# SUBSTITUTION REACTIONS OCCURRING VIA THE ELIMINATION-ADDITION MECHANISM

## PART I. THE REACTIONS OF 1-CHLOROCYCLOPENTENE AND 1-BROMOCYCLOBUTENE WITH PHENYLLITHIUM

## PART II. THE COUPLING REACTION OF PHENYLLITHIUM AND CYCLOPROPYL CHLORIDE AND THE ACTION OF STRONG BASES ON 1-BROMOADAMANTANE

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Finally, I dedicate this thesis to my wife, Mary Anne, who has aided my graduate work in numerous ways.

# ABSTRACT

## PART I

Phenyllithium and 1-chlorocyclopentene couple at 150° to give 1-phenylcyclopentene in 30% yield. The mechanism of this reaction was investigated by reacting phenyllithium and 1-chlorocyclopentene-1-$^{14}$C under similar conditions. Extensive rearrangement of the $^{14}$C label occurred; 1-phenylcyclopentene-x-$^{14}$C was formed with 48.9%, 36.2%, and 14.9% of the $^{14}$C distributed among the 1-, 2-, and 5-positions, respectively. The coupling reaction proceeds by way of the elimination-addition mechanism with the intervention of an intermediate possessing the symmetry properties of cyclopentyne. The 14.9% of 1-phenylcyclopentene-5-$^{14}$C most probably arises from a phenyllithium-induced allylic rearrangement of the double bond of the first-formed 1-phenylcyclopentene-2-$^{14}$C. Alternative substitution mechanisms are discussed.

Piperidine catalyzes the coupling reaction of phenyllithium and 1-chlorocyclopentene. The catalysis is similar in magnitude to that observed for the coupling of phenyllithium and aryl halides.

The reaction of 1-bromocyclobutene and phenyllithium has been studied at temperatures from 42-135°. Phenylacetylene and cyclobutene are formed as reaction products, but no 1-phenylcyclobutene was observed. The mechanism of this unusual phenylacetylene-forming fragmentation reaction has been investigated, and several possible mechanistic courses have been ruled out.

# PART II

Phenyllithium and cyclopropyl chloride couple under mild conditions to give phenylcyclopropane in low yield. The poor nucleophilicity of phenyllithium and the known reluctance of cyclopropyl derivatives to undergo typical unimolecular ($S_N1$) and bimolecular ($S_N2$) nucleophilic substitution reactions make it doubtful that the substitution proceeds by either of these courses. The possibility that substitution occurs via the elimination-addition mechanism was investigated briefly, but experimental difficulties prevented a unique interpretation of the results.

Bridgehead halides are known to be inert to nucleophilic substitution reactions. The possibility that substitution reactions of bridgehead halides might be achieved by way of elimination-addition is very interesting, since this mechanistic route would require the formation of an intermediate in violation of Bredt's rule. 1-Bromoadamantane did not react with potassium amide in liquid ammonia but was converted to adamantane by potassium piperidide in refluxing piperidine.

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# PART I

# THE REACTIONS OF 1-CHLOROCYCLOPENTENE AND 1-BROMOCYCLOBUTENE WITH PHENYLLITHIUM

# INTRODUCTION

In recent years it has been shown that under a variety of conditions non-activated aryl halides undergo nucleophilic substitution via the elimination-addition mechanism involving benzyne-type intermediates (17). This mechanistic course has been established for the amination of aryl halides by alkali amides in liquid ammonia (1), the coupling of aryl halides with phenyllithium (2), and the high-temperature alkaline hydrolysis of aryl halides (3). The successful application of the elimination-addition mechanism to substitution reactions of non-activated aryl halides prompted a study of substitution reactions of non-activated cyclic vinyl halides. Special interest is attached to the possible formation of highly-strained cyclic acetylenic intermediates, like benzyne, which might not be isolable under ordinary conditions. Cyclohexyne has, indeed, been postulated as a reaction intermediate in the coupling reaction of $^{14}C$-labeled 1-chlorocyclohexene with phenyllithium to give $^{14}C$-labeled 1-phenylcyclohexene (4). In studies designed to determine the minimum ring size for operation of the elimination-addition mechanism, the reactions of 1-chlorocyclopentene and 1-bromocyclobutene with phenyllithium have been studied.

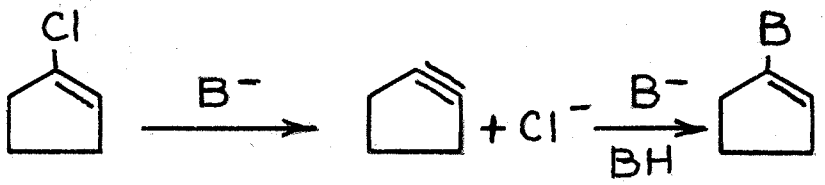
The problem experimentally is first one of ascertaining whether or not substitution can be obtained. Secondly, in the event that

substitution is observed, the problem is one of uniquely establishing the mechanistic course of substitution. This is usually done by considering all possible substitution mechanisms and devising experimental tests to differentiate between them.

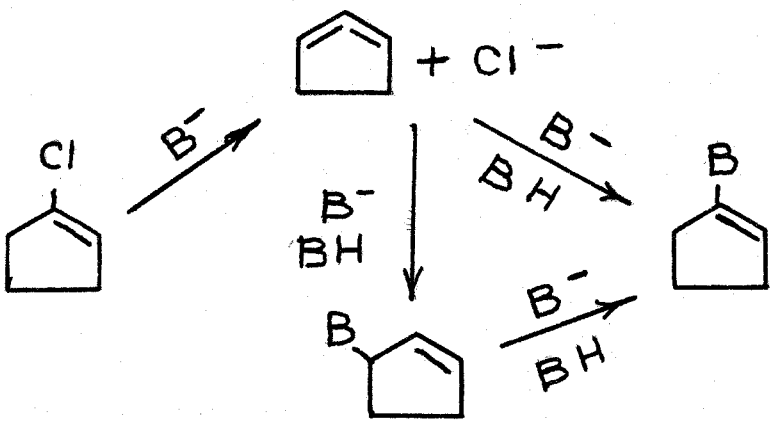
It is of interest theoretically to determine what substitution mechanism is operative as the ring size is decreased. As the size of the ring is made smaller, it is conceivable that the elimination-addition mechanism will become energetically unfavorable relative to other substitution mechanisms. Alternatively, a non-substitution reaction may afford the most favorable path to reaction products. In order to predict the manner in which the substitution mechanism changes as the ring-size is decreased, it is necessary to know what the possible mechanistic courses of substitution are. This information can be gained by examining the limited number of studies dealing with the nucleophilic displacements of vinyl halides (5) and aryl halides (2, 3). Next, it is necessary to know how the various mechanisms change relative to one another as the ring-size is changed. Too little is known of the detailed nature of presently recognized mechanisms, however, to enable such conclusions to be drawn. Known substitution mechanisms will be discussed to provide a background for the interpretation of experimental results. Only the elimination-addition mechanism proceeding by way of acetylenic intermediates will be discussed in detail.

Six general substitution mechanisms have been observed in the

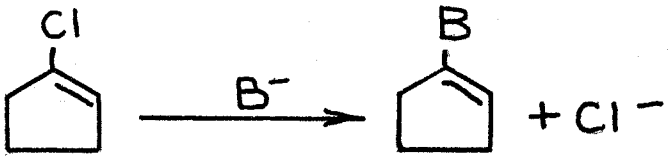
reactions of activated vinyl halides and non-activated aryl halides. It is necessary only to view the long list of incorrect and questionable assignments of substitution mechanisms (5, 6) in these halides to appreciate the importance of considering all known mechanisms. These six general mechanisms [1-6] are depicted as they would occur with 1-chlorocyclopentene. The six substitution mechanisms are: elimination-addition via an acetylenic intermediate [1]:

[1] 

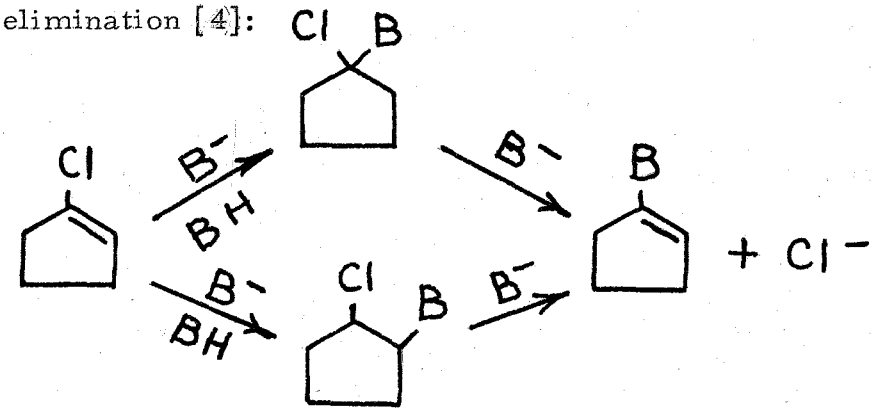

elimination-addition via an allenic intermediate [2]:

[2] 

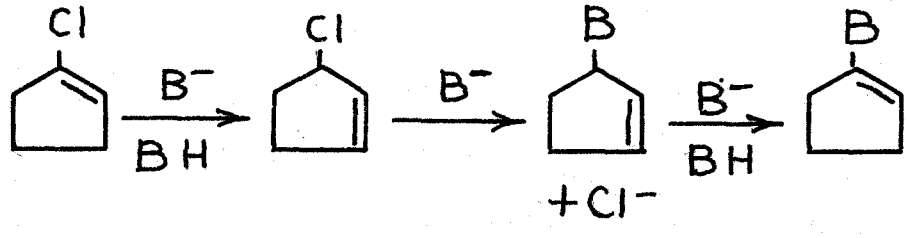

direct displacement [3]:

[3] 

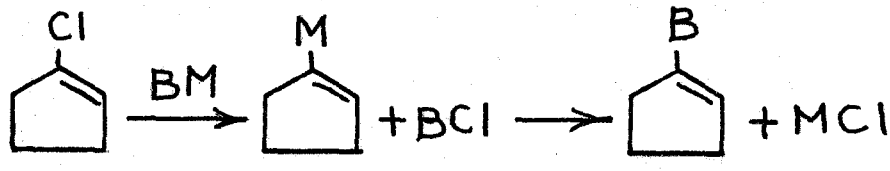
addition-elimination [4]:

[4] 


allylic rearrangement-substitution [5]:

[5] 


metal-halogen interchange followed by coupling [6].

