studied by Curtin and coworkers[25-29]), for the unlabeled phenyl group of (+)-**44** shifts to the same side of the migration terminus originally bonded to the nitrogen. A further consequence of the important observation of Benjamin, Schaeffer and Collins[30] is that at least to the extent (12%) that ion J is involved in the deamination, the intermediate must be an *open carbonium ion*, for the carbon–nitrogen bond must cleave before migration of the unlabeled phenyl. In other studies Collins and coworkers[31-33] established that the optically active amino alcohol **50** undergoes deamination to produce predominately (−)-**52** with inversion (74%) at the migration terminus. The diastereomer (+)-**51**, however, when similarly treated



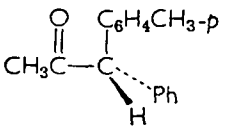
(−)-(**50**)



(+)-(**51**)



(−)-(**52**)



(+)-(**52**)

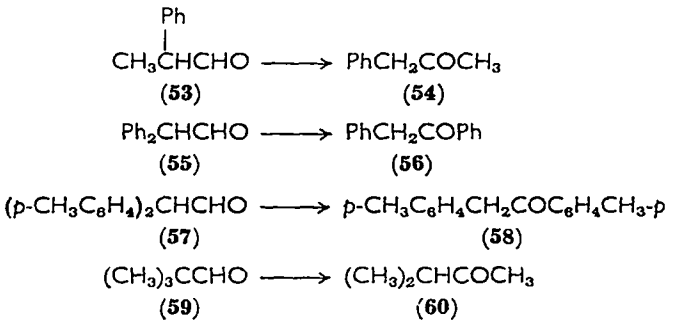
afforded more (+)-**52** than the levorotatory isomer in the approximate ratio 60:40. In the last example preponderant *retention* of configuration has occurred.

C. The Rearrangements of Aldehydes, Ketones, α-Ketols and Related Compounds (Acid-catalyzed)

Aldehydes, ketones, α-hydroxy aldehydes, α-hydroxy ketones, α-epoxy ketones and α-halo ketones all undergo rearrangement

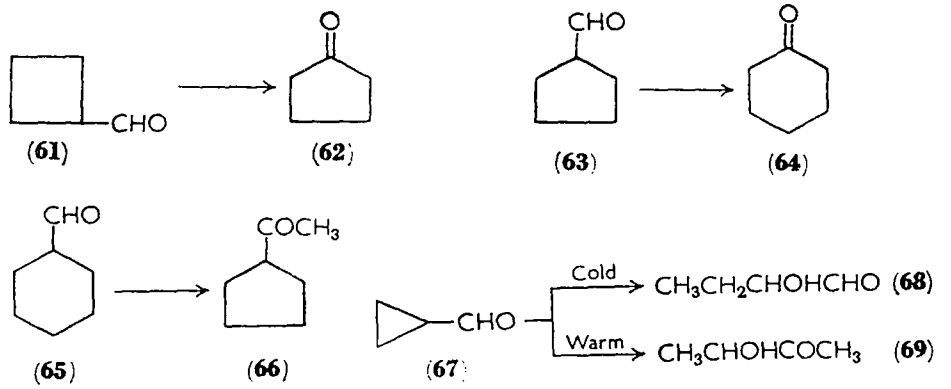
under both acidic and basic conditions. Some of these rearrangements are discussed in this section, whereas others, such as the Favorsky[34-36], and the rearrangement of α-diketones are taken up later.

The scope and synthetic value of the aldehyde–ketone rearrangement were demonstrated many years ago in a series of papers by Danilov and Venus-Danilova[37-43]. The rearrangements of, for example, triphenylacetaldehyde[10,37] to benzhydryl phenyl ketone (**29** → **28**), as well as the following transformations[43] were reported:



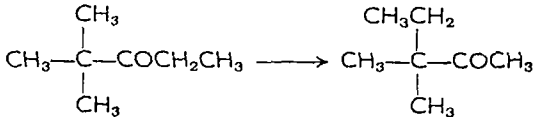
The mechanism of the aldehyde–ketone rearrangement has been clarified by Collins and coworkers[5,11,12], who correlated it with the pinacol rearrangement, and demonstrated that the apparently anomalous reversal of the migratory aptitudes exhibited during certain of these reactions could be explained through an equilibration of several carbonium ion intermediates. It was possible to calculate the migratory aptitudes[12-14] and to show that the normal order[3-5] was not reversed (see section II.A).

Venus-Danilova[44,45] reported the acid-catalyzed rearrangements of the cyclic aldehydes **61**, **63**, **65** and **67** with the results shown,



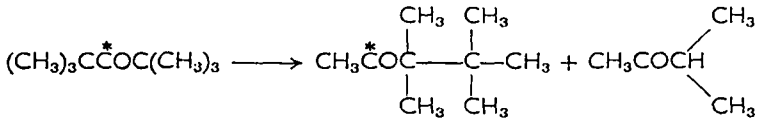
most of which are easily explainable by assuming that normal carbonium processes are taking place. The formation of cyclopentyl methyl ketone (**66**) from cyclohexanecarbaldehyde (**65**) is particularly intriguing.

Zook and coworkers[46,47] found that *t*-butyl ethyl ketone (**70**)



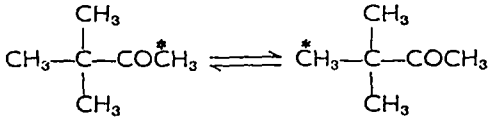
(**70**) (**71**)

was slowly converted, in concentrated sulfuric acid, into *t*-amyl methyl ketone (**71**). The rearrangement[47] of hexamethylacetone (**72**) (in 97% sulfuric acid) is most striking, since both methyl pentamethylethyl ketone (**73**) and methyl isopropyl ketone (**74**) are prod-



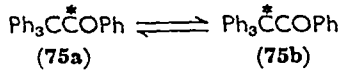
(**72**) (**73**) (**74**)

uced in approximately equal amounts. These same investigators[47] report the rearrangement of eight other ketones under similar conditions. Barton and Porter[48] also studied the rearrangement of **72** to **73** and showed, with ^{14}C-labeling, that the carbonyl carbon of **73** still possesses all of the ^{14}C activity originally present in the carbonyl group of **72**. Rothrock and Fry[49], in their study of the acid-catalyzed rearrangement of *t*-butyl ^{14}C-methyl ketone (**2a**) demonstrated that although no other ketone is formed, the labeled methyl group still undergoes deep-seated rearrangements, for the isotope position isomer (**2b**) was produced. Fry and coworkers[50-52] later demon-



(**2a**) (**2b**)

strated the remarkable isotope positional isomerization, catalyzed by strong acids, shown in the equilibrium **75a** ⇌ **75b**. These same

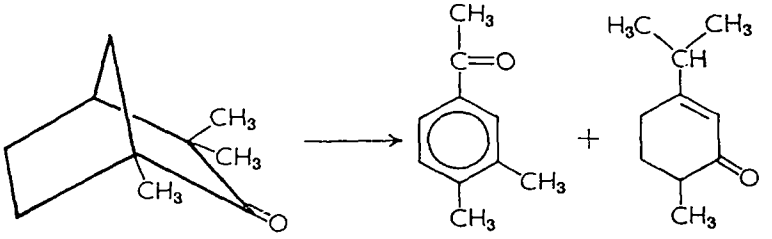


(**75a**) (**75b**)

investigators[50-52] also demonstrated that the action of perchloric

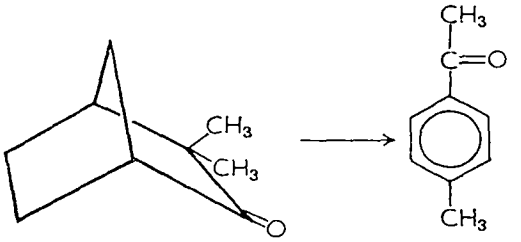
acid upon 2-butanone affords acetone, 2-pentanone, 3-pentanone, 3-hexanone and several unidentified products, illustrating disproportionation as well as rearrangement during the reaction. Similar results[50-52] were obtained by the action of perchloric acid upon 3-pentanone.

Fenchone (**76**), upon treatment with concentrated sulfuric acid,



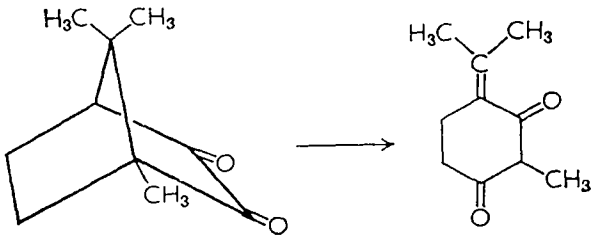
(**76**) (**77**) (**78**)

is converted into 3,4-dimethylacetophenone (**77**) and carvenone (**78**)[53,54]. Lutz and Roberts[55], using ^{14}C, have studied the mechanism of these transformations. In like fashion camphenilone (**79**)



(**79**) (**80**)

affords *p*-methylacetophenone (**80**) in low yield[56], and camphorquinone (**81**) is converted into isocamphorquinone (**82**)[59].

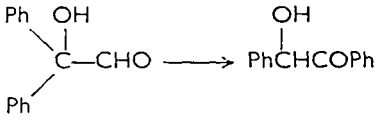


(**81**) (**82**)

All of the reactions so far discussed in section II on acid-catalyzed rearrangements can easily be rationalized through carbonium ion

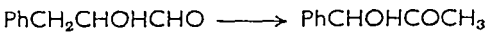
intermediates. The intimate details for many of these rearrangements, however, have not been so well established as for the pinacol and aldehyde–ketone transformations. In some cases (e.g. **65** → **66** and **72** → **73** + **74**) so many discrete steps must be written to explain the observed facts that it would appear worthwhile to reinvestigate these remarkable reactions, for it might be possible to uncover some novel and dramatic carbonium ion processes.

α-Hydroxy aldehydes also undergo rearrangement in acid medium, as shown by the conversion of diphenylglycolaldehyde (**83**) into benzoin (**84**)[58]. Benzylglycolaldehyde (**85**) upon similar treatment (alcoholic solution with a few drops of sulfuric acid) yields acetyl



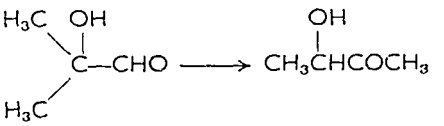
(**83**) (**84**)

phenyl carbinol (**86**)[59], whereas α-hydroxyisobutyraldehyde (**87**)



(**85**) (**86**)

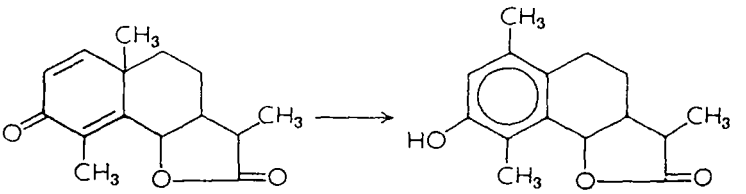
is reported to yield the α-hydroxy ketone **88**[60,61].



(**87**) (**88**)

D. The Dienone–Phenol, Quinamine and Some Related Rearrangements

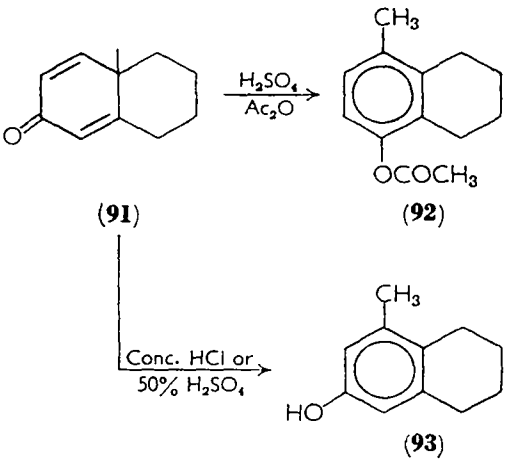
Santonin (**89**), upon being treated with mineral acid, is converted into the desmotroposantonin **90**[62–65], a transformation which appears



(**89**) (**90**)

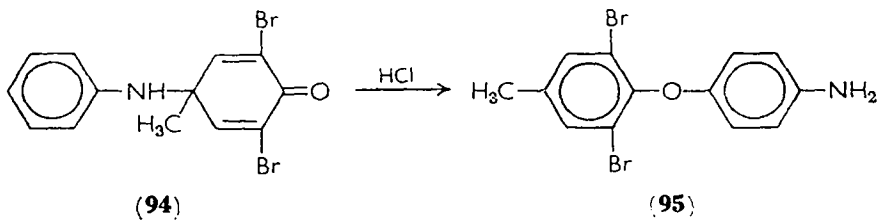
to be the first known example of the dienone–phenol rearrangement. Since the dienone–phenol rearrangement has been reviewed

recently[66] and the mechanism has been very adequately treated, only one other example will be mentioned here, namely the rearrangement, in acetic anhydride and sulfuric acid, of compound **91**. Under the anhydrous conditions employed by Woodward and Singh[67] only the 4-methyl-1-tetralol acetate (**92**) was formed. Treatment of **91** with concentrated hydrochloric acid, or with 50% sulfuric acid, however, afforded the 4-methyl-2-tetralol **93**[68]. The formation of **92** can be rationalized through the intervention of a



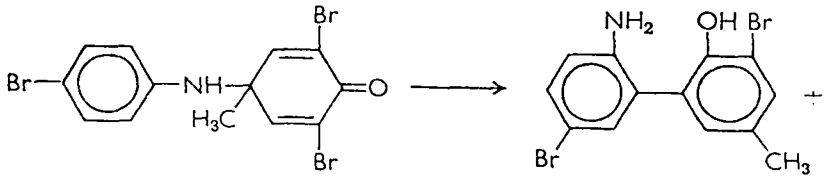
spirane intermediate, whereas **93** must be formed as a result of methyl migration[66].