[6] 


The elimination-addition mechanism has been demonstrated for a large number of vinyl halides; among these are the reaction of vinyl chloride and sodium ethoxide (7), the base-catalyzed substitutions of cis-dichloroethylene (8), trans-1-chloro-2-(p-tolylmercapto)-ethene (9), and trichloroethylene (10) with thiols, and the reaction of vinyl

bromide and potassium sulfite (11). Strong bases and high temperatures facilitated all of the reactions.

The alkaline hydrolysis of halotoluenes at 340° proceeds almost exclusively by an elimination-addition mechanism (3b). Lowering the temperature to 250° changes the mechanistic course to direct substitution, and increasing the base concentration increases the elimination to direct substitution ratio (3b). The influence of these variables is reminiscent of their usual role in controlling the elimination to substitution ratio in alkyl halides (12). For both mechanisms the relative ease of substitution is $I > Br > Cl$ (3b).

The reaction rates of base-catalyzed eliminations in haloalkenes have been shown to be a complex function of the base strength, alkene acidity, vinyl anion stability, and stereochemistry (16, 17). Assuming that cycloalkynes of all ring sizes could be formed as reaction intermediates in elimination reactions of 1-halocycloalkenes, it is difficult to assess how large the differences in the rates of formation of the various cycloalkynes would be. Intuitively, ring size should be an important, if not dominant, factor in determining the relative elimination rates. This would be the case, however, only if there were large differences in energy between the various cycloalkyne intermediates, and if the stability of the cycloalkynes is reflected in the elimination transition state. Experimental evidence pertaining to the mechanism of cis-elimination in vinyl and aryl halides defies a single explanation. Phenyl halides react with potassium amide in liquid ammonia in the

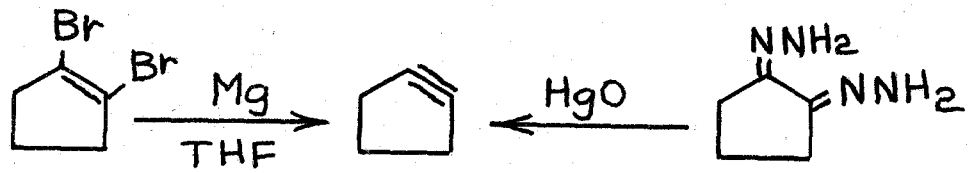
order Br > I > Cl >> F (20) and with phenyllithium and lithium piperidide in the order F > Br > Cl > I (21). In the latter two reactions, it has been argued that removal of the ortho-proton affords the highest energy barrier to products (17, 21). In the elimination reactions of trans-1, 2-dihaloethenes (cis-elimination most likely occurs without inversion (16)) and sodium methoxide, it has been shown that the vinyl carbanions are formed much faster than elimination occurs. It is interesting that the energies of activation for these reactions follow the order I > Br > Cl, but that at a single temperature (60°) the relative rates are I > Br > Cl. From these results, it is not clear to what extent carbon-halogen bond breaking and the energetic nature of the cycloalkyne intermediate would enter into the rate-determining transition state.

The introduction of triple bonds into cyclic systems has occupied the interests of organic chemists for about 65 years. The success, failure, and pertinent observations of these attempts provide valuable information with regard to the limitations of the elimination-addition mechanism. Ruzicka succeeded in 1933 in synthesizing the first cycloalkynes, cyclopentadecyne and cycloheptadecyne, by heating the appropriate 1-bromocycloalkenes with alcoholic potassium hydroxide for fifteen hours (23). Blomquist (24) obtained mixtures of cycloalkynes and cyclic allenes upon treating 1-bromo-2-chlorocyclodecene with sodium in ether (24a) and 1-chlorocyclononene with 50% alcoholic potassium hydroxide (24b) at 330°. He successfully prepared cyclodecyne,

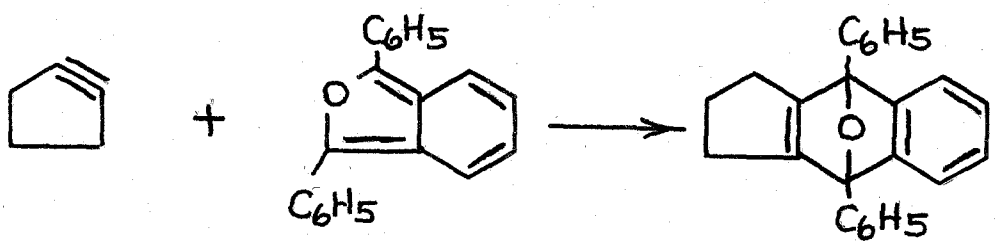
cyclononyne, and cyclooctyne as pure compounds by the alkali-catalyzed oxidative decomposition of 1,2-cycloalkanedione dihydrazones (24). Domnin had tried to synthesize cyclooctyne earlier by treating 1-bromo-1-chlorocyclooctene with sodium in ether and reported a mixture of cyclooctyne, 1,3-cyclooctadiene, and tris-hexamethylenebenzene (25). In 1894 Markownikov reported the synthesis of cycloheptyne (26); this report was later questioned (27). 1-Bromo-2-chlorocycloheptene and sodium in ether affords 1,2-cycloheptadiene, and tris-pentamethylenebenzene (28, 25, 31a).

The careful and original studies of Favorskii in 1912 paved the way for much of the work which has been done on cycloalkynes since then (27). He found that zinc in alcohol, copper, silver, or calcium did not dehalogenate 1,2-dibromocyclohexene. On the other hand, 1,2-dibromocyclohexene and sodium in ether gave dodecahydrotriphenylene (tris-tetramethylenebenzene) and a tetramer, $(C_6H_8)_4$, of undetermined structure. The dodecahydrotriphenylene was carefully characterized by its melting point, carbon-hydrogen analysis, and oxidation to mellitic acid. Favorskii proposed cyclohexyne as an intermediate in the formation of dodecahydrotriphenylene, reasoning that the "free affinities" formed by splitting off bromine atoms with sodium were unable to overcome "cyclic tension" and saturate one another; thus the molecule was unusually reactive and trimerized. Similarly, 1,2-dibromocyclopentene and sodium gave tris-trimethylenebenzene (28). Very recently

Wittig has reported trapping cyclopentyne [7], cyclohexyne (25% yield of adduct), and cycloheptyne (35% yield of adduct), which were generated by the action of magnesium in tetrahydrofuran on the 1,2-dibromocycloalkenes and oxidation of 1,2-cycloalkane dione dihydrazones (29). No evidence was obtained (30) for the formation of cyclohexyne from the




[7]



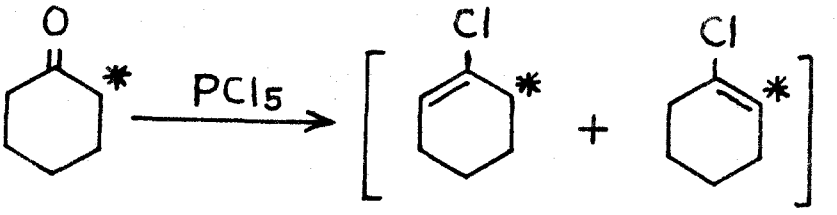

pyrolyses of 1-cyclohexenyl acetate and benzoate at 500°. Domnin reports a number of unsuccessful attempts to prepare methyl-substituted cyclohexynes (31).

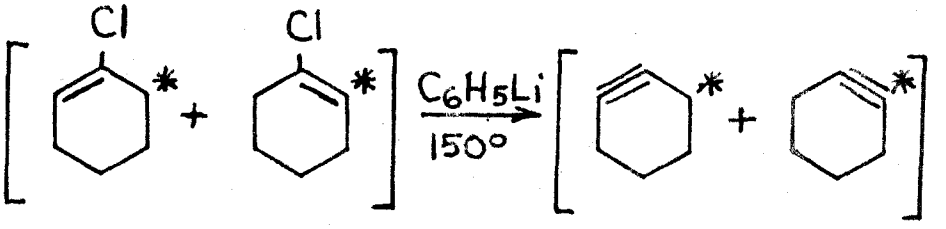
Scardiglia has studied the reaction of 1-chlorocyclohexene with sodium ethoxide in ethanol (32). No reaction was observed at 78° for 48 hr., no more than 29% reaction was observed at 220° for 15 hr., and no 1-chlorocyclohexene was recovered after 1 hr. at 340°. Additionally, it was found that 0%, 10%, and 5% 1-chlorocyclohexene were recovered from the reaction of alkali amides with 1-chlorocyclohexene in liquid ammonia after 2.0, 0.5, and 0.25 hr., respectively (32). Only polymeric products were observed. 1-Chlorocyclohexene did not react with sodium phenylacetylide in liquid ammonia (32). These

experiments amply demonstrate that reaction of 1-chlorocyclohexene with nucleophiles is greatly facilitated by strong bases and elevated temperatures, which are conditions that favor elimination.

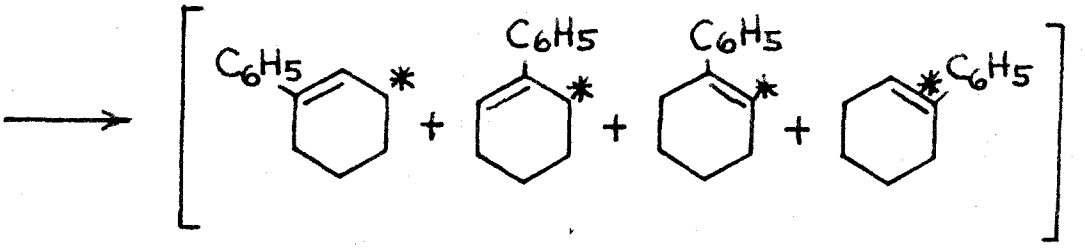
Wittig and Harborth (33) have reported 5% yields of 1-phenylcyclohexene from 1-chlorocyclohexene and phenyllithium at 100°. Since it appeared that this coupling reaction might well proceed via the elimination-addition mechanism involving a cyclohexyne intermediate, Roberts and Scardiglia (4) investigated the reaction of phenyllithium and 1-chlorocyclohexene-2,6-$^{14}C_2$, which had been prepared from cyclohexanone-2-$^{14}C$ and phosphorous pentachloride [8]. If phenyllithium and 1-chlorocyclohexene-2,6-$^{14}C_2$ react by way of a preliminary elimination, equal amounts of cyclohexyne-1-$^{14}C$ and cyclohexyne-3-$^{14}C$ would be formed [9]. Since phenyllithium may add to each of these two isotopic cyclohexynes in two equally probable ways, 1-phenylcyclohexene-x-$^{14}C$ would be expected to be formed with 25% of the $^{14}C$-label distributed in the 1-, 2-, 3-, and 6-positions [9]. A 28% yield of 1-phenylcyclohexene-x-$^{14}C$ was converted to 1-phenyl-2-(2,4-dinitrophenylmercapto)-cyclohexene-x-$^{14}C$ and oxidized to benzoic acid [10]. The benzoic acid possessed (23.0 ± 0.7) % of the total activity of the 1-phenylcyclohexene-x-$^{14}C$ derivative. Thus 23% of 1-phenylcyclohexene labeled at the 1-position was formed in comparison to 25% predicted for the elimination-addition mechanism involving cyclohexyne as an intermediate. The small difference between

[8]

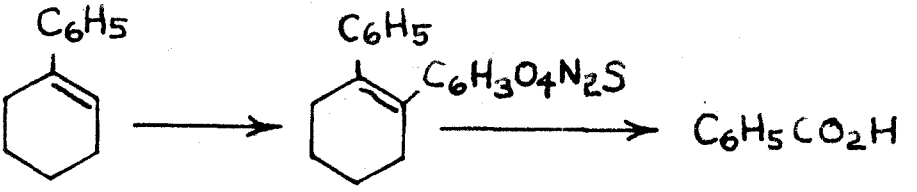



[9]




[10]




where $C_6H_3O_4N_2S$ = 2,4-dinitrophenylmercapto-

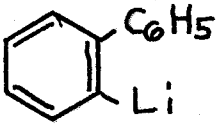
experimental and theoretical results was attributed to competing, non-rearranging reactions or inter- and intra-molecular $^{14}C$-isotope effects in the preparative or degradative sequences.

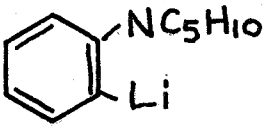
In 1908 Willstätter heated 1-bromocyclobutene with potassium hydroxide at 210°. He obtained a 30% yield of acetylene and suggested that this unusual reaction might proceed by way of cyclobutyne (14). This work has been repeated recently and confirmed (19).

Huisgen has observed a marked catalysis by piperidine in the coupling reactions of phenyllithium and halobenzenes (34), which are known to follow the elimination-addition mechanism (2). Although phenyllithium is the stronger base, lithium piperidide has been shown to be a 30-90 times more efficient agent in forming benzyne. The addition of piperidine presumably catalyzes the coupling reaction in the following manner. Phenyllithium reacts irreversibly with piperidine giving lithium piperidide [11], which subsequently reacts with halo-

[11] $C_6H_5Li + H\,NC_5H_{10} \longrightarrow C_6H_6 + Li\,NC_5H_{10}$

[12] $Li\,NC_5H_{10} + C_6H_5X \longrightarrow C_6H_4 + H\,NC_5H_{10} + LiX$

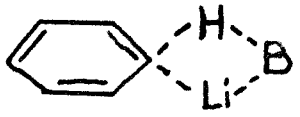
[13] $C_6H_4 + Li\,C_6H_5 \longrightarrow$ 

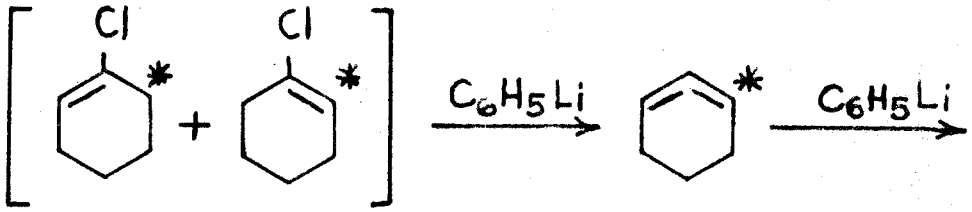

[14] $C_6H_4 + Li\,NC_5H_{10} \longrightarrow$ 

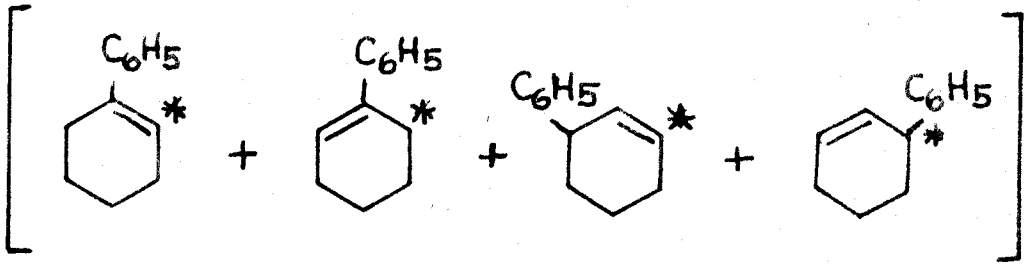

benzene at a rate 30-90 times faster than phenyllithium [12]. The

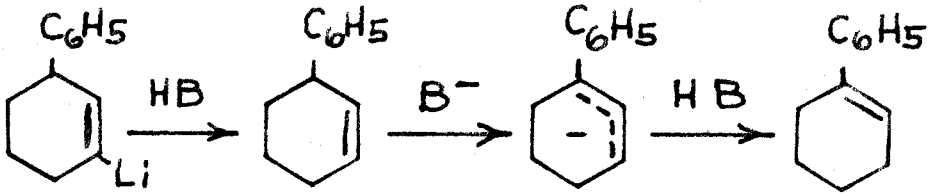
benzyne formed may react with phenyllithium [13] or lithium piperidide [14], while the piperidine which is regenerated reacts with phenyllithium or the products of [13] and [14]. The greater reactivity of the lithium piperidide has been explained by assuming that the first step in the coupling reaction [12] proceeds by an ortho-metalation involving a four-membered cyclic transition state (34) [15]. The unshared pair of electrons on the nitrogen favors the formation of this transition state. It would appear, however, that proton removal would be facilitated by the unshared pair of electrons regardless of whether or not the metalation went through a cyclic transition state. That a similar catalytic effect holds for the coupling reactions of organolithium compounds with vinyl halides is not reported.

Elimination-addition via an allenic intermediate [2] has been suggested as a mechanism of substitution for vinyl halides (5, 35). Mixtures of allenes and acetylenes result in the preparation of acetylenes from vinyl halides (36), but it is not clear that the allenes are formed in the initial elimination step. It may be that an acetylene is the exclusive elimination product and is subsequently isomerized to isomeric allenes and acetylenes. The latter reaction is well known (37). For the reaction of Scardiglia and Roberts (4) between labeled 1-chlorocyclohexene and phenyllithium to have proceeded by this mechanism [16], it would have been necessary for one-half of the phenyllithium to add at the middle and one-half at the ends of the allenic system. Thus the

[15]  LiB = $LiNC_5H_{10}$, $LiC_6H_5$

[16] 



[17] 

addition step cannot be a highly selective process for it would be expected to form the more stable allyl anion in preference to the vinyl

anion (44). Since no 3-phenylcyclohexene-x-$^{14}$C was observed, it was also necessary that the 3-phenyl-isomer (which is formed in the addition step as a vinyl anion) receive a proton and be isomerized to 1-phenylcyclohexene-x-$^{14}$C. The two steps of this isomerization are not without precedent (38, 39). In view of the number of assumptions necessary to rationalize the observed substitution in terms of an allenic intermediate, the elimination-addition mechanism involving a cyclohexyne intermediate seems to be the superior explanation.

The direct displacement mechanism of vinyl halides [3] is analogous to the direct nucleophilic displacements observed in aromatic halides (15, 16). The rates of reaction of a number of varied vinyl halides with iodide ion reveal that direct displacements are extremely difficult (13, 16). Substitution is facilitated in highly fluorinated olefins and in haloalkenes that can stabilize a negative charge on the neighboring vinyl carbon atom. Direct displacement in vinyl halides has been reviewed (16).

The addition-elimination mechanism [4] has been demonstrated for the base-catalyzed reaction of thiols with ethylidene dichloride (9), the reaction of potassium sulfite with ethylidene dichloride (11), the base catalyzed reaction of 1, 2-dichloro-1-(p-tolylmercapto)-ethene with sodium p-toluenethiolate, and numerous reactions of fluoroolefins (40).

The allylic rearrangement-substitution mechanism [5] has been

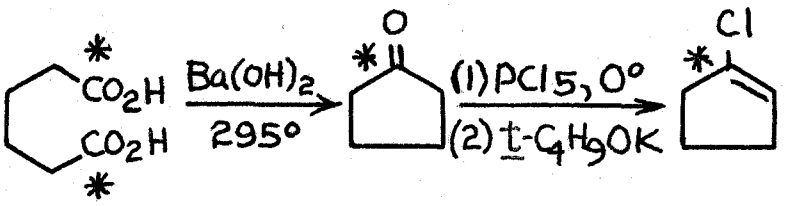
reasonably well established for the reaction of sodium methoxide with 2-bromo-3-methyl-2-butenoic acid (41). This mechanism has been proposed for several other reactions (42).

Substitution via halogen-metal interconversion [6] has been observed with vinyl halides (55) and is well known for other halides (38).

## RESULTS AND DISCUSSION

It has been found that 1-chlorocyclopentene and phenyllithium when heated in a steel bomb at 150° for 1.3 hr. afford a 30% yield of 1-phenylcyclopentene. The mechanism of this coupling reaction was investigated by studying the reaction of 1-chlorocyclopentene-1-$^{14}C$ and phenyllithium. The radioactive chloride was synthesized from adipic-1,6-$^{14}C_2$ acid via cyclopentanone-1-$^{14}C$ [18] and degraded (Fig. 1) to establish that the $^{14}C$ label had not rearranged in the

[18]




synthesis; the chloride had 97.3% of the $^{14}C$ in the 1-position (Table I). The reaction of 1-chlorocyclopentene-1-$^{14}C$ and phenyllithium was carried out under conditions similar to those employed for the coupling reaction with non-labeled chloride. The 1-phenylcyclopentene-x-$^{14}C$ was degraded by the scheme shown in Figure 1 and the $^{14}C$ distribution determined (Table I).