The acid-catalyzed rearrangements of quinamines (anilinocyclohexadienones)[69,70] resemble the dienone–phenol rearrangement, although the mechanisms of these two reactions are not necessarily similar. Miller[71,72] has recently studied the two major types of rearrangement exhibited by several such quinamines. When the aniline residue contains no *para* substituent, as in structure **94**,



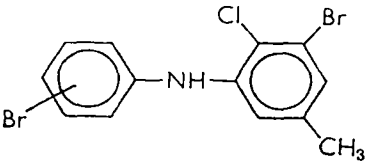
treatment of the quinamine with hydrochloric acid yields a substituted aminodiphenyl ether as shown in structure **95**. When the

para position is substituted (**96**), there are two major products, a substituted biphenyl (**97**) and the amine (**98**). Miller prefers a mecha-



(**96**)

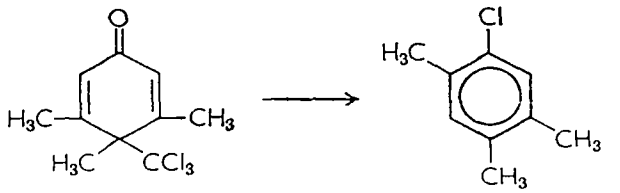
(**97**)



(**98**)

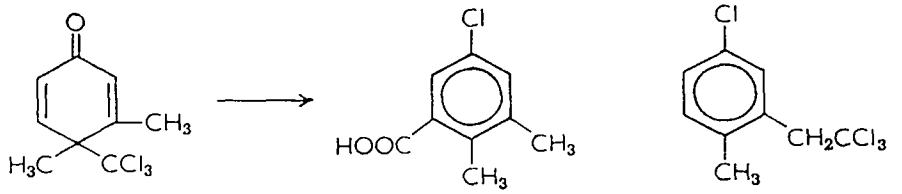
nism for these transformations in which π-complex intermediates are formed.

Newman and coworkers[73] studied the rearrangement, in poly-



(**99**) **100**

phosphoric acid, of the dienone **99** to 1-chloro-2,4,5-trimethylbenzene (**100**). With polyphosphoric acid, dienone **101** yields the acid **102**, whereas when **101** is treated with phosphorous penta-

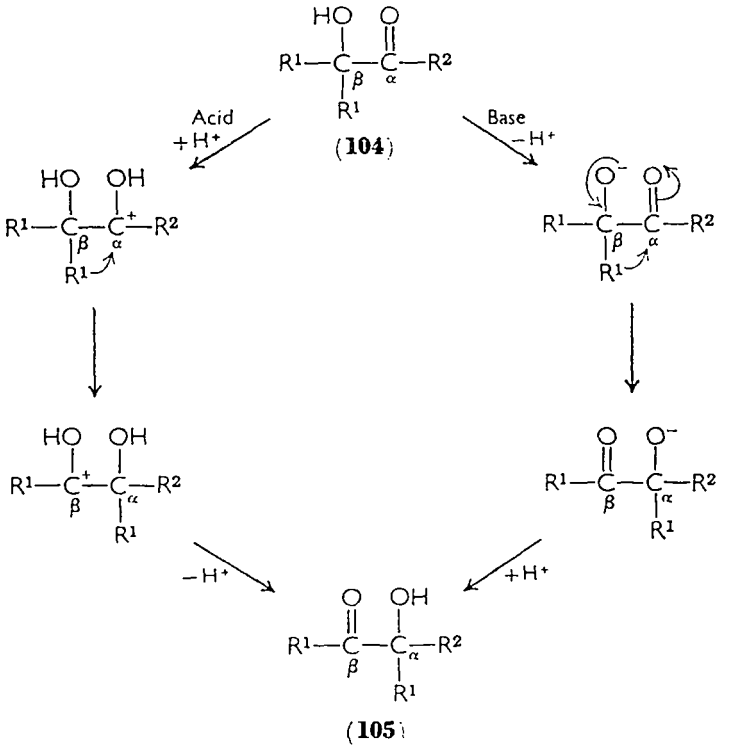


(**101**) (**102**) (**103**)

chloride[73]) 1-chloro-3-(β-trichloroethyl)-4-methylbenzene (**103**) is produced.

E. The α-Ketol and Related Rearrangements (Base-catalyzed)

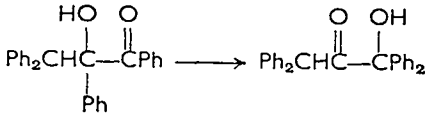
Most ionic molecular rearrangements involve migration of some group with its bonding electrons to an adjacent electron-deficient center. Such rearrangements are called 1,2-shifts. In a carbon-to-carbon rearrangement electron release to the migration origin (C_β) assists the rearrangement, whereas electron deficiency at the migration terminus (C_α) is required. If the assistance at C_β is sufficient, then the electron deficiency at C_α need not be large. In the reactions just discussed acid was used to promote a deficiency of electrons at C_α, whereas in the reactions to be considered now, base brings about electron release at C_β. The migration terminus will be electron-deficient because of an attached electronegative atom; in the benzilic acid rearrangement, for example, C_α is the carbon of a carbonyl group, and in certain Favorsky rearrangements it is a carbon attached to halogen. The similarity of the acid- and base-catalyzed rearrangements is illustrated in the following two-reaction sequences through which the α-ketol **104** can be converted either by acid or by base into the isomer **105.**



(**104**)

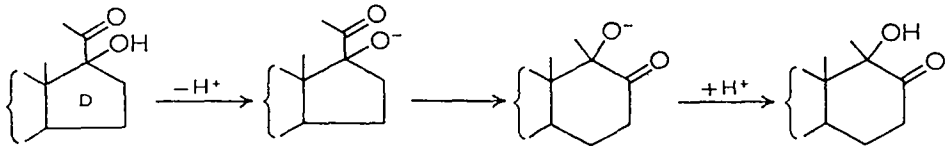
(**105**)

Two examples of the base-promoted rearrangement of α-ketols are (*a*) the formation of 2-oxo-1,1,3,3-tetraphenyl-1-propanol (**107**) from α-benzhydrylbenzoin (**106**)[74], and (*b*) the conversion of α-hydroxybutyraldehyde into acetoin[75]. The synthetic value of the



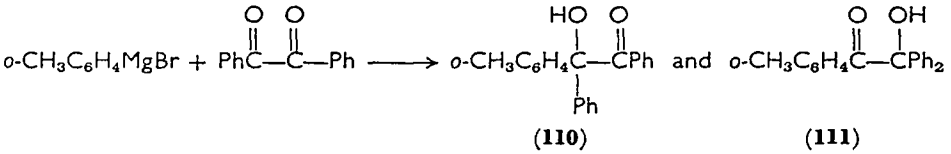
(106) **(107)**

α-ketol rearrangement, particularly in ring expansions to produce D-homosteroids, has been discussed by the Fiesers[76]. Ruzicka and Meldahl first observed this ring expansion in the treatment of 17-hydroxy-20-oxo steroids (**108**, ring D only shown) with alkali[77].



(108) **(109)**

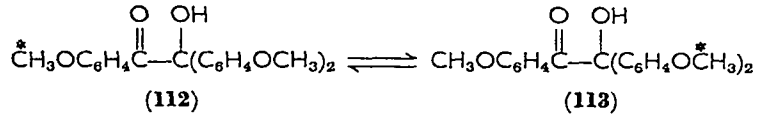
The possibility of rearrangement is always present during reactions which produce α-ketols, such as the benzoin condensation or the addition of one equivalent of an organometallic reagent to a diketone. A good example is the addition[78] of *o*-tolylmagnesium bromide to benzil to yield a compound which was mistakenly called '*α-o*-tolylbenzoin (**110**)'. The incorrect structure was the cause of some



(110) **(111)**

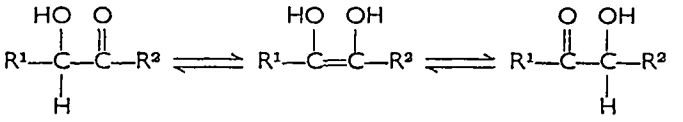
confusion[79] until subsequent workers isolated both the expected product (**110**) and the rearranged product (**111**) and proved their structures[80]. The '*α-o*-tolybenzoin' was shown, in fact, to be α-phenyl-2-methylbenzoin (**111**). Analogous rearrangements have been observed in the additions of mesitylmagnesium bromide to anisil[81], of mesitylmagnesium iodide to benzil[82], and of *o*-tolyllithium to benzil[83]. An interesting example of the rearrangement of an α-ketol under basic conditions was observed with *α-p*-methoxyphenylanisoin (**112**) labeled with ^{14}C in one of the methoxy groups[80]. Equilibration of the position of labeling in this case (**112** ⇌ **113**) is

analogous to the racemization of an optically active compound in that there is no free energy difference between reactant and product.



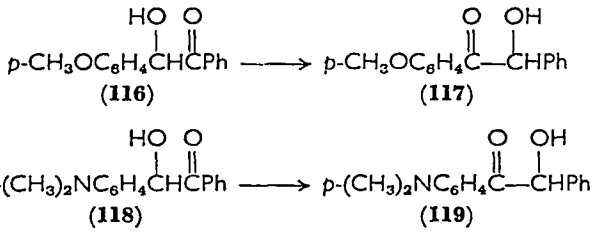
(112) (113)

The base-promoted α-ketol rearrangement resulting in a change of the carbon skeleton probably occurs only when the carbinol group is tertiary. If one R^1 in **104** is hydrogen, enolization presents a route for an isomerization (**114** ⇌ **115**) which is easily brought about by base. When R^1 and R^2 (in **114**) are aryl groups, the



(114) (115)

compound is a benzoin and its stability relative to **115** is easily predicted on the basis of ordinary electronic effects. Two such isomerizations (**116** → **117**[84] and **118** → **119**[85]) are shown. Because



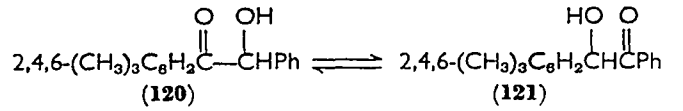
(116) (117)

(118) (119)

the catalyst (cyanide ion) for benzoin condensation is basic, the equilibrium **114** ⇌ **115** is established in the reaction of two aldehydes during the mixed benzoin condensation. If one isomer is markedly more stable, as from condensation[86] of benzaldehyde with *p*-dimethyl-

$$PhCHO + p\text{-}(CH_3)_2NC_6H_4CHO \xrightarrow{CN^-} \mathbf{119}$$

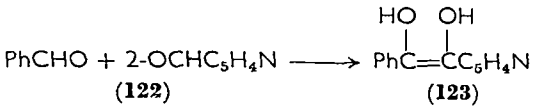
aminobenzaldehyde, then only one benzoin (**119**) is isolable. In other cases, e.g. with 2,4,6-trimethylbenzoin, both isomers (**120** and **121**) are isolable[87]. Synthetic techniques have been developed for



(120) (121)

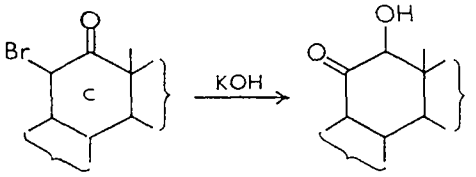
obtaining even the unstable isomer of a mixed benzoin[88]. In some

cases, particularly those involving certain heterocyclic aryl groups for R^1 or R^2 in the benzoin, the intermediate 'enediol' can be isolated from a condensation of mixed aldehydes, as for example, the production of **123** from benzaldehyde and 2-formylpyridine (**122**)[89]. In a recent review of enediols the stabilizing influence of chelation on structures like **123** has been discussed[90].



(122) (123)

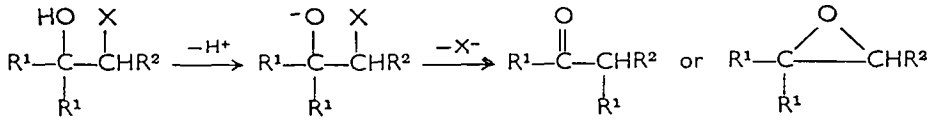
Acyloins **114**, where R^1 and R^2 are aliphatic or alicyclic residues, may also undergo easy equilibration with base to form **115**. Such a possibility should be considered when base-promoted reactions are used in the syntheses of α-hydroxy ketones, for example, by the hydrolysis of α-halo ketones. In the following illustration (**124** to **125**), which is taken from synthetic work in the steroid field, the substituted cyclohexane ring in **124** represents the c ring of 11β-brome-



(124) (125)

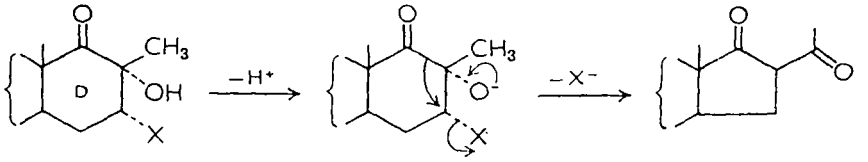
12-oxocholanate[91]. With certain structural features, the intermediate enediol may be more stable than either α-hydroxy ketone; ascorbic acid is an example. Isomerization of an aldose to a ketose, e.g. mannose to fructose, an important biosynthetic process effected by isomerase enzymes[92], most likely proceeds through an enediol, i.e. **114** to **115** with R^2 = H. The same carbohydrate rearrangement is brought about *in vitro* by alkali alone[93].