In general, there was excellent experimental agreement among the activities of the various degradation products. The single exception was the lack of agreement between the activities of the benzoic-α-$^{14}C$ acid (VII, (46.8 ± 0.8) %) obtained directly from the oxidation of 1-phenylcyclopentene-x-$^{14}C$ and the benzoic-α-$^{14}C$ acid (VIII, (48.9 ± 0.8)%)

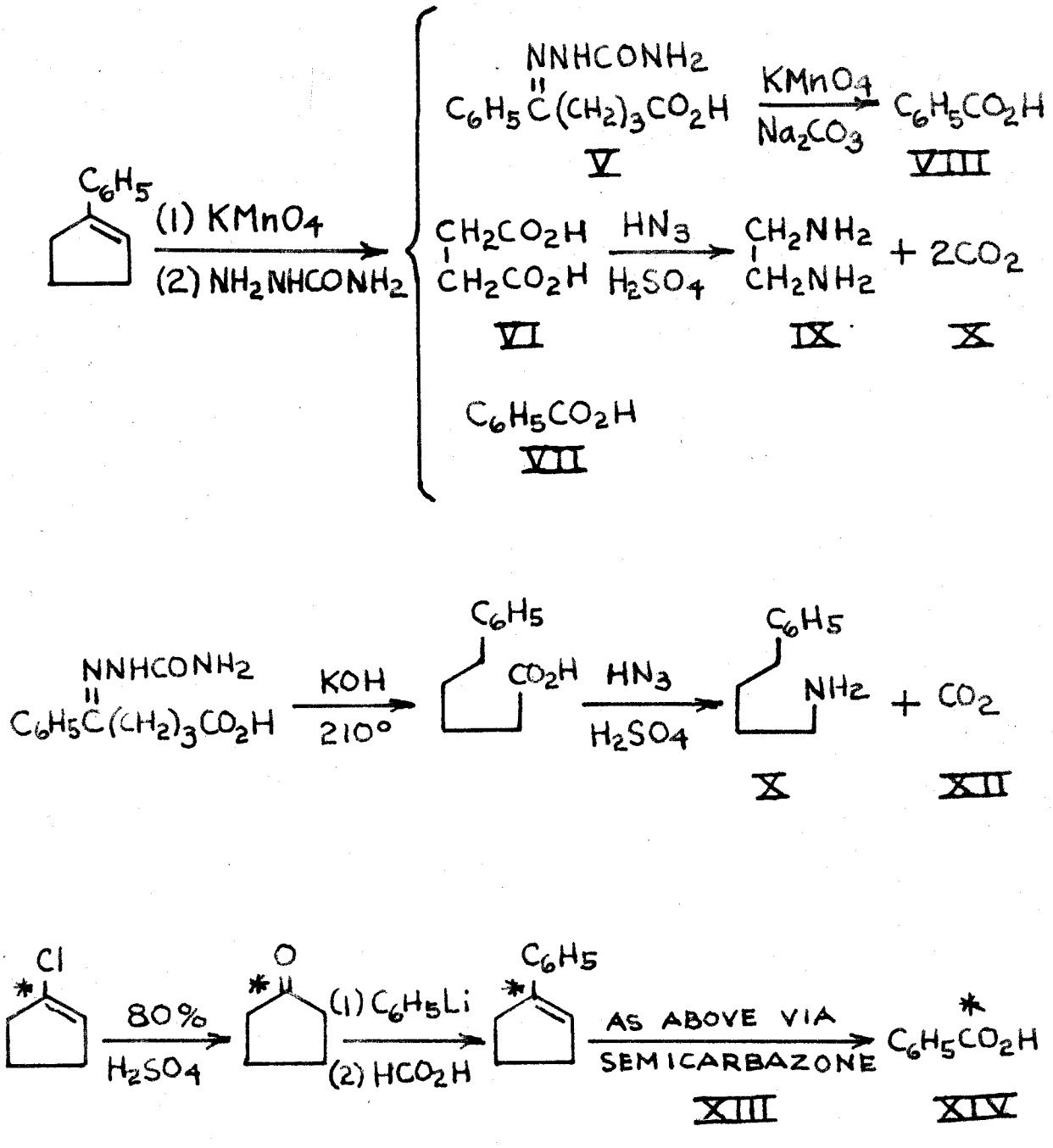



Figure 1.-Degradation schemes for 1-phenylcyclopentene-x-$^{14}$C and 1-chlorocyclopentene-1-$^{14}$C.

Table I

Radioactive Analyses of Degradation Products of 1-Phenylcyclopentene-x-$^{14}$C and 1-Chlorocyclopentene-1-$^{14}$C.

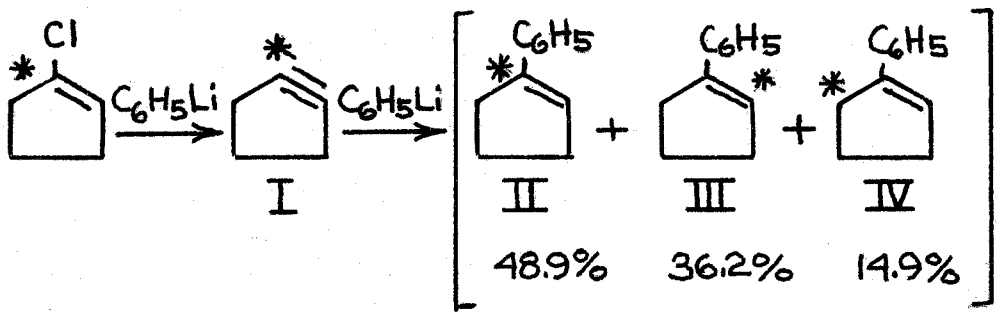
| Compound Analyzed[a] | Measured activity[b,i] | Total activity[c], % |
|---|---|---|
| 1-Phenylcyclopentene-1-$^{14}$C(II) | | 48.9 |
| 5-Phenyl-5-oxopentanoic-x-$^{14}$C Acid semicarbazone (V) | 2.331 ± 0.002 | (100) |
| Benzoic-α-$^{14}$C acid (VIII) | 1.339 ± 0.007 | 48.9 ± 0.8(V) |
| Benzoic-α-$^{14}$C acid (VII) | 1.091 ± 0.007 | 46.8 ± 0.8(V) |
| Succinic-x-$^{14}$C acid (VI) | 1.172 ± 0.005 | 50.3 ± 0.7(V) |
| 1-Phenylcyclopentene-2-$^{14}$C (III) | | 36.2 |
| $CO_2$[f] (XII) | 0.844 ± 0.003 | 36.2 ± 0.5(V) |
| 4-Phenyl-1-aminobutane-x-$^{14}$C[e](XI) | 1.461 ± 0.009 | 62.7 ± 0.8(V) |
| 1-Phenylcyclopentene-5-$^{14}$C (IV) | | 14.9 |
| Succinic-x-$^{14}$C acid[g] (VI) | 0.470 ± 0.002 | (100) |
| $2CO_2$[f] (X) | 0.466 ± 0.003 | 99.2 ± 1.1(VI) |
| 1,2-Diamoethane-x-$^{14}$C[d] (IX) | 0.000 ± 0.001 | 0.0 ± 0.3 (VI) |
| 1-Chlorocyclopentene-1-$^{14}$C[h] | | |
| 5-Phenyl-5-oxopentanoic-x-$^{14}$C acid semicarbazone (XIII) | 1.150 ± 0.004 | (100) |
| Benzoic-α-$^{14}$C acid (XIV) | 1.119 ± 0.004 | 97.3 ± 0.7(XIII) |

[a]Samples converted to carbon dioxide following the oxidation procedure suggested by D. D. Van Slyke and J. Folch, J. Biol. Chem., 136, 509 (1940). [b]Activities in microcuries per millimole (μc/mmole); determined using an ionization chamber and a vibrating-reed electrometer (Applied Physics Corporation, Model 30). [c]Relative to the compound indicated in parenthesis. [d]1,2-Diaminoethane-x-$^{14}$C as dibenzamide. [e]4-Phenyl-1-aminobutane-x-$^{14}$C as benzamide. [f]$CO_2$ as barium carbonate. [g]Succinic-x-$^{14}$C acid (VI), diluted. [h]1-Chlorocyclopentene-1-$^{14}$C, diluted. [i]Error quoted as probable error.

from the oxidation of 5-phenyl-5-oxopentanoic-x-$^{14}$C acid semicarbazone (V). The discrepancy might reasonably arise from two sources. First, the difference is not much greater than the combined probable errors of the two values and may result from the experimental error alone. Alternatively, since the 1-phenylcyclopentene-x-$^{14}$C oxidation was conducted in the presence of 1-2 mole per cent of ethylbenzene and even a larger amount of biphenyl, oxidation of either of these hydrocarbons to benzoic acid would lower the activity of the benzoic-α-$^{14}$C acid (VII).

Clearly, the coupling reaction proceeded with rearrangement, for the $^{14}$C label was distributed in the 1-, 2-, and 5-positions of the 1-phenylcyclopentene-x-$^{14}$C [19]. Coupling via the elimination-addition

[19]

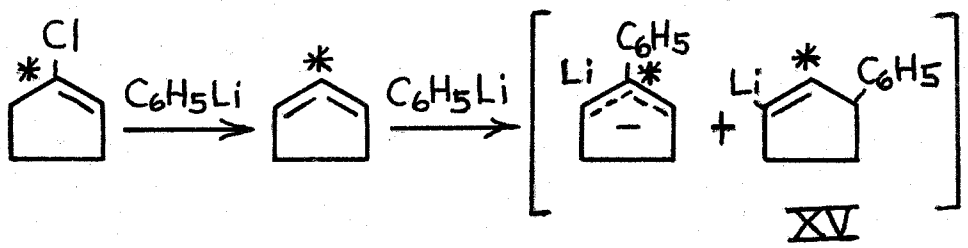



mechanism with the intervention of a cyclopentyne (I) intermediate would afford, in the absence of kinetic isotope effects (18), a 1:1 mixture of 1-phenylcyclopentene-1-$^{14}$C and 1-phenylcyclopentene-2-$^{14}$C. The amount of 1-phenylcyclopentene-1-$^{14}$C (II) observed experimentally (48.9%) is in excellent agreement with the predicted value for elimination-addition. The 14.9% of 1-phenylcyclopentene-5-$^{14}$C (IV) formed most

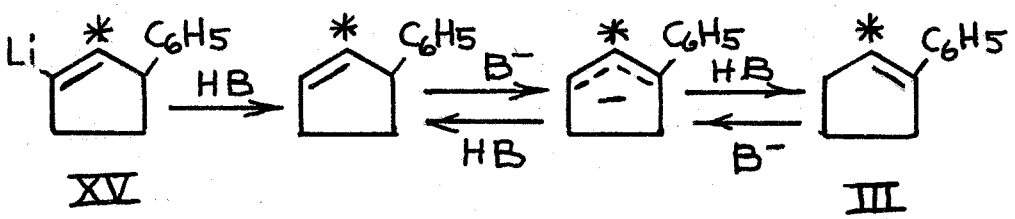
probably arises from a base-induced (phenyllithium or lithium ethoxide that is formed by ether cleavage) allylic rearrangement (39) of the double bond of the first-formed 1-phenylcyclopentene-2-$^{14}$C (III). This being the case, the experimental results are consistent with the substitution taking place via an entity possessing the symmetry properties of cyclopentyne.

The addition-elimination mechanism [4] could conceivably produce the observed $^{14}$C distribution, but this mechanism is rendered unlikely by the following observations. Scardiglia (32) found that 1-chlorocyclohexene reacts with potassium amide, sodium phenylacetylide, sodium ethoxide, and phenyllithium in a manner which suggests that it is the base strength and not the nucleophilicity of the attacking nucleophile which is important in promoting reaction. In the addition-elimination mechanisms which have been carefully studied (5, 9, 11), the reaction occurs without rearrangement.

The elimination-addition mechanism via an allenic intermediate could give the observed $^{14}$C distribution [20], assuming that one-half




[20]



of the phenyllithium adds to the middle and one-half to the ends of the allenic system and that the 1-lithio-3-phenylcyclopentene-2-$^{14}$C (XV) formed rearranges to 1-phenylcyclopentene-2-$^{14}$C (III). Although benzyne-type intermediates are highly reactive, they display a remarkable orientation selectivity toward attacking nucleophiles (17, 43). It would, therefore, be surprising if an allenic intermediate did not add phenyllithium to give a preponderance of the more stable (44) allylic anion. For the experimental results of the coupling reaction of 1-chlorocyclopentene-1-$^{14}$C and phenyllithium to be rationalized in terms of this elimination-addition mechanism, the allenic intermediate must display some measure of selectivity since a statistical addition of phenyllithium was not observed. In view of even this modest selectivity, it appears unreasonable that the phenyllithium should add to both five- and six-membered ring allenic intermediates to give essentially identical (within experimental error) proportions of middle to end addition.

In summary, the trimers of cyclohexyne and cyclopentyne obtained by Favorskii (27, 28) and the adducts of cyclohexyne and cyclopentyne isolated by Wittig (29) suggest that cyclohexyne and cyclopentyne can exist as reaction intermediates. The observed rearrangement in the coupling reaction of 1-chlorocyclohexene-2, 6-$^{14}C_2$ and phenyllithium is consistent with the reaction proceeding by way of a cyclohexyne intermediate; the demonstrated importance of the base strength in the reactions of 1-chlorocyclohexene with various nucleophiles (32) supports an elimination-addition mechanism. Finally, the coupling

reaction between 1-chlorocyclopentene-1-$^{14}$C and phenyllithium follows a course involving an entity possessing the symmetry properties of cyclopentyne. Thus it can be argued convincingly that the nucleophilic substitution reactions at elevated temperatures of 1-chlorocyclohexene and 1-chlorocyclopentene with phenyllithium proceed by way of the elimination-addition mechanism via cycloalkyne intermediates.

It should be noted, however, that the results obtained in these coupling reactions do not demonstrate strictly the intervention of the free hydrocarbons, cyclohexyne and cyclopentyne; they only show that intermediates with the symmetry properties of cyclohexyne and cyclopentyne are involved. Symmetrical intermediates, such as halide and metal complexes of benzyne, have been proposed and discussed for aromatic nucleophilic substitution reactions proceeding by the benzyne mechanism (1a, 17). Such discussions can be reasonably extended to reactions involving cycloalkyne intermediates. Furthermore, cyclohexyne and cyclopentyne have been written in this thesis as the classical cycloalkyne structures. This has been done for convenience and does not imply knowledge of the electronic structure for these entities.

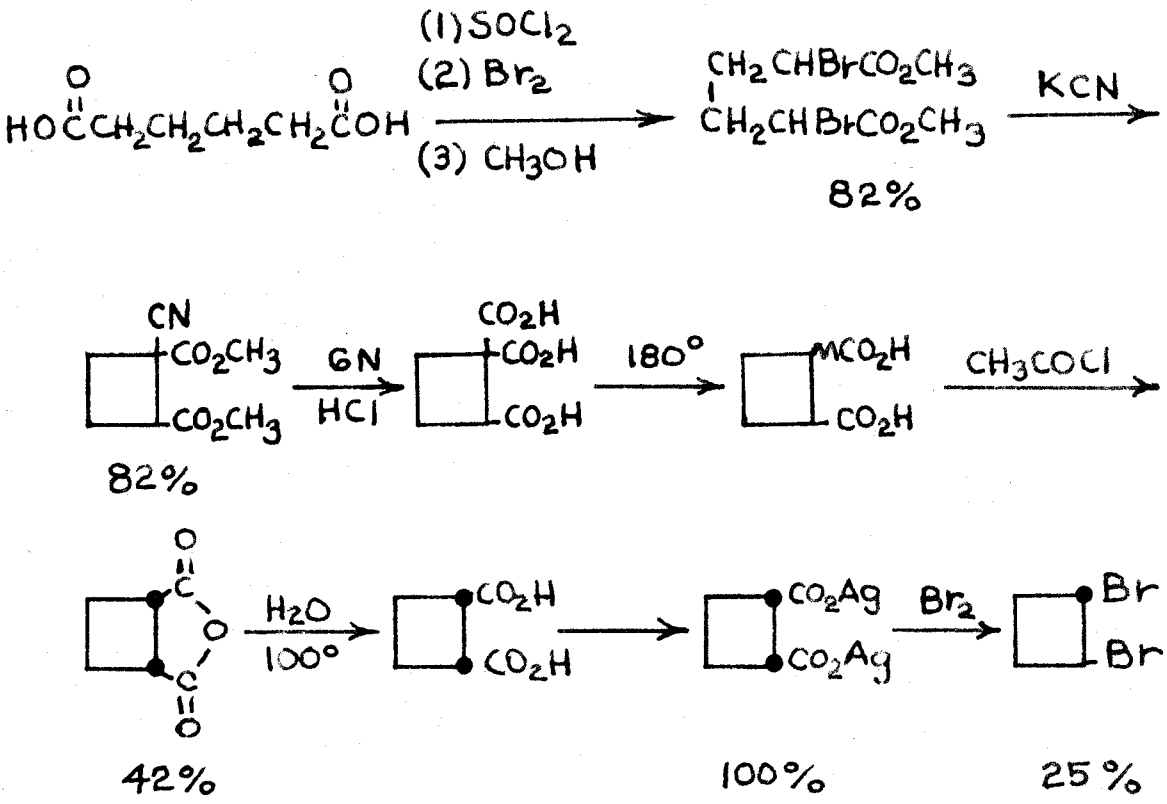
A (20 $\pm$ 5)% yield of 1-phenylcyclopentene was obtained by heating 1-chlorocyclopentene and phenyllithium in the presence of piperidine at 36° for 24 hr. Since this seemed to be an unusually large amount of coupling under such mild conditions, the reaction was examined to see if piperidine exerts a catalytic effect similar to that observed in coupling

of phenyllithium with aryl halides (34). Two identical solutions of phenyllithium and 1-chlorocyclopentene were prepared; piperidine was added to one of the solutions, and both solutions were thermostated at 27° for 24 hr. The reaction mixtures were analyzed by v-p-c. 1-Phenylcyclopentene was formed in (9.7 ± 0.3)% yield from the reaction in the presence of piperidine and in (1.86 ± 0.06)% yield from phenyllithium and 1-chlorocyclopentene alone. The catalytic effect is roughly the same as that observed with phenyllithium and halobenzenes (34).

Trans-1,2-dibromocyclobutane was synthesized by general procedures previously reported in the literature (45,46,129) (Fig. 2, Method A). Several of the steps were modified to give improved yields. Using a modified isolation procedure, average yields of 82% were obtained in the Fuson ring-closure (46) of dimethyl 2,5-dibromoadipate to dimethyl 1-cyano-1,2-cyclobutanedicarboxylate. Additionally, it was found that prolonged heating of dimethyl 1-cyano-1,2-cyclobutanedicarboxylate with 6N hydrochloric acid gave near theoretical yields of a mixture of cis- and trans-1,2-cyclobutanedicarboxylic acids (Fig. 2, Method B). The disilver salts obtained from this mixture of acids gave comparable yields of trans-1,2-dibromocyclobutane to those obtained from disilver cis-1,2-cyclobutanedicarboxylate.

1-Bromocyclobutene was prepared by Willstätter in 1905 (14) by heating trans-1,2-dibromocyclobutane with pulverized potassium hydroxide. It was found, however, that 1-bromocyclobutene could be

METHOD A.




METHOD B.

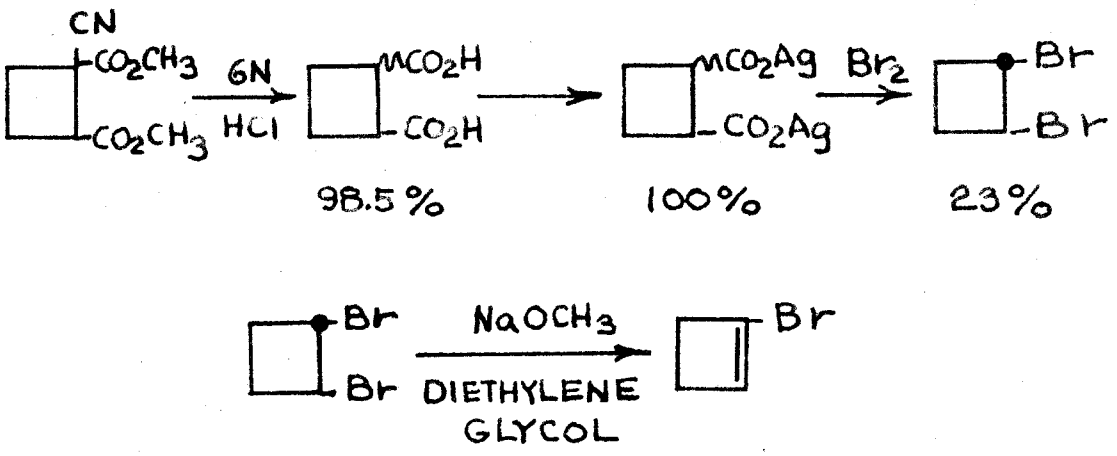



Figure 2.-Synthesis of 1-bromocyclobutene.

prepared in higher purity by using sodium methoxide in diethylene glycol as the dehydrohalogenating agent. 1-Bromocyclobutene was formed in 46-56% yields, and 10-11% of the trans-1,2-dibromocyclobutane was recovered. In these preparations, 107-114% of the theoretical bromide ion (based on 1-bromocyclobutene as the stoichiometric product) was liberated. Changing the reaction time from 5 to 12 hr. did not alter significantly the yields of 1-bromocyclobutene, recovered starting material, or liberated halide ion. These observations suggest that 1-bromocyclobutene is reasonably stable to the reaction conditions and that about 30% of the trans-1,2-dibromocyclobutane liberates two moles of bromide ion. Perhaps 3-bromocyclobutene is formed in addition to the vinyl isomer; being an allylic bromide, it would be expected to react further with base. Attempts to detect solvolysis products of 3-bromocyclobutene in the water-soluble reaction products were unsuccessful.