We have already pointed out that the base-induced α-ketol rearrangement with a tertiary carbinol (**104** → **105**) is analogous to the acid-induced pinacol rearrangement. One might also anticipate that tertiary carbinols α-substituted with good leaving groups might undergo a base-induced rearrangement, **126** → **127**, analogous to the



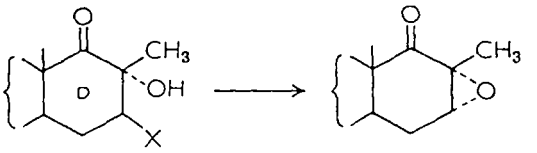
(126) (127) (128)

semipinacolic change, but a competing reaction which generally predominates is epoxide (**128**) formation. When stereochemical factors favor the rearrangement, however, ketone formation (**126** → **127**) does occur. The substituted D-homo ring of a pregnone derivative is shown in **129**; the leaving group is *cis* to the tertiary hydroxyl and therefore unsuitably located for epoxide formation; hence base causes the indicated rearrangement to **130**[94]. When the leaving



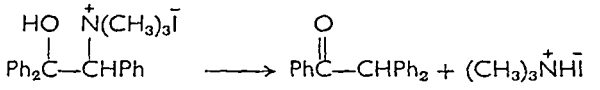
(**129**, X = OSO_2CH_3) (**130**)

group in the same system is *trans* to the tertiary hydroxyl, as in **131**, treatment with base results in simple epoxide (**132**) formation[95].



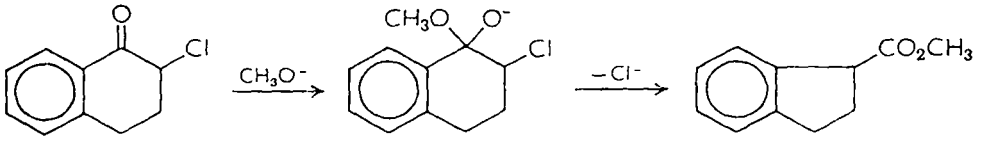
(**131**, X = Br) (**132**)

Another example of the rearrangement **126** to **128** is the formation[96]



(**133**) (**28**)

of benzhydryl phenyl ketone from **133**, and still other examples have been recognized[97]. Further, the ionic intermediate necessary for this rearrangement may be attained by attack of a nucleophile on an α-halo ketone. Thus the rearrangement[98] of 2-chloro-1-tetralone (**134**) by methoxide ion as the nucleophile probably proceeds as shown. An analogous reaction is formation of 1-phenyl-

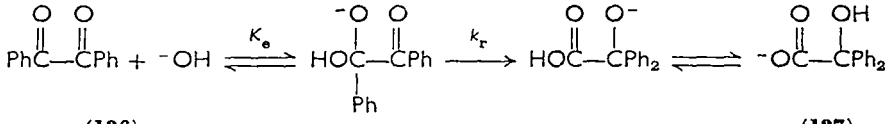


(**134**) (**135**)

cyclohexanecarboxylic acid from 1-chlorocyclohexyl phenyl ketone and hydroxide ion[99]. (Cases of the Favorsky reaction involving 'cyclopropanone' intermediates are discussed later.)

F. The Benzilic Acid and Related Rearrangements

The benzilic acid rearrangement is by far the best known 1,2-shift effected by base-promoted electron release to the migration origin (C_β). In fact the formation of benzilic acid (**137**) from benzil (**136**) would appear to be the first recognized molecular rearrangement reaction, having been discovered by Liebig in 1838[100]. There is little doubt that the mechanism of this reaction involves reversible addition (K_e) of hydroxide ion to one carbonyl group to give an intermediate anion which is completely analogous to the anionic intermediate in the α-ketol rearrangement (**104** → **105**). Following this, the 1,2-shift occurs in a rate-determining step (k_r) and prototropic equilibration yields the product. While alternatives to this



(**136**) (**137**)

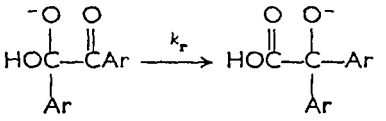
mechanism have been debated both before and since, in 1928 Ingold proposed these three steps as shown[101], and today there exists an extensive body of confirming data arising from application of virtually all of the physical organic chemist's tools, such as isotopic tracer techniques, kinetic analysis, migratory aptitude determinations, etc.

Reversibility of the first step (K_e) was established by the Roberts and Urey demonstration[102] that benzil exchanges oxygen in ^{18}O-enriched water in the presence of base more rapidly than it rearranges. Kinetically the overall reaction is second-order, first in benzil and in hydroxide ion, and certain bases such as phenoxide ion do not effect the reaction[103]. Thus, if the second step (k_r) is rate-determining, the overall second-order rate coefficient will contain the equilibrium constant of the first step (equation 1).

$$\text{Rate} = k_r K_e[\text{benzil}][\text{hydroxide}] \qquad (1)$$

From a study of the steric effect on the benzilic acid rearrangement, Eastham, Nations and Collins concluded that the transition state for the process closely resembles the intermediary anion produced in the first step[104]. In other words the key 1,2-shift has proceeded but

very little before the energy maximum for reaction is passed, and hence this energy requirement is predictable from the structure of the intermediary anion (**138**)[105]. Electron-attracting substituents on

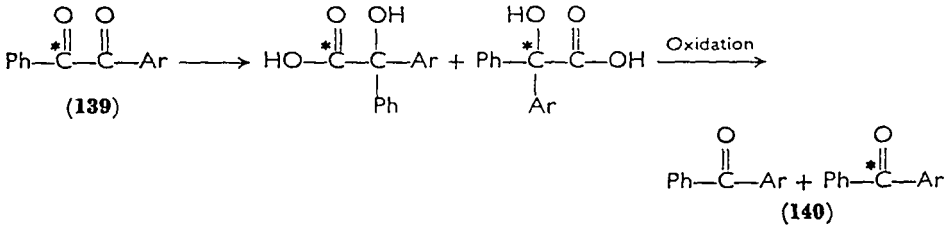


(**138**)

the aromatic ring (Ar in **138**) should stabilize this ion and enhance the overall reaction rate of a symmetrical benzil, whereas electron-releasing substituents then should slow the reaction. Indeed it is found that methoxy-, methyl- or amino-substituted benzils rearrange slower[106], while chloro-substituted benzils rearrange faster[107] than does benzil itself.

Numerous authors have proposed other transition states[108,109], particularly those in which the key 1,2-shift in **138** is *accompanied* by proton migration, i.e. a concerted process which obviates the prototropy Ingold depicted as a third and distinct step. Eastham and colleagues rejected the concerted process on the grounds that the required transition state would not resemble **138**[104]. Hine rejected it on the grounds that the rearrangement in a deuterated system is not retarded, as would be expected were proton transfer involved in the rate-determining step[110].

With an unsymmetrical benzil (**139**), whichever aromatic residue rearranges, the product structure is the same. Hence percentage migrations of Ar groups in **139** must be determined by isotopic labeling, e.g. as outlined below for **139** labelled with ^{14}C in the carbonyl adjacent to phenyl. It is seen that the ratio of radioactivity



(**139**) (**140**)

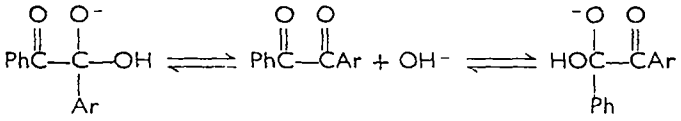
of the aryl phenyl ketone to that of the starting benzil will be the fraction of reaction proceeding by migration of the aryl group; values for a few selected aryl groups are shown in Table 1.

Inspection of Table 1 reveals that migratory aptitudes in the benzilic acid rearrangement do not correlate with those in the pinacol

TABLE 1. Percentage migrations of Ar in PhCOCOAr.

Ar	Migration (%)	Ref.
o-Tolyl	2·7	104
p-Methoxyphenyl	31·8	111
p-Tolyl	38·8	108
m-Chlorophenyl	81·2	108
Benzyl	100	112

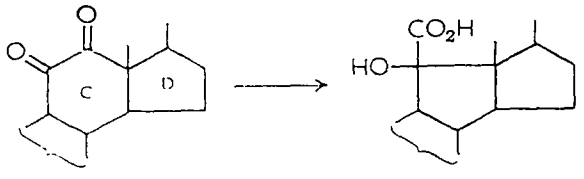
rearrangement, in which electron-releasing groups on an aryl group favor its migration. Here, however, electron release by an aryl group decreases the equilibrium concentration of the intermediate anion (**141**) in which Ar can migrate. Thus, since the relative amount of



(**141**) (**139**) (**142**)

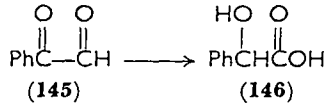
aryl *vs.* phenyl migration must be a function of the relative concentrations of this ion (**141**) and the ion (**142**) in which phenyl can migrate, electron release by the aryl group retards its migration. Conversely, ion **141** and aryl migration would be favored by an electron-attracting aryl group. In other words K_e is the factor which dominates the overall rate of migration expressed in equation (1). On this basis the effects revealed by data in Table 1 and by results with a number of other labeled unsymmetrical benzils can be explained. These results, as well as an historical summary of other mechanistic studies on the benzilic acid rearrangement, are available[113].

Examples of α-diketone systems which have been observed to undergo the benzilic acid rearrangement are multitudinous. Just a few examples are shown here to stress the generality of this reaction. The reaction will proceed in purely aliphatic systems and has been used to contract the steroid ring C (**143** → **144**). Hydrogen migrates

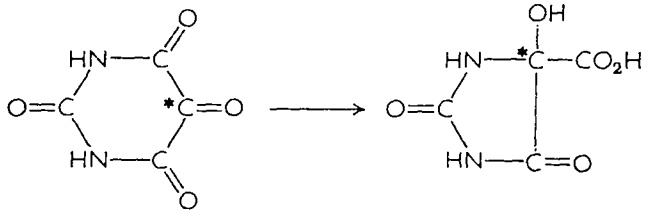


143 (**144**)

preferentially to phenyl[114] in the reaction **145** → **146**. Certain heterocyclic systems also rearrange, and in one such case, that of



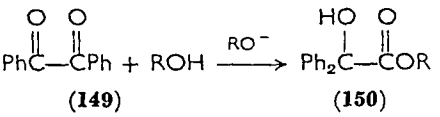
(145) **(146)**



(147) **(148)**

alloxan (**147** → **148**), nitrogen has been shown to migrate preferentially to carbon[115].

An interesting facet of the benzilic acid rearrangement is that it can be effected by certain bases other than hydroxide ion, in some cases even by bases and in solvents neither of which contain oxygen. Selman and Eastham have cited some examples and rationalized this unpredictable result, that is, unpredictable on the basis of the general mechanism **136** → **137**. A predictable result, but one not observed until rather recently, is that alkoxide ion will effect rearrangement of benzil to an alkyl benzilate. There were repeated studies of the reaction of benzil with alkoxide dating back to the last century, but it was not until 1956 that Doering and Urban[81] elucidated the conditions for the *benzilic ester rearrangement* (**149** → **150**). These workers formed both methyl and *t*-butyl esters

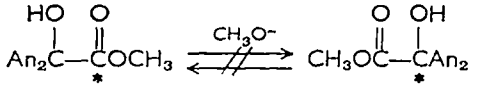


(149) **(150)**

by this rearrangement, rationalized the failures of previous workers to obtain esters, and gave a kinetic analysis of the rearrangement. All of their findings are consistent with the Ingold mechanism, cf. **136** → **137**, with the hydroxyl shown replaced with alkoxyl and without the third step (prototropy).

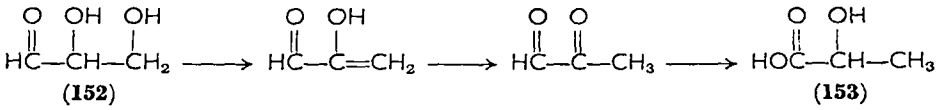
The view is held by some that the benzilic acid type rearrangement is reversible[116]. This view now seems unlikely since Eastham and Selman subjected ^{14}C-carbonyl labeled anisilic acid and its methyl

ester (**151**) to both mild and vigorous basic conditions and found no rearrangement of the ^{14}C-label[117].



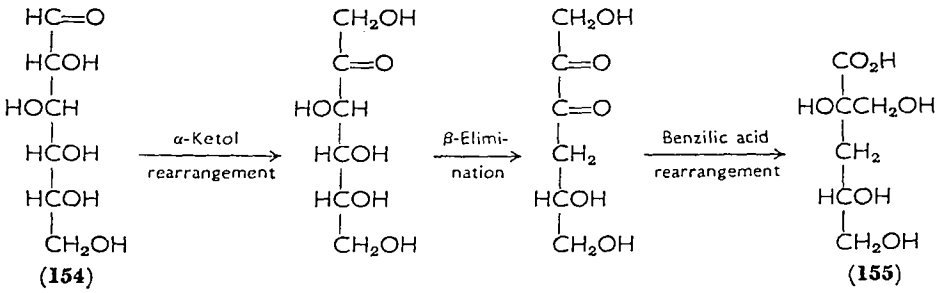
(**151**, An = *p*-$CH_3OC_6H_4$)

Because α-diketones undergo the benzilic acid rearrangement, any compound which is converted into an α-diketone by base may be expected to yield a rearrangement product. Thus, since base with an α,β-dihydroxy carbonyl compound can cause dehydration (β-elimination) to an α-diketone (or its enol)[118], the base may lead ultimately to an α-hydroxy acid. The transformation of glyceraldehyde to lactic acid (**152** → **153**) is an example of the two-step sequence[119]. To this sequence one must add a third step, the α-ketol



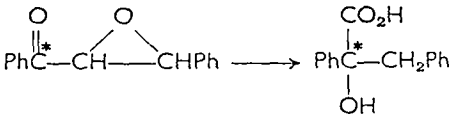
(**152**) (**153**)

rearrangement, in considering many of the alkali-induced transformations of carbohydrates. Thus the formation of some isosaccharinic acid (**155**) from glucose (**154**) may proceed as shown. Base-catalyzed carbohydrate rearrangements have been reviewed[120].



(**154**) (**155**)

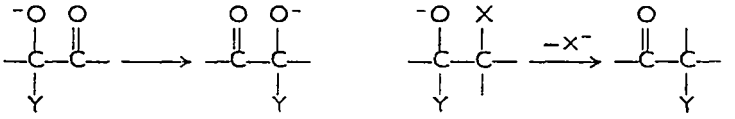
α,β-Epoxy ketones can also rearrange with base to α-diketones and hence produce α-hydroxy acids, as illustrated here with the rearrangement of labeled benzilideneacetophenone oxide (**156**)[112].



(**156**) (**157**)

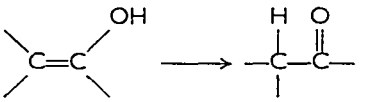
G. Generalizations Concerning Certain Ketogenic Rearrangements

To generalize the class of reactions which includes the α-ketol, benzilic acid and related rearrangements, we see that a property common to all is the formation of a carbonyl group from an oxide ion at C_β (migration origin) as the migrating group takes its bonding electrons to C_α (migration terminus). It is possible to look upon the energy gained in forming the carbonyl group as the 'driving force' for the reaction; perhaps all such cases should be classed as *ketogenic rearrangements*. Acceptance of electrons by C_α from the migrating group results either in addition to a carbonyl group at C_α or in nucleophilic substitution there. Selman and Eastham[113] have tabulated sixteen different functional arrangements for C_β—C_α which have been observed to rearrange; those cases involving nucleophilic substitution at C_α were not included. Perhaps the most interesting feature of these rearrangements is the variety of migrating groups which have been observed[113]. In general, then, one should anticipate the possibility of a ketogenic rearrangement with any ions of structures K or L, or in any reactions which may give rise to these ions.



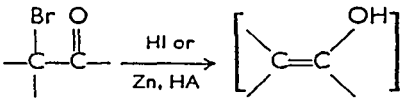
K L

The classical ketogenic reaction is reversal of enolization, commonly called ketonization. Although this process itself (equation 2) is



(2)

not generally classified as a molecular rearrangement, the enol may be an intermediate in rearrangement reactions (cf. **152** → **153**) leading to ketones. Hence one important aspect of ketonization, the stereochemistry of the process, is worthy of consideration here. A



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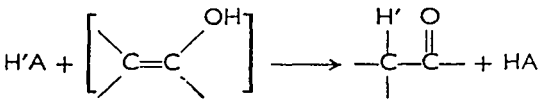
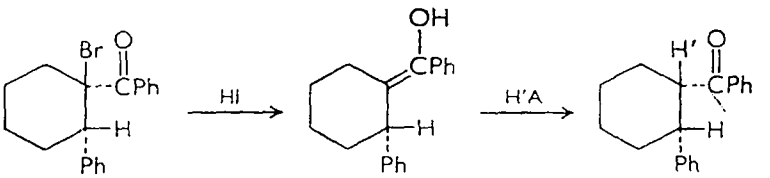


(4)

reaction which has proved useful in generating enols that ketonize, and which has been amenable to stereochemical studies, is the reduction of an α-bromo ketone to remove halogen. This reduction (equations 3 and 4) is accomplished in acid (HA) by either zinc or hydrogen iodide.

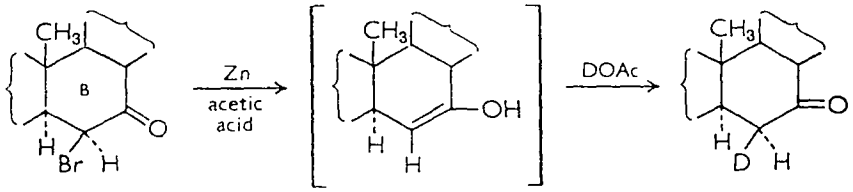
The stereochemistry of the ketone produced (equation 4) is apparently controlled by the direction of approach by acid to the enol. Thus Zimmerman has pointed out several cases in which approach to one side of an enol is obviously favored, and ketonization in these places the entering hydrogen on the less hindered side[121]. For example, debromination of 1-benzoyl-1-bromo-2-phenylcyclohexane (**158**) with hydrogen iodide produces *cis*-1-benzoyl-2-phenylcyclohexane (**160**), despite the fact this *cis* compound is less stable than the *trans* isomer[122]. The 2-phenyl group on one side of



(**158**) (**159**) (**160**)

enol **159** sterically hinders the approach of a proton donor to that side.

If the ketonization produces a cyclohexanone, there is a strong tendency for the hydrogen atom introduced (H′ in equation 4) to be axial. Corey and Sneen[123] have given a rational analysis of the electronic effect which favors the axial approach of the proton donor to a six-membered enol. An illustration of the effect[123], debromination of a 6-bromo-7-oxo steroid (**161**) with zinc and deuteroacetic acid (DOAc) produced a 6β-deutero steroid (**163**); deuterium was introduced into the axial position despite considerable hindrance to this approach by the axial methyl group of the steroid 10-position.

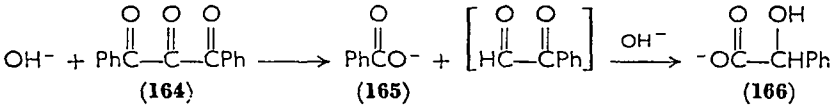


(**161**) (**162**) (**163**)

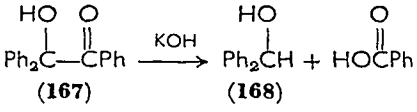
More recently Zimmerman employed both electronic and steric factors in rationalizing the stereochemistry of ketonization[124].

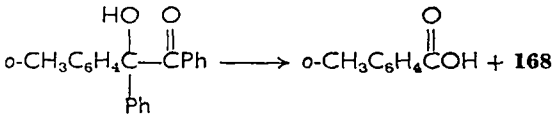
H. The Favorsky and Related Rearrangements

A competing reaction for benzilic acid type rearrangements, nucleophilic substitution on the carbonyl group, is fostered by strongly basic reaction conditions and is another consequence of the electron deficiency of carbon in the carbonyl group. Attachment of a second electron-withdrawing group to this group so enhances its electron deficiency, i.e. increases the electrophilicity of the carbonyl carbon, that S_N2 reactions readily occur there. For example, hydroxide ion causes cleavage of diphenyl triketone (**164**) to benzoic acid (**165**) and phenylglyoxal, which itself then rearranges to mandelic acid (**166**)[111].

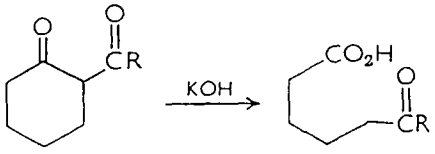


Under vigorous alkaline conditions, α-ketols undergo a similar cleavage (e.g., phenylbenzoin (**167**) to benzyhydrol (**168**) and benzoic acid), and this cleavage may be preceded by rearrangement of the ketol, e.g., *o*-tolybenzoin (**169**) to *o*-toluic acid (**170**) and benzhydrol.





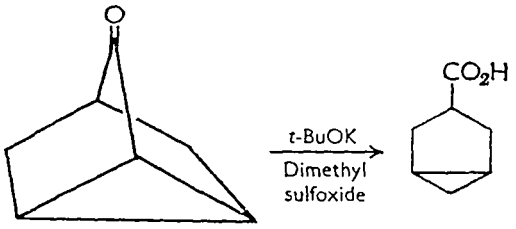
There are many other strictly analogous cases of carbon–carbon bond cleavage by nucleophilic substitution on the carbonyl group, including three such varied reactions as the 'acid hydrolysis' of β-dicarbonyl compounds[125], the haloform reaction[126], and aroyl cyanide alcoholysis[117], illustrated below. Even monofunctional



$$(CH_3)_3CCCH_3 \xrightarrow[NaOH]{Br_2} (CH_3)_3CCO_2H + HCBr_3$$

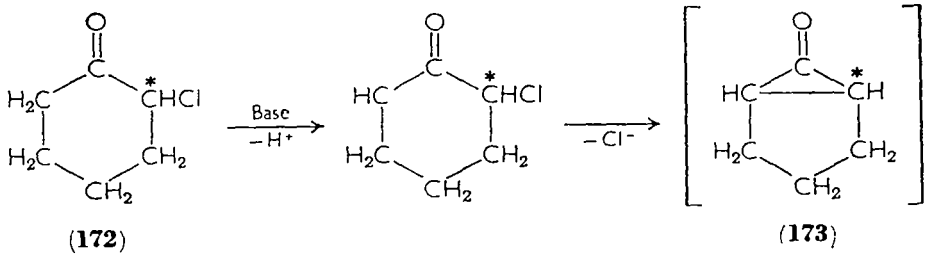
$$p\text{-}CH_3OC_6H_4CCN \xrightarrow{CH_3OH} p\text{-}CH_3OC_6H_4COCH_3 + HCN$$

ketones, if they cannot enolize, can be directly cleaved when treated with a sufficiently powerful base. A recent example is the cleavage of the tricyclic ketone (**171**) with potassium *t*-butoxide in dimethyl sulfoxide[127].

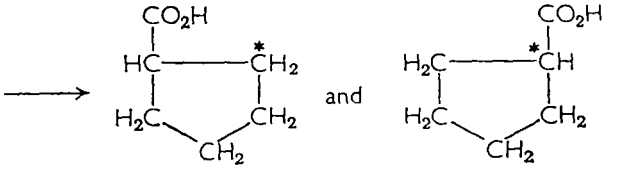


(**171**)

Bond cleavage from the carbonyl group in a cyclopropanone system should be particularly facile. Such electrophilicity of a cyclopropanone system (a consequence of the considerable *s* character of all three ring bonds) makes isolation of the structure itself elusive, but provides a rationale for its intermediacy in the Favorsky rearrangement[128]. Perhaps the best evidence for a cyclopropanone intermediate in the reaction of an α-halo ketone comes from the work of Loftfield with ^{14}C-labeled 2-chlorocyclohexanone (**172**)[129]. Starting

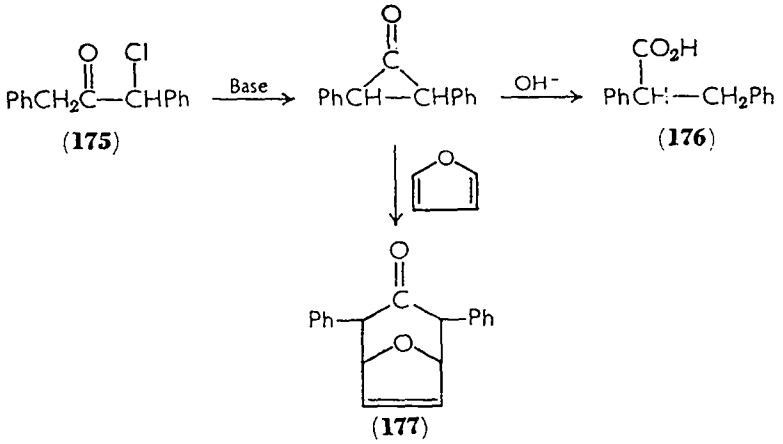


(**172**) (**173**)



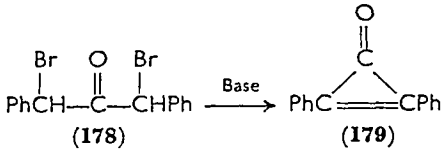
(**174**)

with the ketone specifically labeled at the 2-position, cyclopentanecarboxylic acid (**174**) was obtained in which the label was distributed between the 1- and 2-positions. This finding is consistent with the interpretation that the reaction proceeds by an intramolecular alkylation to give the symmetrical cyclopropanone **173**, which is then cleaved to give the acids. Additional evidence for this type of symmetrical intermediate comes from work with α-chlorodibenzyl ketone (**175**), which under the ordinary Favorsky conditions yields diphenylpropionic acid (**176**). However, Fort recently found that this ketone in the presence of the base and furan yields the Diels–Alder type adduct **177**, i.e. the cyclopropanone intermediate was 'trapped'[130].



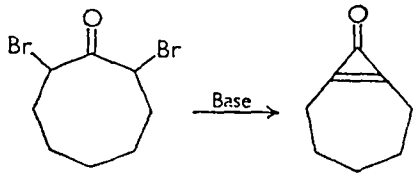
(**175**) (**176**) (**177**)

The α,α-dihalo derivative (**178**) of dibenzyl ketone undergoes dehydrohalogenation to the quite stable cyclopropenone system.



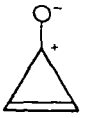
(**178**) (**179**)

Breslow treated **178** with triethylamine in methylene chloride and



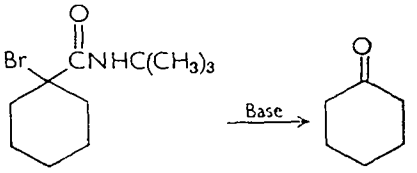
(**180**) (**181**)

obtained diphenylcyclopropenone (**179**) in 50–60% yield. Analogously, 2,8-dibromocyclooctanone (**180**) yielded cyclopheptenocyclopropenone (**181**). The special stability of a cyclopropenone may be rationalized by noting that when this system is written in valence-bond structure **182**, it abides by the aromaticity rule $(4n+2)$ of Hückel in which $n = 0$[131].