The reaction of 1-bromocyclobutene and phenyllithium at temperatures from 42° to 135° has been studied. The products included ethylene, cyclobutene, phenylacetylene, ethylbenzene, and biphenyl. The desired coupling product, 1-phenylcyclobutene, was not detected in any of the reactions. Although these experiments were designed primarily to detect the presence of 1-phenylcyclobutene, useful information was obtained concerning some of the observed reaction products. This information is summarized in Table II.

Table II

Summary of Reactions of 1-Bromocyclobutene and Phenyllithium

| Reaction Conditions | | | | | Reaction Products[d] | | | |
|---|---|---|---|---|---|---|---|---|
| Temp., °C | Reacn. time, hr. | $C_4H_5Br$, mole | $C_4H_5Br$ conc., m./l. | $C_6H_5Li/C_4H_5Br$[a] | Yield $C_8H_6$,[b] % | $C_8H_6/C_8H_{10}$[c] | Bromide ion lib., % | Base consumd.,[f] % |
| 135±5 | 2.25 | 0.133 | 0.355 | 3.0 | 15±3 | 2.6 | 92 | 106 |
| 100.0±0.5 | 2.4 | 0.00342 | 0.13 | 5.0 | 25±11 | 7.5 | 120 | 102 |
| 75±1 | 5.0 | 0.00376 | 0.19 | 7.0 | 27±10 | 8.0 | 80 | --- |
| 42±2 | 2.75 | 0.00404 | 0.16 | 5.5 | -±-[e] | 11.2 | 60 | --- |

[a]Molar ratio of phenyllithium to 1-bromocyclobutene. [b]Phenylacetylene. [c]Ratio of the v-p-c peak areas of phenylacetylene to ethylbenzene. [d]Methods of analysis described in the Experimental section. [e]Phenylacetylene was detected but the yield was not determined. [f]Based on 1-bromocyclobutene.

Several general features of the table deserve comment. Roughly one mole of base was consumed for each mole of bromide ion that was liberated. The amount of bromide ion formed at a particular temperature is of limited value in interpreting the results of Table II, since halide ion may be formed by a number of different processes. For example, 60% reaction was observed even at 42°; metal-halogen interchange followed by coupling of bromobenzene and phenyllithium may be the major source of bromide ion at this temperature. At higher temperatures 1-bromocyclobutene and phenyllithium may react predominantly by another mechanism.

Next, phenylacetylene was formed at all temperatures. The amount of phenylacetylene in the reaction products did not decrease as the temperature was lowered from 135° to 75°.

Finally, there was a significant increase in the ratio of phenylacetylene to ethylbenzene as the temperature was decreased. This was apparently due to the formation of less ethylbenzene.

The reaction of 1-bromocyclobutene and phenyllithium at 135° was studied in the greatest detail. The products included ethylene, cyclobutene ($\geqslant 7\%$), phenylacetylene (15%), ethylbenzene, biphenyl, and a large quantity of a dark-brown, non-distillable residue. 1-Phenylcyclobutene was not detected in the reaction products.

Both the ethylene and the ethylbenzene may be trivial products resulting from the reaction of phenyllithium with the solvent. It is well

known that organolithium compounds react with ether to give ethylene and lithium ethoxide (47) among other products, especially at high temperatures. Ethylbenzene is probably formed by the addition of phenyllithium to ethylene (48, 49) or by an α-metalation (very likely an α-elimination) mechanism (49) involving the ether. In this connection, phenyllithium solution was heated at 100° for 2.6 hr.; ethylbenzene was isolated in about 4% yield. No phenylacetylene was observed (v-p-c analysis).

Cyclobutene was undoubtedly formed by way of halogen-metal interconversion [21a], for this reaction is known to proceed with other bromides even at low temperatures (38). The cyclobutene was detected in the ether removed from the reaction mixture, and a 7.1% yield of cyclobutene was isolated as trans-1,2-dibromocyclobutane. It is probable that a greater amount of cyclobutene was formed.

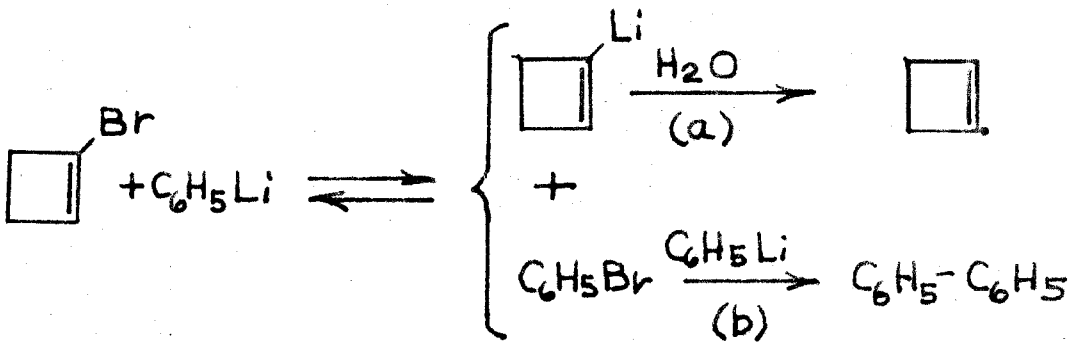
The observed biphenyl may be accounted for in a number of ways. Biphenyl is formed when phenyllithium is prepared. It also arises from the reaction of phenyllithium and the bromobenzene which is formed by halogen-metal interconversion [21b].

That phenylacetylene was isolated in the reaction was quite unexpected. Since phenylacetylene is not formed by heating phenyllithium solutions in the absence of 1-bromocyclobutene, the two acetylenic carbon atoms reasonably originate from the vinyl halide. An appealing path to phenylacetylene would be by way of 1-phenylcyclobutene. Direct thermal decomposition of 1-phenylcyclobutene to phenylacetylene and

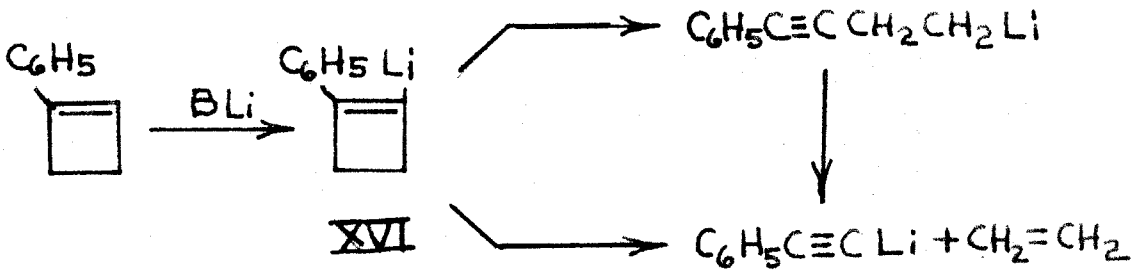
ethylene would hardly be expected at this reaction temperature (119). Thermal decomposition was ruled out by synthesizing 1-phenylcyclobutene and showing that it does not give phenylacetylene when heated to 100-130°. A base-catalyzed fragmentation of 1-phenylcyclobutene [22] is not unreasonable. In fact, a somewhat similar base-catalyzed ring-opening and fragmentation has been reported for 2-phenyltetrahydrofuran (52) [23]. Related fragmentation reactions in acyclic systems are common and have been reviewed (53). 1-Phenylcyclobutene and phenyllithium solution were heated at 75° and 53°, but no phenylacetylene was formed. 1-Phenylcyclobutene was recovered in good yield from the solution heated at 53° for 19 hr. Although this precludes the intervention of 1-phenylcyclobutene in the formation of phenylacetylene, it does not rule out the intermediacy of 2-lithio-1-phenylcyclobutene ([22], XVI), that could reasonably be formed by a route not involving 1-phenylcyclobutene. The greater acidity (44) of the allylic protons in 1-phenylcyclobutene may prevent the formation of the 1-lithio-2-phenylcyclobutene (XVI). It has been established that exchange of similar vinyl protons by basic reagents is difficult (16).

Willstätter's observation that 1-bromocyclobutene and pulverized potassium hydroxide at 210° give acetylene (14) suggested that acetylene may be formed from 1-bromocyclobutene and phenyllithium. The lithium carbide generated in this manner might subsequently yield phenylacetylene [24, 25]. This mechanism seems reasonable since bromobenzene is formed

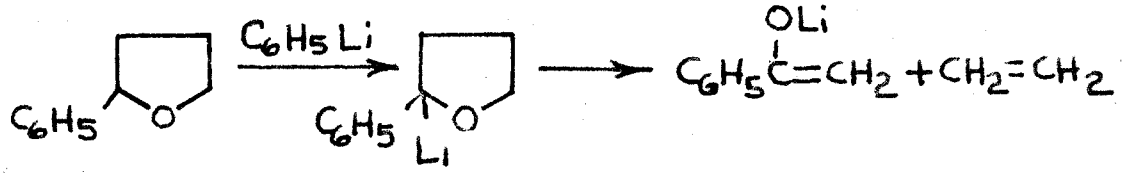
[21]


Br
+C6H5Li
Li
H2O
(a)
+
C6H5Br
C6H5Li
(b)
C6H5-C6H5

[22]


C6H5
BLi
C6H5Li
C6H5C≡C CH2CH2Li
XVI
C6H5C≡C Li +CH2=CH2

[23]


C6H5
C6H5Li
C6H5
O
Li
OLi
C6H5C=CH2 +CH2=CH2

[24] 


[25] 


by halogen-metal interconversion [21] and phenylacetylene is known to be a good competitor for benzyne (54). Varying amounts of lithium acetylide, bromobenzene, and phenyllithium were heated at 75° for 5.0 hr. No phenylacetylene was formed in any of the reactions. The lithium acetylide seemed quite insoluble in the ether, so lithium carbide was generated by passing acetylene gas directly into a phenyllithium solution. Lithium carbide formed in this manner was no more effective in producing phenylacetylene. These experiments do not exclude the possibility that phenylacetylene might be formed from lithium carbide generated directly in the reaction mixture while the reaction is in progress.