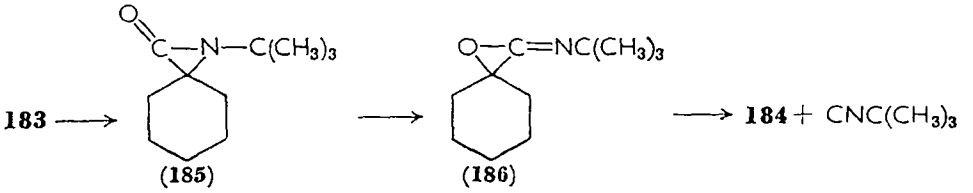
(**182**)

Other workers have adduced additional evidence for the formation of cyclopropanones as intermediates when α-halo ketones are treated with base[132] although there is no general agreement as to the proper set of valence bond structures to use to represent this intermediate[133]. An analogous heterocyclic system, an α-lactam, has been proposed by Baumgarten as a likely intermediate in certain reactions of α-haloamides[133]. In this connection the base-induced conversion of 1-bromo-1-*N*-*t*-butylcarboamidocyclohexane (**183**) into cyclohexanone (**184**) is of interest. Sheehan and Lengyel[134]



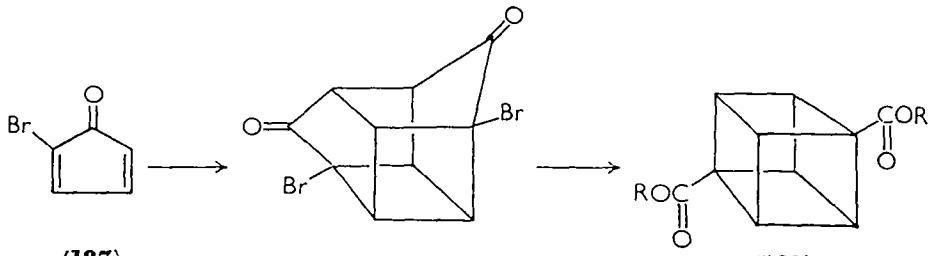
(**183**) (**184**)

propose that this reaction may proceed through the α-lactam **185**, which isomerizes to the epoxide **186**; the epoxide then loses *t*-butyl isocyanide, which was isolated.



(**185**) (**186**)

Synthetic applications of the Favorsky reaction were reviewed in 1960[135]. A recent interesting utilization involves two such rearrangements in the same compound as the final step in a preparation of cubanedicarboxylic acid (**188**). The α,α′-dibromodiketone needed for this preparation, which was effected by Eaton and



(187) (188)

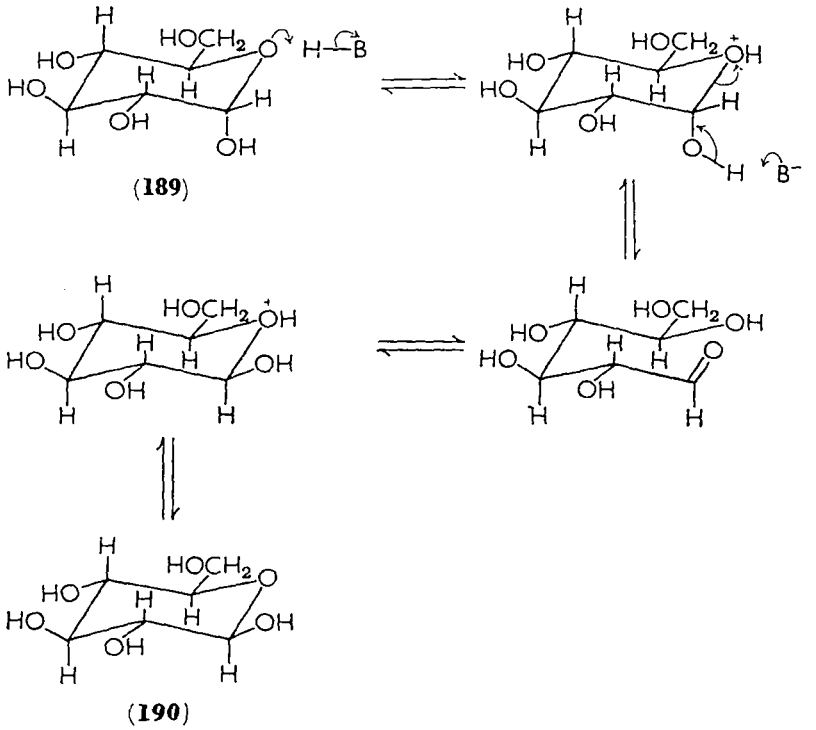
Cole[136], was obtained by dimerization of 2-bromocyclopentadienone (**187**).

I. Ring–Chain Tautomerism

Mechanistic similarities between acid- and base-induced rearrangements involving the carbonyl group have been stressed in this chapter. We have pointed out that the intramolecular 1,2-shift may be either preceded by association with an acid and followed by dissociation involving a base or *vice versa*. While both acid and base are thus involved, their involvement is commonly with hydrogen ion transfers (prototropy). For example, if base initiates a rearrangement by proton abstraction (e.g. the α-ketol rearrangement, **104** → **105**) the conjugate acid of the base is then available to serve in the subsequent step. In protic solvents several acids and bases and their conjugates may be recognized and may give rise to general acid and base catalysis of rearrangements[137]. The necessity of both acid and base for a rearrangement was first demonstrated in what was also the first reaction to be interpreted in the modern school of mechanistic organic chemistry: mutarotation. Indeed, Lowry's interpretation of the influence of both acid and base on the kinetics of mutarotation apparently coincided with Lowry's and Brönsted's postulation of their classical theory of the nature of acids and bases[138].

Mutarotation of sugars is a special type of a relatively large class of rearrangements known as ring–chain tautomerism. Many, but not all, rearrangements in this class involve the carbonyl group and are equilibrium processes. In mutarotation the carbonyl group is involved only as an intermediate; two (or more) ring forms of a sugar are equilibrated by each being reversibly converted to the chain (carbonyl) form. The process is illustrated below for glucose (**189** → **190**), where HB and B represent all available acids and bases, respectively, in the reaction medium. The development of this mechanism was reviewed by Lowry in 1925 in three papers,

which make provocative reading[139]. By that time all of the excellent early kinetic analyses of the reaction by Hudson[140] and others could be correlated with this mechanism, as could the finding by Lowry that the rearrangement would not occur if *both* HB and B were not present. Lowry had found[139] that while mutarotation was negligibly



(**189**)

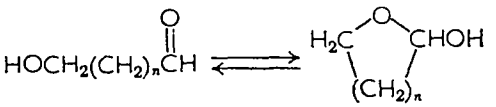
(**190**)

slow in dry cresol (HB) or in dry pyridine (B), it was rapid in a mixture of the solvents; it was also rapid in either solvent containing water, which is amphoteric.

Similarly, using other phenols and amines, Swain and Brown more recently have shown that the kinetics of mutarotation of a glucose derivative in dilute benzene solution are first-order in each species, acid, base and carbohydrate[141]. These workers found that an amphoteric organic structure, 2-hydroxypyridine, was particularly powerful as a catalyst for mutarotation[142]. Using these and other data, Swain[143] postulated a termolecular process involving the sugar, base and acid in one concerted step rather than in the two types of equilibria shown here (**189** → **190**). Swain's 'termolecular process' has not been generally accepted[144].

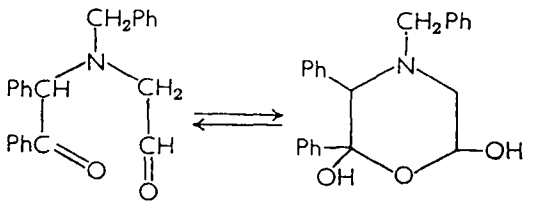
In accord with its historical role, mutarotation was the first organic reaction mechanism to be investigated via the kinetic isotope effect. In 1933 Pacsu[145] showed that mutarotation of glucose in H_2O is faster than in D_2O, where all of the hydroxylic hydrogens exchange essentially instantaneously. This is the normal effect expected for the mechanism shown (**189** → **190**) according to modern interpretations of kinetic isotope effects[146]. Another isotopic study consistent with this mechanism showed that the ^{18}O-exchange rate between water and the 1-position of glucose is much slower than mutarotation[147].

Mechanistic aspects of ring–chain tautomerism involving the carbonyl group other than in sugars have not been nearly so extensively investigated, although a large number of these reactions are recognized. Of course, the simple ω-hydroxy aldehydes (**191**), analogous to sugars, equilibrate with the cyclic form (**192**); the amount of cyclic form at equilibrium decreases with larger rings[148].



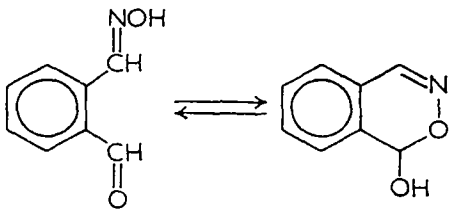
(**191**) (**192**)

Hydroxy ketones also tautomerize (e.g. mutarotation of fructose), and suitable keto aldehydes in the presence of water do the same.



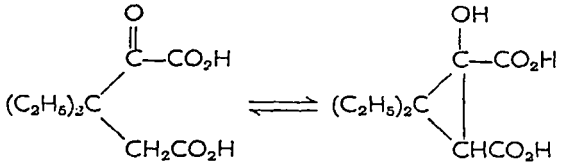
(**193**) (**194**)

Thus the morpholine derivative **194** is formed from compound **193** by hydration[149]. Functions other than simple hydroxyl groups will



(**195**) (**196**)

add reversibly to carbonyl, as in the tautomerism between **195** and **196**, discovered by Griffiths and Ingold[150]. In a suitable system even the carbon–hydrogen bond will tautomerize by carbonyl addition, as illustrated by **197** and **198**[151].

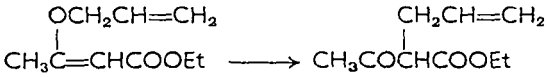


(197) **(198)**

Structural[152] and mechanistic[153] aspects specifically of mutarotation have been reviewed, and so has the generality of ring–chain tautomerism[154].

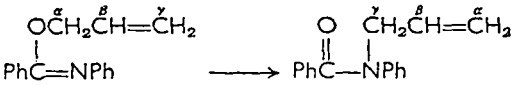
III. THERMAL REARRANGEMENTS

Aldehydes, ketones and amides are produced during many thermal reorganization reactions, and dienones have been identified as intermediates in certain Claisen rearrangements. Two recent reviews[155,156] consider the scope and mechanism of the Claisen and similar thermal rearrangements, the first example of which appears to be transformation of *o*-allylacetoacetic ester (**199**) into 4-carboethoxy-1-hexen-5-one (**200**)[157]. In the same paper[157]



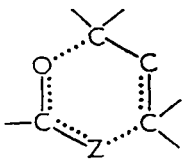
(199) **(200)**

Claisen reported the analogous rearrangement, under similar conditions, of *o*-allylacetylacetone.



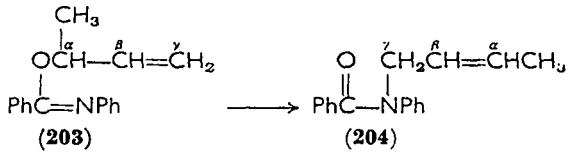
(201) **(202)**

A closely related reaction is the allylic rearrangement[158] of *N*-phenylbenzimidoyl allyl ether (**201**) to *N*-allylbenzanilide (**202**).



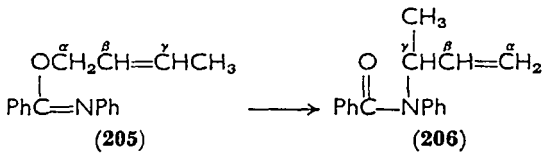
M

Such reactions (**199** → **200** and **201** → **202**) are of a general class which can be thought of as proceeding through bonding electron changes within a cyclic transition state (M). Consistent with the foregoing interpretation are the observations that *N*-phenylbenzimidoyl α-methylallyl ether (**203**) afforded *N*-γ-methylallylbenz-



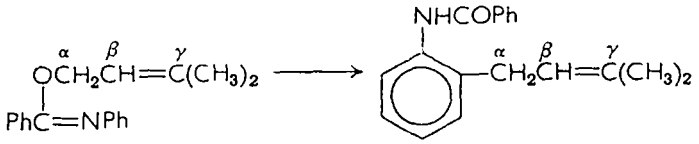
(**203**) (**204**)

anilide (**204**), and the γ-methylallyl analog (**205**) yielded *N*-α-methylallylbenzanilide (**206**)[158].



(**205**) (**206**)

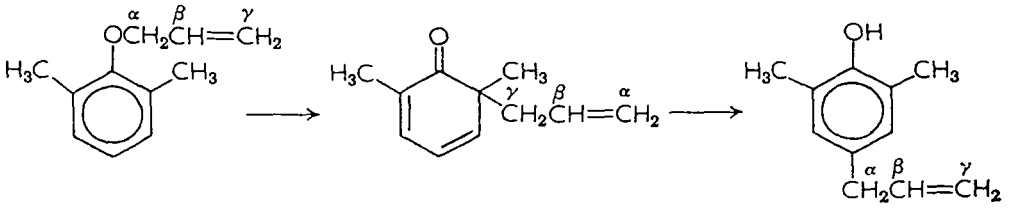
Lauer and Lockwood[159] prepared *N*-phenylbenzimidoyl γ,γ-dimethylallyl ether (**207**) and showed that rearrangement was to the



(**207**) (**208**)

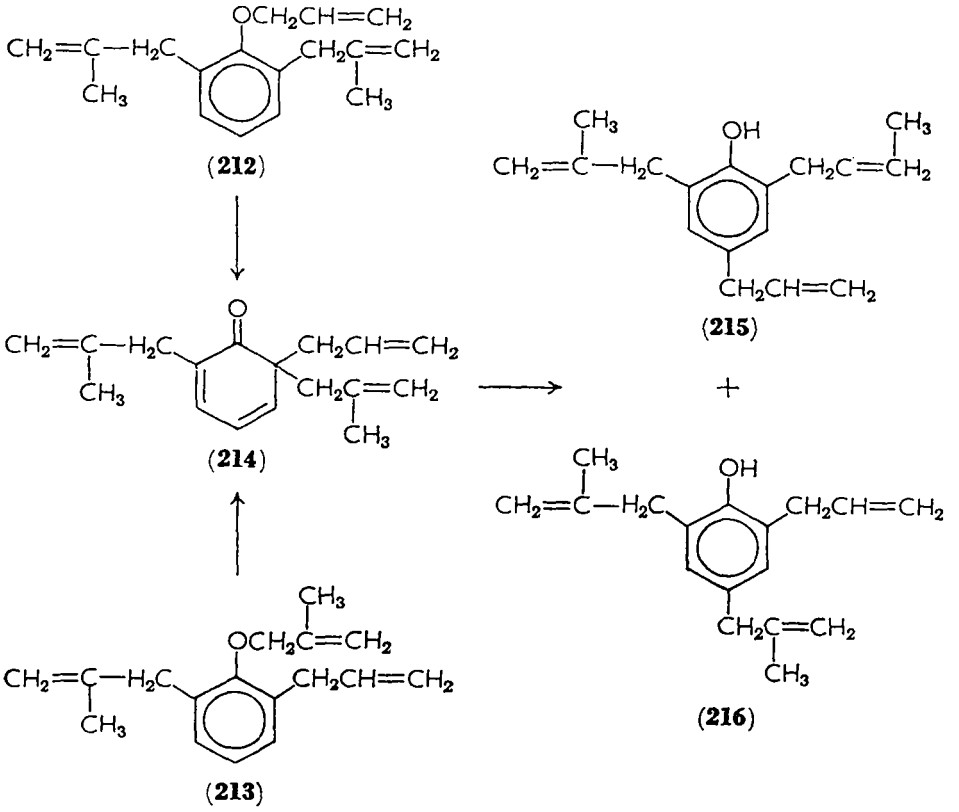
ortho position of the benzanilide ring *without* inversion of the allyl residue, for *o*-benzamide-γ,γ-dimethylallylbenzene (**208**) was produced. This reaction involves two allylic transformations and resembles the *para*-Claisen rearrangement (*vide infra*).

The intermediate formed in the *ortho*-Claisen rearrangement may be thought of as an enolizable dienone, although the question of whether it is a real intermediate or a transition state has not been settled[155,156]. In the *para*-Claisen rearrangement (e.g. **209** → **211**) however, there is no *o*-hydrogen available for enolization of the dienone intermediate (**210**), which should, therefore, be identifiable in the reaction mixture. Conroy and Firestone[160] demonstrated the presence of **210** in the rearrangement of **209** by trapping the intermediate with maleic anhydride to produce a Diels–Alder adduct. Curtin and Johnson[161] demonstrated the presence of the dienone **214** during rearrangement of **212** and **213** by showing that both



(209) (210) (211)

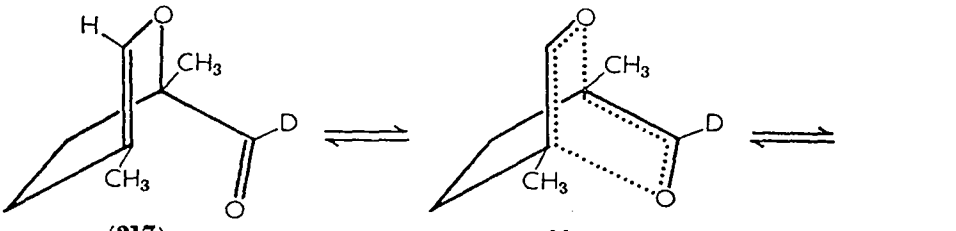
reactants afforded mixtures of the two possible rearrangement products **215** and **216.**



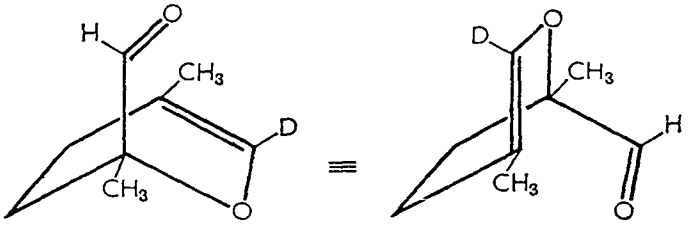
(212) (214) (213) (215) (216)

Lutz and Roberts have observed an isotope position isomerization during the thermal rearrangement of methacrolein dimer[162]. The deuterated isomer of this dimer yielded **218** with maintenance of stereospecificity. The change was explained by postulation of the the transition state N.

Thermal rearrangement of the vinyl ether of 4-cholesten-3β-ol

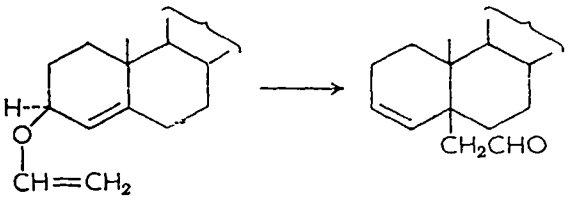


(217) N



(218) (218)

(**219**) leads to Δ^3-5β-cholesterylacetaldehye (**220**)[163,164], whereas



(**219**) (**220**)

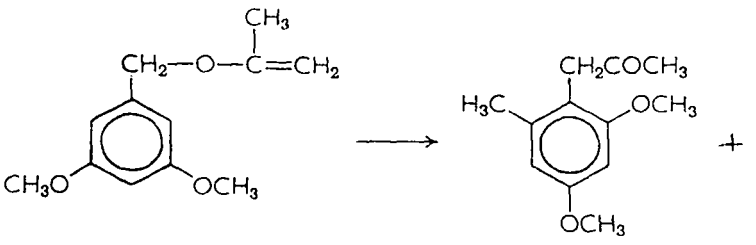
benzyl vinyl ether (**221**) yields β-phenylpropionaldehyde (**222**)[165].

$$\underset{(\mathbf{221})}{PhCH_2OCH{=}CH_2} \longrightarrow \underset{(\mathbf{222})}{PhCH_2CH_2CHO}$$

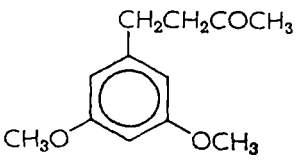
A similar reaction is the thermal conversion[166] of benzyl α-styryl ether (**223**) to β-phenylpropiophenone (**224**). Several examples of

$$\underset{(\mathbf{223})}{PhCH_2{-}O{-}\overset{\overset{Ph}{|}}{C}{=}CH_2} \longrightarrow \underset{(\mathbf{224})}{PhCH_2CH_2COPh}$$

thermal rearrangements of benzyl vinyl ethers are provided by Le Noble and Crean[167], who report that 3,5-dimethoxybenzyl isopropenyl ether (**225**) is converted, upon being heated at 240°c, into a mixture of 80% of 2,4-dimethoxy-6-methylphenylacetone (**226**) and about 10% of 3,5-dimethoxybenzylacetone (**227**). The



(225) (226)



(227)

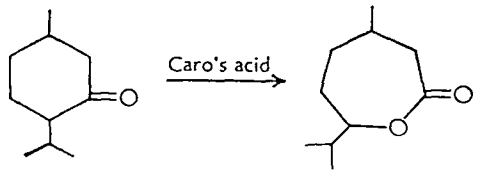
m-methoxybenzyl isopropenyl ether, when similarly treated yielded the two analogous ketones in approximately equal yields.

Thermal reorganization reactions involving ketones are but a small fraction of the overall class which includes the Cope rearrangement[156]. Such rearrangements most probably occur through cyclic transition states (M), and these are much more difficult to identify and study than are ionic or radical intermediates. As a result, the Cope and related rearrangements have not until recently begun to receive the intensive mechanistic study which has been expended on other reactions. The mechanistic aspects of these thermal reorganization reactions have been discussed at some length by Doering and Roth[168] and by Rhoads[156].

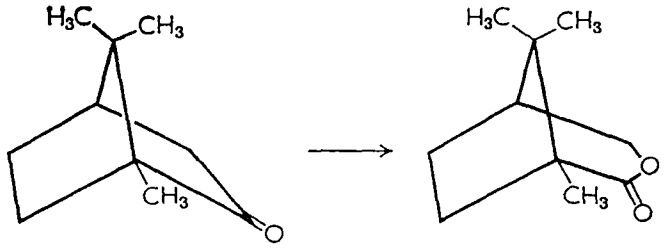
IV. OXIDATIVE REARRANGEMENTS

Many carbon-to-oxygen and carbon-to-carbon rearrangements take place during decomposition of the primary products of reaction of organic compounds with oxygen, with sulfur, with hydrogen peroxide, or with peroxy acids.

One of the best-known and most widely studied of the carbon-to-oxygen rearrangements is the Baeyer–Villiger reaction[169] of ketones with Caro's acid[170]. Menthone (**228**), for example, is converted into the ε-lactone **229**, and camphor (**230**) yields campholide (**231**)[169]. Ruzicka and Stoll[171] extended the series to include 13- to 17-membered monocyclic ketones which yielded 14- to 18-membered lactones upon treatment with Caro's acid. Friess[172], Friess and

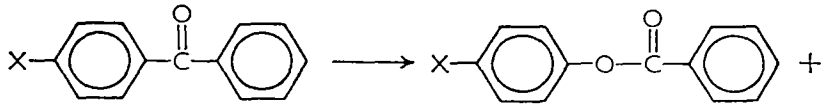


(228) (229)

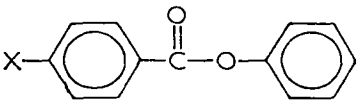


(230) (231)

Farnham[173], and Doering and Speers[174] studied the mechanism of the reaction and noted the migratory aptitudes for rearrangement of several unsymmetrical ketones with peracetic or perbenzoic acids. For example, in a study[174] of the oxidative rearrangements of the unsymmetrical ketones (**232**) (to yield esters **233** and **234**), it was



(232) (233)



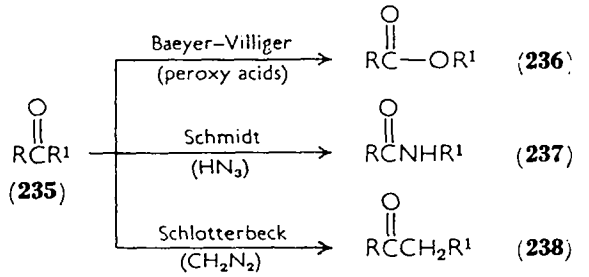
(234)

found that if X = methyl or methoxyl, the *p*-substituted phenyl migrates more readily than the phenyl (that is, more **233** was produced than **234**). The phenyl, however, migrates in preference to *p*-chloro-, *p*-bromo-, *p*-nitro- and the *p*-phenylammonium groups. Cyclohexyl methyl ketone yields cyclohexyl acetate, and acetophenone yields phenyl acetate[172] when similarly treated.

Three mechanisms have been proposed for the Baeyer–Villiger reaction; these are adequately discussed in the paper[174] by Doering and Speers. In a later paper[175] it was shown that when ^{18}O-labeled

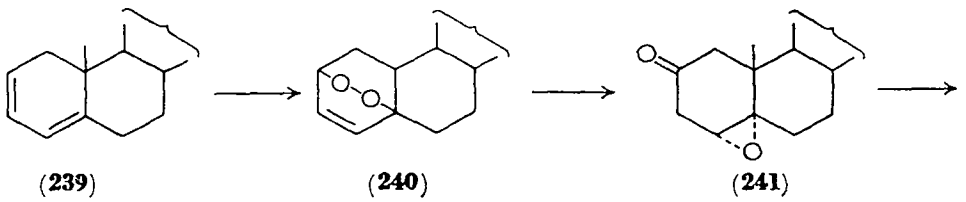
benzophenone is treated with perbenzoic acid, none of the label appears in the ether oxygen of the product (phenyl benzoate), but that all of it is still in the carbonyl oxygen. This result, which demonstrates that the rearrangement is concerted and intramolecular, is consistent with a mechanism proposed originally by Criegee[176].

The Baeyer–Villiger reaction bears a formal similarity to the Schmidt reaction of ketones with hydrazoic acid[177], and to the carbene-insertion reaction which occurs when a ketone is treated with diazomethane[178]. These three reactions are illustrated in the formulae **235** → **236**, **237** or **238**. The Schlotterbeck reaction[178] is use-

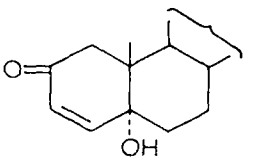


ful in the ring expansion of cyclic ketones, and has been employed in the conversion of camphorquinone into the methyl ether of homocamphorquinone[179].

Dienes often undergo autoxidation or photo-oxidation to yield cyclic peroxides which subsequently rearrange to hydroxy ketones. $\Delta^{2,4}$-Cholestadiene (**239**)[180] on photo-oxidation yields the peroxide (**240**) which upon exposure to sunlight rearranges to the keto oxide (**241**).

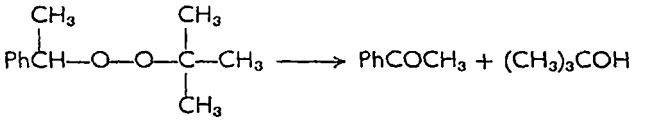


(**239**) (**240**) (**241**)



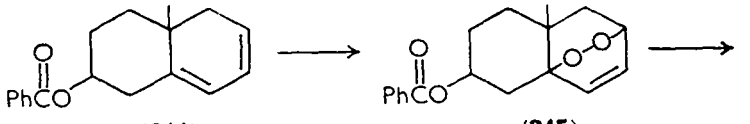
(**242**)

The keto alcohol (**242**) is obtained by heating **241**. The rearrangement of the peroxide (**240** → **242**) is the intramolecular equivalent of the decomposition[181] of α-phenylethyl-*t*-butyl peroxide (**243**) to

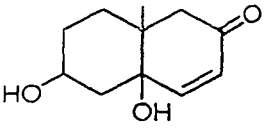


(**243**)

acetophenone and *t*-butyl alcohol. Examples of similar transformations are the rearrangements of the autoxidation products of methanofuran[182], and dehydroergosterol acetate[183], and of the photo-oxide **245** (in methanolic potassium hydroxide) to the keto glycol **246**[184].