Since the dark-brown, pentane-insoluble residue apparently accounted for most of the products derived from 1-bromocyclobutene, it was investigated in some detail. The residue contained no halogen, but the carbon-hydrogen analysis showed that it did contain about 5%

oxygen and that the carbon:hydrogen ratio was 1.147:1.000. Oxidation of the residue with alkaline permanganate afforded only benzoic acid in an amount that required that at least 11.5% (by weight) of the residue must be a phenyl substituent. The infrared spectrum of the residue showed that the phenyl substituent was not conjugated. Additionally, weak absorptions were present at the cyclobutane correlation regions. Considerable difficulty was encountered in obtaining an n-m-r (nuclear magnetic resonance) spectrum of the residue, for marked signal broadening was observed. The spectrum consisted of two broad absorptions. In a number of solvents and at varying concentrations, the ratio of the areas of the phenyl hydrogens (identified by their chemical shift) to the areas of the second signal ranged from 5:4.6 to 5:2.2. Little or no absorption was present in the vinyl-hydrogen portion of the spectrum.

Although no 1-phenylcyclobutene was isolated, it is possible that 1-phenylcyclobutene was formed but was not stable under the reaction conditions and decomposed or polymerized. Cyclobutene undergoes appreciable ring-opening at temperatures as low as 150° to give 1,3-butadiene (50). Had the 1-phenylcyclobutene isomerized to 2-phenyl-1,3-butadiene, the latter compound would have polymerized under the reaction conditions (51). The lack of a conjugated phenyl group in the infrared spectrum and vinyl hydrogens in the n-m-r spectrum of the reaction residue render it unlikely that a major portion of the residue is polymeric 2-phenyl-1,3-butadiene. All of the data for the brown residue

is reasonably consistent, however, with the material being a polymer of 1-phenylcyclobutene. Nevertheless, the available information on the residue hardly permits an unequivocal assignment of structure to this material.

In summary, simple substitution has not been observed in the reaction of 1-bromocyclobutene and phenyllithium. Phenylacetylene was a reaction product and the mechanism of its formation has been investigated briefly. Several possible reaction paths to phenylacetylene have been eliminated or rendered unlikely. Consideration of the ways that phenyllithium and 1-bromocyclobutene may react reveals the difficulty in determining the mechanism of phenylacetylene formation. There are five reasonable sites of attack by phenyllithium in 1-bromocyclobutene; they are the bromine atom, the carbon atom of the 1-position and the protons of the 2-, 3-, and 4-positions. Reaction at one or more of these sites may lead to phenylacetylene. In spite of this difficulty, a knowledge of the mechanism of phenylacetylene formation is desirable, since it may yield information concerning the mechanism of nucleophilic substitution in 1-bromocyclobutene.

# EXPERIMENTAL(91)

1-Chlorocyclopentene was prepared by treating the crude reaction products obtained by the action of phosphorous pentachloride on cyclopentanone with potassium t-butoxide. In a typical preparation phosphorous pentachloride (39.0 g., 0.187 mole) and 200 ml. of methylene chloride were placed in a 300-ml., three-necked, round-bottomed flask fitted with a mechanical stirrer, thermometer, and pressure-equalizing Hershberg dropping funnel. The flask was immersed in an ice bath and 12.6 g. (0.150 mole) of cyclopentanone in 10 ml. of methylene chloride was added over 1.75 hr. The reaction temperature was maintained at 3-6° during the addition. The solution was stirred 1 hr. at 5° and 1 hr. at room temperature (24°). The resulting pale-yellow solution was poured onto 100 g. of crushed ice, and the mixture was stirred. The organic phase was separated, washed twice with water, stirred with 100 g. of crushed ice and 50 ml. of 10% sodium hydroxide, and finally washed once again with water. The methylene chloride solution was dried over 4 g. of anhydrous calcium chloride, and the solvent was removed through Heli-Pak Column C.

Potassium t-butoxide solution was prepared by heating 4.3 g. (0.11 mole) of potassium under reflux in 200 ml. of anhydrous t-butyl alcohol (92) until all of the potassium reacted. The potassium t-butoxide was added to the crude chloride mixture, and the resulting solution

maintained at the boiling point of the mixture for 3 hr. The dehydrohalogenation mixture was poured into 500 ml. of water, and 150 ml. of methylene chloride was added. In order to remove material which was not soluble in either of the two liquid phases, the mixture was filtered through a coarse sintered-glass filter. The methylene chloride solution was separated, washed six times with 200-ml. portions of water, and dried over 3 g. of anhydrous calcium chloride. The methylene chloride was removed using Heli-Pak Column C. Final distillation was accomplished through semimicro Column F. 1-Chlorocyclopentene (7.69 g., 50%), b.p. 101-103° (745 mm.), $\underline{n}^{25}_{D}$ 1.4632 (lit. (93) b.p. 115°, $\underline{n}^{25}_{D}$ 1.4637) was obtained in 98% purity (v-p-c).

Since the physical properties reported for 1-chlorocyclopentene vary widely (93,94), and 3-chlorocyclopentene is reported as a by-product in the preparation of 1-chlorocyclopentene from phosphorous pentachloride and cyclopentanone (94), the structure of 1-chlorocyclopentene was carefully established. Contrary to the literature (94) 1-chlorocyclopentene is reasonably stable if stored in a sealed tube in the absence of moisture or hydrochloric acid; it does decompose slowly, however. A typical sample of 1-chlorocyclopentene which was homogeneous to v-p-c, b.p. 102-103°, $\underline{n}^{25}_{D}$ 1.4638, did not react with alcoholic silver nitrate solution and had the correct elemental analysis.

Anal. Calcd. for $C_5H_7Cl$: C, 58.54; H, 6.88; Cl, 34.57. Found: C, 58.49; H, 7.00; Cl, 34.44.

The infrared spectrum of 1-chlorocyclopentene revealed only a single absorption in the carbon-carbon double bond stretching region at 1628 $cm.^{-1}$. A strong band at 810 $cm.^{-1}$ is characteristic of the carbon-hydrogen out-of-plane deformation of a triply-substituted double bond (95). The n-m-r (nuclear magnetic resonance) spectrum of this halide consisted of a multiplet at 4.45 p.p.m. (internal standard) reasonably representing the vinyl hydrogen and very complex absorption extending from 8.34 p.p.m. to 7.25 p.p.m. The ratio of the areas of these two absorptions was 1:5.75.

The Reaction of Phenyllithium and 1-Chlorocyclopentene at 150°.

In a 500-ml. stainless-steel bomb was placed 6.78 g. (0.0663 mole) of 1-chlorocyclopentene and 250 ml. (0.312 mole) of 1.25 M phenyllithium (38) in ether. The phenyllithium possessed no measurable amount (v-p-c) of bromobenzene and only a very small amount of biphenyl. The steel bomb was sealed and placed in an oil bath maintained at about 150° for 1.3 hr. The bomb was cooled, opened, and the contents washed out with ether and water. The ether layer was separated, washed twice with water, and dried twice over 5-g. portions of anhydrous calcium chloride. The ether was removed using Heli-Pak Column C. Distillation was completed using semimicro Column F. 1-Phenylcyclopentene (2.91 g. $(30 \pm 2)\%$, v-p-c analysis of distilled fractions) was obtained which was identical in infrared spectrum to a sample prepared by the method of Baddeley (96). The main fraction of phenylcyclopentene, b.p. 90-92° (7 mm.) (lit. (96) b.p. 107-108°, 12 mm.), was contaminated with

biphenyl. Recrystallization of the distillation residue (2.30 g.) three times from methanol afforded 1.80 g. of biphenyl, m.p. 69.8-70.4° (lit. (97) m.p. 71°).

In an experiment conducted under similar conditions 7.96 g. (0.0776 mole) of 1-chlorocyclopentene and 200 ml. (0.304 mole) of 1.52 M phenyllithium (38) solution yielded 3.80 g., (34 ± 5)% (v-p-c analysis of distilled fractions), of 1-phenylcyclopentene. The principal fraction (representing 80% of the total 1-phenylcyclopentene collected), b.p. 92-94° (13 mm.), $n_D^{25}$ 1.5734-1.5750 (98)), was contaminated with biphenyl.

Reaction of 1-Chlorocyclopentene and Phenyllithium in the Presence of Piperidine at 36°. In a 500-ml., three-necked, round-bottomed flask fitted with a reflux condenser and a dry-nitrogen inlet were placed 7.50 g. (0.073 mole) of 1-chlorocyclopentene, 154 ml. (0.200 mole) of 1.30 M phenyllithium (38) solution, 2.72 g. (0.0319 mole) of piperidine, and 100 ml. of anhydrous ether. A positive atmosphere of dry nitrogen was maintained in the reaction vessel, the pressure being controlled by a mercury pressure valve (99). The solution was heated at the reflux temperature (36°) for 12 hr. More piperidine (1.36 g., 0.0160 mole) was added and the heating continued for 12 more hr. About 100 ml. of water was added cautiously to the reaction mixture. The ether layer was separated, washed twice with water, and dried twice over 8-g. portions of anhydrous calcium chloride. The main portion of

ether was removed through Heli-Pak Column A. The remainder of the distillation was accomplished with spinning-band Column B (stainless-steel band, 1500 r.p.m.). 1-Phenylcyclopentene (2.06 ± 0.52 g., (20 ± 5)%, v-p-c analysis of distilled fractions) was obtained using a reflux ratio of about 75:1. Slightly more than 65% of the 1-phenylcyclopentene collected boiled in the range 101-110°, (13-14 mm.) $n^{25}_D$ 1.5720-1.5763 (lit. (96) b.p. 107-108°, 12 mm., $n^{25}_D$ 1.5734-1.5750 (98)).

1-Phenylcyclopentene from 1-Chlorocyclopentene and Phenyllithium Enhanced Coupling in the Presence of Piperidine. In each of two 250-ml., round-bottomed flasks which had been oven-dried and flushed with dry nitrogen, were placed 3.000 g. (0.02925 mole) of 1-chlorocyclopentene and 100 ml. (0.081 mole) of 0.81 M phenyllithium solution in ether. Piperidine (0.62 g., 0.0073 mole) was added to one of the flasks. Both flasks were sealed with a greased glass stopper and wired tightly closed. The flasks were thermostated in a water bath at 27.0 ± 0.5°. After 6.0 hr., an additional 0.62 g. (0.0073 mole) of piperidine was added to the flask already containing piperidine. Both reaction mixtures were decomposed with water after a total reaction time of 24.0 hr. The ether phases were separated, washed twice with water, washed with 3 N hydrochloric acid, and dried twice over 1-g. portions of anhydrous calcium chloride. Most of the ether was removed through Heli-Pak Column C (reflux ratio 50:1).