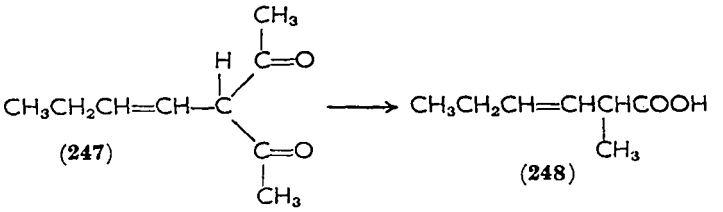


(**244**) (**245**)

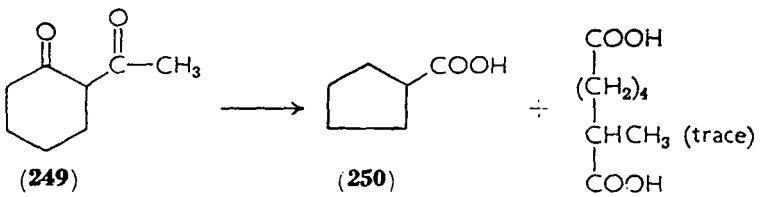


(**246**)

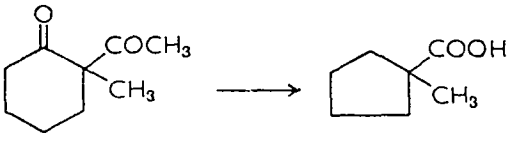
Payne[185] studied the results of the action of slightly acidic hydrogen peroxide on the series of β-diketones **247**, **249**, **251** and **253**.



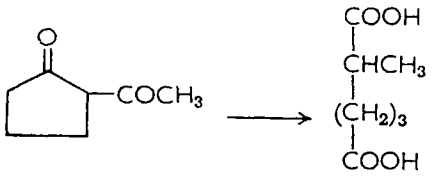
(**247**) (**248**)



(**249**) (**250**)

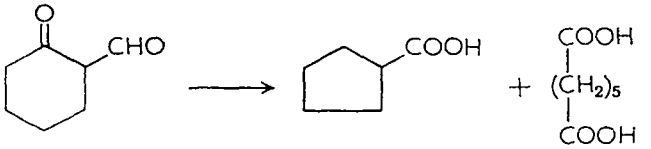


(251) (252)



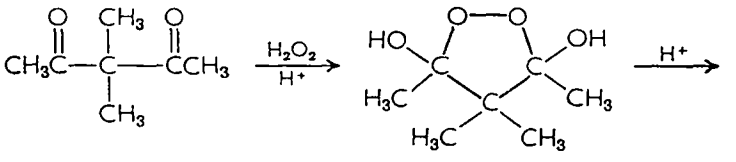
(253) (254)

The yields of the major products were 80–87%. 2-Oxocyclohexanecarbaldehyde (**255**) yielded cyclopentanecarboxylic acid (**250**) plus

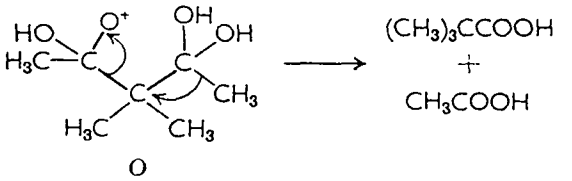


(255) (250) (256)

pimelic acid (**256**) in yields of 26% and 41%, respectively. The β-diketone **257** yields trimethylacetic and acetic acids. Payne[185]



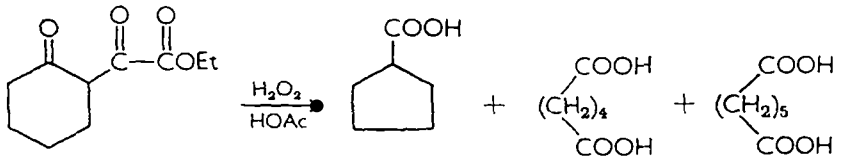
(257) (258)



O

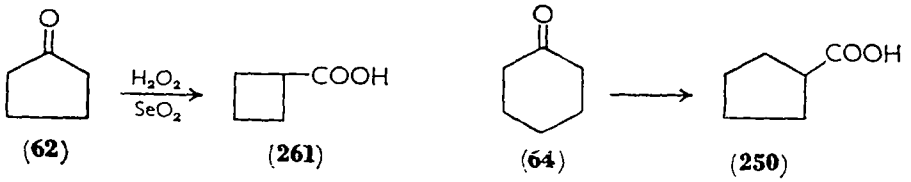
believes the mechanism of this, and similar rearrangements, involves formation of a peroxide bond (e.g., in **258**), bond scission to yield a cation (e.g. O) which then suffers cleavage and alkyl migration. A

similar intermediate has been proposed[186] in the acid-catalyzed oxidation of **259** to cyclopentanecarboxylic acid (**250**) plus adipic (**260**) and pimelic (**256**) acids.

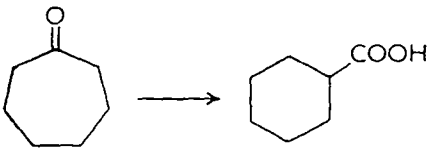


(**259**) (**250**) (**260**) (**256**)

Payne[187] also found that hydrogen peroxide in the presence of selenium dioxide will cause ring contraction of monocyclic ketones to carboxylic acids, e.g. with **62**, **64** and **262**. The yields are 23–34%.

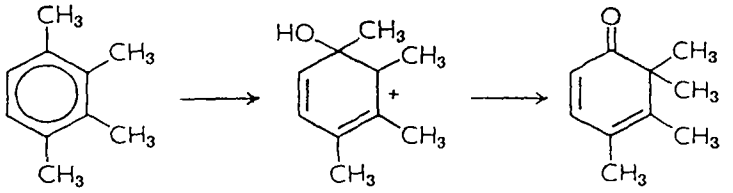


(**62**) (**261**) (**64**) (**250**)

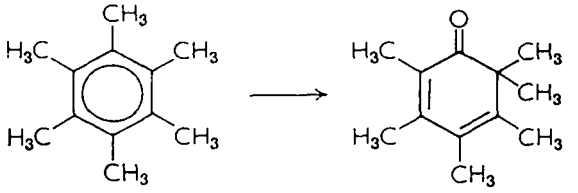


(**262**) (**263**)

When treated with trifluoroperacetic acid and boron trifluoride[188,189] prehnitene (**264**) and hexamethylbenzene (**266**) are oxidized, with accompanying methyl migration, to the dienones **265** and **267**. The mechanism of the reaction is suggested[189] (e.g. for prehnitene) to proceed through attack on the hydrocarbon by OH^+



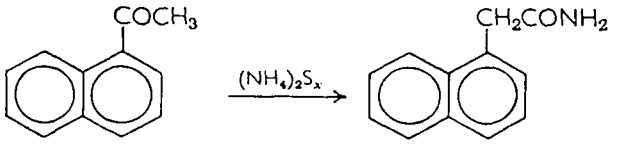
(**264**) I' (**265**)



(**266**) (**267**)

to yield an intermediate P which then suffers methyl migration and loss of a proton to produce the dienone.

In 1887 Willgerodt[190] reported that 1-acetylnapthalene (**268**), upon being heated with ammonium polysulfide in a sealed tube at 210–230° for several days, was converted into 1-naphthylacetamide (**269**)[191]. The reaction was shown to be a general one by extension



(**268**) (**269**)

to such ketones as acetophenone, propiophenone and butyrophenone to produce, respectively, phenylacetamide, β-phenylpropionamide and γ-phenylbutyramide. In some cases the ammonium salt of the corresponding acid was also obtained. It was shown rather early[192] that the carbon skeletons of the alkyl aryl ketones probably did not rearrange since branched alkyl skeletons remained intact during conversion of these ketones to amides. This observation has been adequately substantiated by King and McMellan[193], by Carmack and DeTar[194], and by Shantz and Rittenberg[195]. Subsequently M. Calvin and his coworkers[196], in one of the early tracer experiments with ^{14}C, concluded that in the conversion of aceto-1-^{14}C-phenone into phenylacet-2-^{14}C-amide there was no rearrangement of the carbon atoms of the side chain. They stated, however, that the ammonium salt of phenylacetic acid appeared to be produced through an alternate mechanism in which some rearrangement of the carbon skeleton did occur. This latter conclusion was later shown by Brown, Cerwonka and Anderson[197] to be erroneous. Any mechanistic interpretation must take into account the foregoing observations plus the fact that the Willgerodt reaction involves not only oxidation of the terminal carbon of an alkyl sidechain but also the reduction, probably by hydrogen sulfide, of an

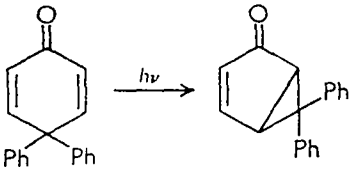
oxo group to a methylene. Two reviews[198,199] consider the scope and mechanism of the Willgerodt and related reactions.

Several important modifications of the Willgerodt reaction have been worked out, the first of which is that of Kindler[200], who carried out the reactions of alkyl aryl ketones with sulfur and amines at high temperatures. Others[201] have employed dioxane and morpholine, respectively, as solvents; use of the latter solvent does away with the necessity of a sealed tube reactor.

V. PHOTOCHEMICAL REARRANGEMENTS

Aldehydes and ketones are particularly susceptible to photo-chemical rearrangement, for the absorption of ultraviolet light (about 2700–3000 Å) by these groups leads to activated states which can undergo several kinds of transformation. In recent reviews[202–204] there are thorough discussions of the present state of knowledge of the triplet- and singlet-state intermediates, energy-transfer agents, and the types of spectral transition believed to be associated with particular transformations. The presentation here is limited, therefore, to an enumeration of several types of photochemical rearrangement which have been observed for compounds containing the aldehyde or ketone groups, with only occasional reference to the mechanistic importance of these rearrangements.

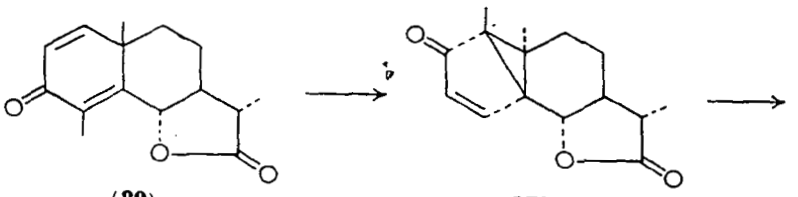
Many ketones are converted photochemically into other ketones whose carbon skeletons have been altered. Although the structures of reactant and product might imply noninvolvement of the carbonyl group, the carbonyl is, in fact, intimately associated with the reaction. A good example is the photochemical rearrangement of 4,4-diphenylcyclohexadienone (**270**) to 6,6-diphenylbicyclo[3.1.0]-



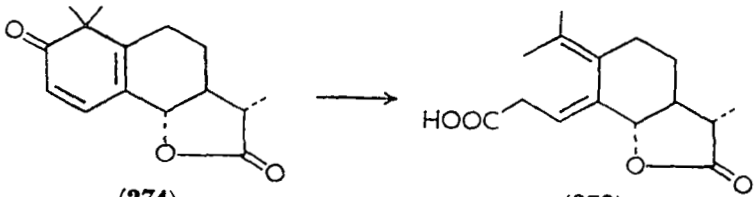
(**270**) (**271**)

hex-3-en-2-one (**271**), which Zimmerman and Swenton[205] have shown to proceed through a triplet state. The mechanism of the

conversion **270** → **271** is important to the photochemical transformation of santonin (**89**) through luminosantonin (**272**) and the intermediate (**274**) to photosantonic acid (**273**)[206-208], as are the

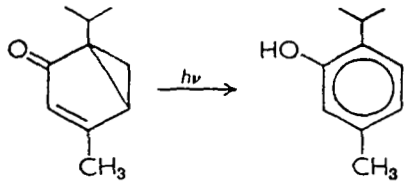


(**89**) (**272**)

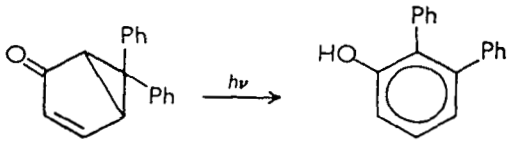


(**274**) (**273**)

related rearrangements **275** → **276** and **277** → **278**. γ-Tropolone methyl ether, colchicine, and other derivatives of cycloheptatrienone, upon irradiation, are converted into bicyclic compounds[202]. α-Tropolone as well as α-tropolone methyl ether (**279**) undergo similar

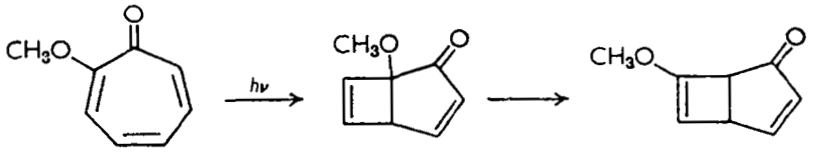


(**275**) (**276**)



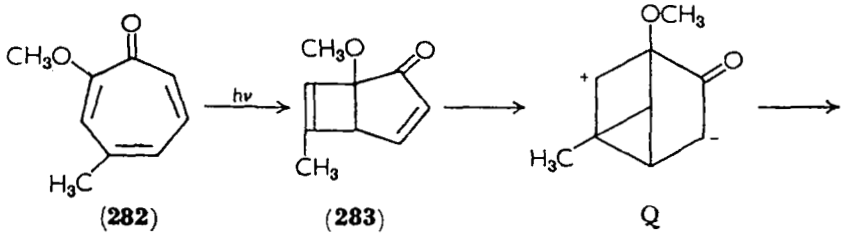
(**277**) (**278**)

cyclization reactions[209], and Dauben and coworkers[210] have shown that the initial product (**280**) undergoes a further photochemical rearrangement to yield the isomeric ether **281**. The latter reaction (**280** → **281**) could be explained either by a shift of the methoxyl

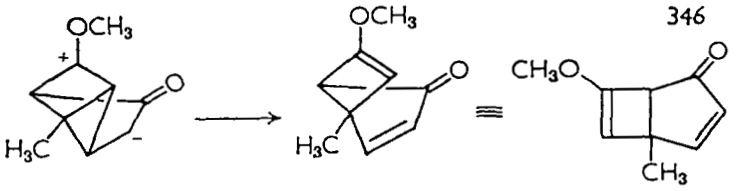


(279) (280) (281)

group, or by rearrangement of the carbon skeleton of **280**. The question was answered in favor of the skeletal rearrangement[210] by a study of the photochemical reaction of the 4-methyltropolone methyl ether (**282**) which yielded **283** and thence, on further



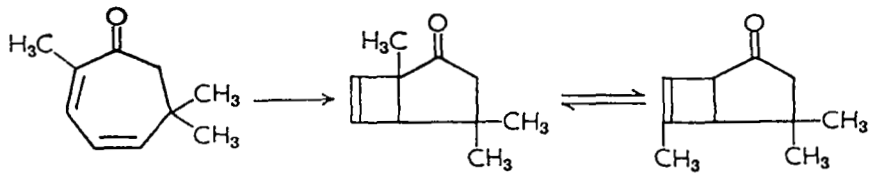
(282) (283) Q



R (284) (285)

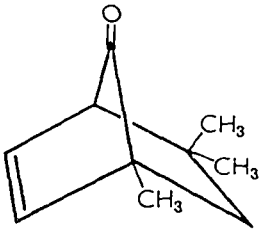
irradiation, the isomeric structure **285** through the postulated intermediates Q and R.

Another example of a ketone-to-ketone conversion is the formation[211] of the equilibrium mixture **287** ⇌ **288** upon irradiation



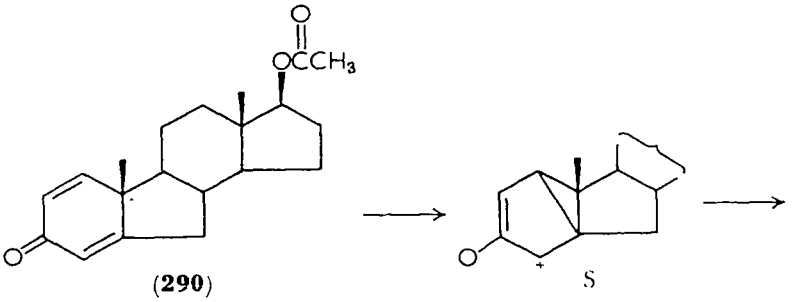
(286) (287) (288)

of eucarvone (**286**) in acetic acid-ethanol. When irradiation is carried out in aqueous acetic acid, 1,5,5-trimethylbicyclo[2.2.1]-7-hepten-7-one (**289**) is also produced[212].

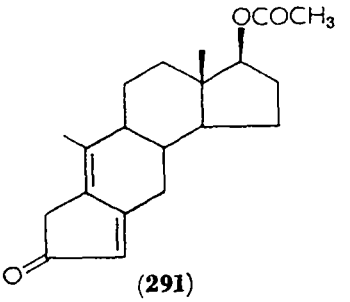


(289)

Recently the irradiation[213] of B-nor-1-dehydrotestosterone acetate (**290**) in dioxane (2537Å) was shown to cause rearrangement of the

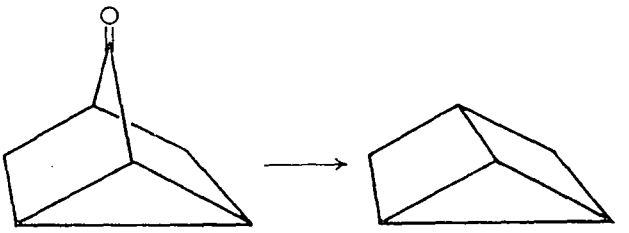


(290) S



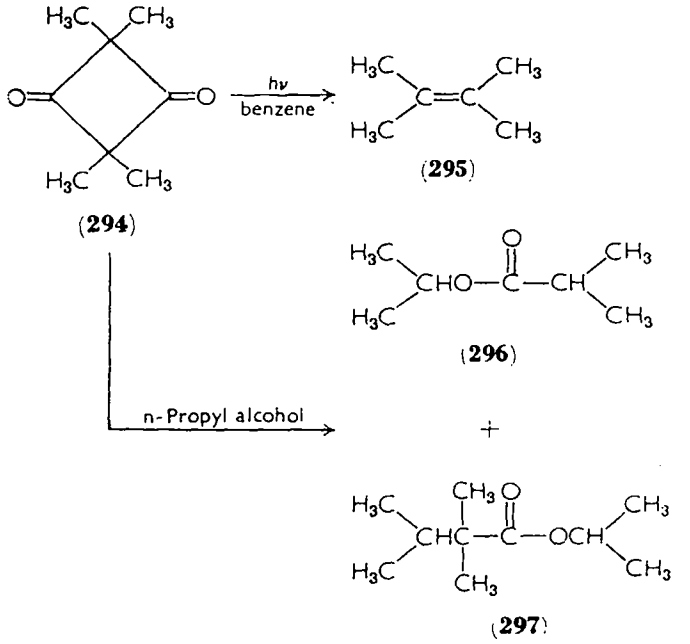
(291)

A and B rings to yield a product which most probably possesses structure **291**. The rearrangement is similar to those previously studied by Zimmerman[205] and others[207-210].



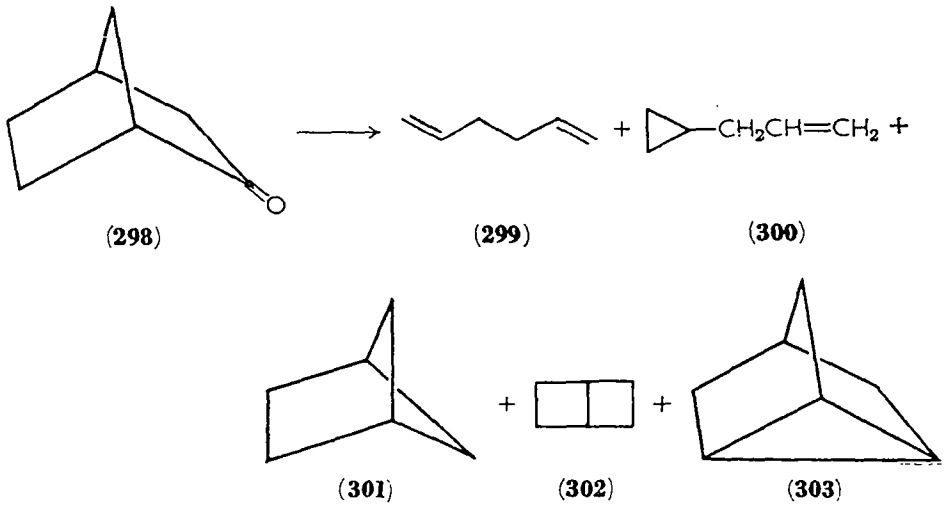
(292) (293)

Decarbonylation with the formation of new carbon–carbon bonds is often a consequence of the photochemical irradiation of ketones. An example is the mercury-sensitized photolysis[214] of nortricyclanone

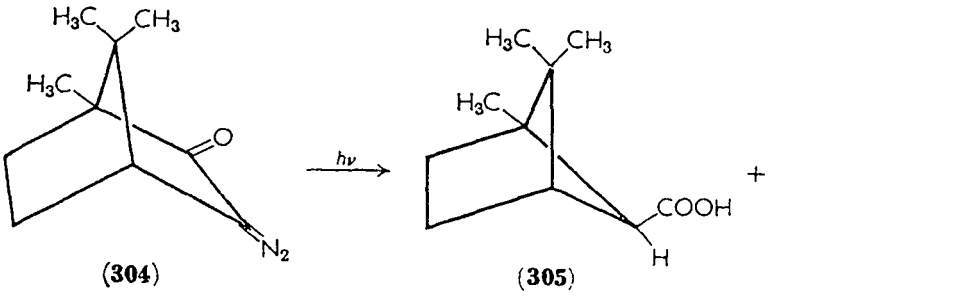


(294) (295) (296) (297)

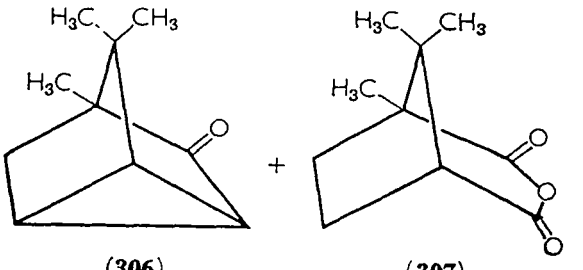
(292) to yield tricyclo[2.2.0.0^{2,6}]hexane (293). Irradiation of symmetrical tetramethylcyclobutanedione (294) yields tetramethylethylene (295)[215] when benzene is the solvent, whereas in n-propyl



(298) (299) (300) (301) (302) (303)



(304) (305)

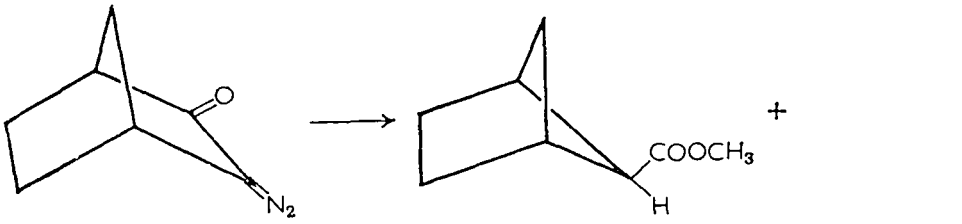


(306) (307)

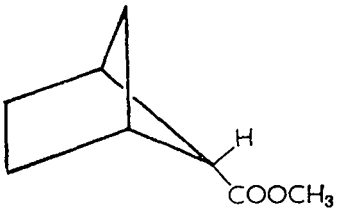
alcohol solution the same compound is converted into the two esters **296** and **297.**

Srinivasan[216] reports that the mercury-photosensitized decomposition of norbornanone (**298**) yields all of the products **299–303.**

The photolysis[217] of diazocamphor (**304**), obtained by the action of base on the tosylate of camphorquinonehydrazone, yields *exo*-1,5,5-trimethylbicyclo[2.1.1]hexane-6-carboxylic acid (**305**). The



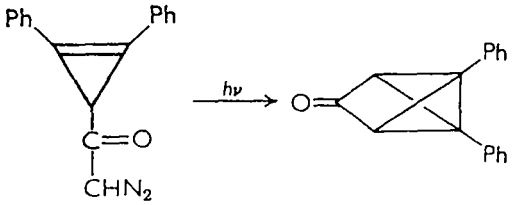
(308) (309)



(310)

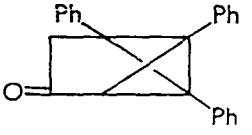
stereochemistry of **305** was proven by Meinwald and coworkers[218], who also identified additional products of the reaction to be the ketone **306** and the anhydride **307.** Photolysis of the analogous diazo ketone **308** in methanol yielded a mixture of the *exo-* (**309**) and *endo*-methylbicyclo[2.1.1]hexane-5-carboxylates (**310**)[219].

Photochemical rearrangement of diazoketones has led to some very interesting, new fused-ring systems. Masamune[220], for example, photolyzed 3-(2-diazoacetyl)- 1,2-diphenyl-1-cyclopropene (**311**) and

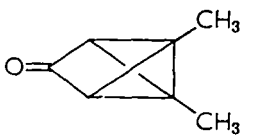


(**311**) (**312**)

obtained the highly strained ketone **312.** The similar compounds **313** and **314** have also been prepared by the action, on analogous diazo-



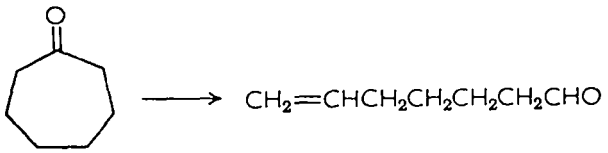
(**313**)



(**314**)

ketones[221,222] of copper-powder catalyst, a reaction which often yields products of similar nature to those obtained photochemically.

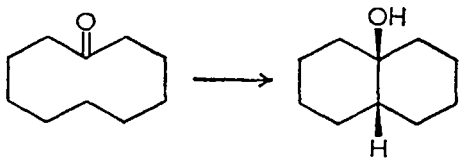
Cyclic aliphatic ketones cleave when photolyzed. The cleavage reaction has been studied by Srinivasan[223,224], who subjected cyclopentanone, cyclohexanone and 2-methylcyclohexanone to vaporphase photolysis. In each case an unsaturated aldehyde was produced, as illustrated by the formation of 6-heptenal (**315**) from



(**262**) (**315**)

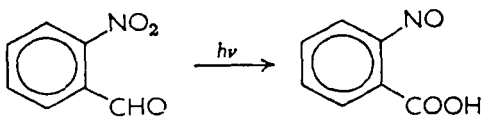
cycloheptanone (**262**). By-products in the reaction were carbon monoxide, propylene and traces of cyclohexane, 1-hexene and

ethylene. Other workers had found that cyclodecanone (**316**), however, undergoes self-condensation to yield *cis*-9-decalol (**317**)[225] in 35% yield.



(**316**) (**317**)

o-Nitrobenzaldehyde (**318**) yields *o*-nitrosobenzoic acid (**319**)



(**318**) (**319**)

when exposed to light[226]. The reaction takes place both in alcoholic solution and in the solid state. This, and other photochemical rearrangements involving transfer of oxygen, have been adequately discussed by de Mayo and Reid[202].

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