The reaction mixtures were analyzed by v-p-c using a weighed quantity of a chemical marker (100). Redistilled iodobenzene (b.p. 186-

187° (745 mm.) $\underline{n}^{25}_{D}$ 1.6170, Matheson, Coleman & Bell reagent, lit. (101) b.p. 188.3°, $\underline{n}^{25}_{D}$ 1.6172) was employed as the marker, and Perkin-Elmer Column C (175°) was used for the analyses. An accurately known weight of iodobenzene was quantitatively transferred to each of the two reaction mixtures. In addition, a standard mixture of iodobenzene and 1-phenylcyclopentene (homogeneous to v-p-c) was prepared. The v-p-c spectrum of the reaction mixtures consisted of four cleanly separated peaks, iodobenzene (5.7 min.), 1-phenylcyclopentene (9.6 min.), unknown (12.4 min.), and biphenyl (17.0 min.). The product of the peak height times the width at half-peak was used as a measure of the peak areas. Three determinations were made for each sample, and the error in measuring the peak areas was computed as probable error (102). It was assumed that the peak areas were directly proportional to the mole of compound present. A constant ($C = 0.917 \pm 0.015$) was computed from the iodobenzene-1-phenylcyclopentene standard mixture which related the ratio of peak areas of iodobenzene ($A_I$) and 1-phenylcyclopentene ($A_p$) to the ratio of moles ($M_I$:$M_p$) of the two components [26]. It was then possible to calculate the yield of 1-phenylcyclopentene in the two

$$C\,\frac{A_I}{A_p} = \frac{M_I}{M_p} \qquad [26]$$

reaction mixtures using (26). 1-Phenylcyclopentene was formed in $(1.86 \pm 0.06)\%$ yield in the reaction without piperidine; in the reaction with piperidine, a yield of $(9.7 \pm 0.3)\%$ was obtained. Assuming that

there was a 1:1 mole correspondence between the peak areas of 1-phenylcyclopentene and biphenyl, 5.5% biphenyl (relative to 1-chlorocyclopentene) was present in the reaction with piperidine and 6.2% in the absence of piperidine. The unknown constituent was present in roughly equal amounts in both reactions. The biphenyl to unknown peak area ratio was about 2:1, respectively.

Cyclopentanone-1-$^{14}C$. Adipic-1,6-$^{14}C_2$ acid (103) (0.0471 g., total activity 1.0 mc.) was washed with reagent acetone into a 500-ml., round-bottomed flask containing 29.05 g. of adipic acid. A total of 100 ml. of acetone was added. All of the adipic acid did not go into solution, and the mixture was digested on a steam bath for 15 min. The solvent was removed affording 29.10 g. (0.2000 mole, specific activity 5.0 μc./mole) of adipic-1,6-$^{14}C_2$ acid.

Barium hydroxide pentahydrate (2.00 g., 0.00635 mole) was ground to a fine powder. Portions of adipic-1,6-$^{14}C_2$ acid were blended into the powder until 29.10 g. (0.2000 mole) had been added. This mixture was transferred to a 50-ml. modified Claisen flask with a 10-cm. Vigreux column and condenser. The flask was sealed off with a hand torch so that the condenser outlet was the only opening in the system. The Claisen flask was connected to a 50-ml., two-necked flask which was in turn connected to a 2-ℓ., three-necked, round-bottomed flask. The large three-necked flask was fitted with a mechanical stirrer, filled with 1-ℓ. of saturated barium hydroxide solution, and connected to a wash bottle with a fritted-glass bubbler which was

filled with saturated barium hydroxide solution.

The reaction flask was immersed in a Woods-metal bath which was heated by a heating mantle. Power input to the heating mantle was controlled by a relay actuated by a thermocouple in the bath. The temperature of the bath was raised from 100° to 290° over a 1.0-hr. period and then maintained at 288 ± 2° for 1.5 hr. Six additional hr. of heating at 293 ± 2° were required for completion of the reaction.

Anhydrous potassium carbonate was added to the cyclopentanone-water mixture obtained as distilled reaction products. The upper, cyclopentanone, phase was decanted with a medicine dropper; the aqueous phase was washed six times with 3-ml. portions of methylene chloride. The methylene chloride extracts were combined with the separated cyclopentanone phase and dried over 0.5 g. of anhydrous potassium carbonate. Distillation was accomplished through semimicro Column F. Cyclopentanone (15.948 g., 95%), b.p. 127-128° (743 mm.), $\underline{n}^{20}_{D}$ 1.4368 (lit. (104) b.p. 129°, $\underline{n}^{20}_{D}$ 1.4366), was obtained which gave a single peak in the v-p-c (Perkin-Elmer Column A, 100°).

The barium carbonate precipitated in the large three-necked flask was collected by suction filtration, washed with filtered distilled water, washed with filtered acetone, and dried for three days at 25° and 0.1 mm. The yield was 35.9 g. (91%).

1-Chlorocyclopentene-1-$^{14}$C. Phosphorous pentachloride (49.5 g., 0.238 mole) and 200 ml. of methylene chloride were placed in a 300-ml., three-necked, round-bottomed flask fitted with mechanical stirrer, thermometer, and pressure-equalizing Hershberg dropping

funnel. Cyclopentanone-1-$^{14}$C (15.95 g., 0.190 mole) and 15 ml. of methylene chloride were added over a 2.0-hr. period to the reaction mixture which was maintained at 0 ± 5°. The solution was stirred at about 5° for 1.0 hr.; finally, the reactants were allowed to warm to 20° during 1.0 hr.

The reaction mixture was added with mechanical stirring to 150 g. of crushed ice. The organic layer was separated, washed once with water, and washed twice by stirring with 200 g. of crushed ice and 50 ml. of 40% sodium hydroxide. After a final washing with water, the methylene chloride solution was dried over 4 g. of anhydrous calcium chloride. The solvent was removed through Heli-Pak Column C.

The crude halide mixture was refluxed 2.0 hr. with 200 ml. of 0.8 M potassium t-butoxide in t-butyl alcohol, which had been prepared as described above. The dehydrohalogenation products were poured into 500 ml. of water, and the halide was taken up in methylene chloride. The aqueous layer was washed twice with solvent, and the combined extracts were washed six times with water. After drying over 10 g. of anhydrous calcium chloride (350-400 ml.), the solvent was removed using Heli-Pak Column C. Final distillation was accomplished with semimicro Column F. 1-Chlorocyclopentene-1-$^{14}$C (10.01 g., 52%), b.p. 102-103° (lit. (105) b.p. 102-103°), of about 98% purity (v-p-c, Perkin-Elmer Column C, 96°) was obtained.

Table III

Distillation of 1-Phenylcyclopentene-x-$^{14}C$

| Fraction | Wt., g. | B.p. | Press., mm. | Pottemp. | Wt., g. |
|---|---|---|---|---|---|
| 0 | 12 ml. | 34-78 | 742 | 80-140 | |
| 1 | 1.10 | 25 | 20 | 25 | |
| 2 | 0.50 | 40 | 20 | 120 | |
| 3 | 0.40 | 46 | 20 | 130 | 0.06[a] |
| 4 | 0.35 | 46-60 | 20 | 140 | 0.07[a] |
| 5 | 0.18 | 90 | 20 | 150 | 0.04[a] |
| 6 | 0.28 | 90-110 | 20 | 153 | 0.06[a] |
| 7 | 2.19 | 114 | 15 | 153-160 | 1.42[b] |
| 8 | 2.45 | 120 | 10 | 170 | 0.62[b] |
| 9 | 1.00 | 130 | 10 | 190 | 0.05[b] |
| 10 | 0.24 | 140 | 10 | 210 | |
| 11 | 0.26 | 150 | 10 | 220-260 | |

[a]Estimate of minimum amount present in fraction from v-p-c data.
[b]v-p-c-Analyzed 1-phenylcyclopentene-biphenyl mixtures using standard mixture. Method reliable to 3%.

solution (prepared from 105 ml. of 0.128 M carbonate-free sodium hydroxide solution and 6.80 g. of potassium dihydrogen phosphate diluted to 200 ml.) and 8.77 g. (0.0555 mole) of potassium permanganate. The oxidizing solution was thermostated at 30°. 1-Phenylcyclopentene-x-$^{14}C$, 2.04 g. (0.0142 mole, fractions 7 and 8 of Table III), and 50 ml. of spectro-grade isooctane were added to the reaction flask and stirring

started (5000 r.p.m.). The temperature of the reaction rose to a maximum 43° in about 20 min.; the stirring was continued for 1.0 hr.

The aqueous phase of the reaction mixture was made strongly alkaline with 10% sodium hydroxide solution and continuously extracted with ether for 3.0 hr. The aqueous phase was acidified with 6 N sulfuric acid and continuously extracted with ether for 48 hr. The crude mixture of acids (1.98 g.) obtained from the extract was chromatographed on a 20-mm. (i.d.) containing 40 g. of 100 mesh silicic acid, 10 g. of Hyflo-Supercel, and 45 g. of water. Chloroform was used as the solvent. All but 0.25 g. of the crude acid mixture dissolved in 30 ml. of chloroform. The solution of acids was put on the column, and 1.645 g. of a mixture of benzoic-α-$^{14}$C and 5-phenyl-5-oxopentanoic-x-$^{14}$C acids was obtained using chloroform (450 ml.) as an eluent. The 0.25 g. of acid, which did not dissolve in chloroform, dissolved in 90-10 chloroform-n-butanol and was placed on the column. Using successively 90-10 (300 ml.), 80-20 (250 ml.), and 75-20 chloroform-n-butanol mixtures as eluents, 0.215 g. of acid, m.p. 178.0-184.5°, was obtained. Attempts to purify this acid by recrystallization from various solvents were unsuccessful. Rechromatographing this material on a similar silicic acid-Hyflo Supercel column using 85-15 chloroform-n-butanol as an eluent afforded 0.146 g. of succinic-x-$^{14}$C acid (8.7%) m.p. 186.0-186.8° (lit. (106) m.p. 184.5-185.0°).

The 1.645 g. of mixed benzoic-α-$^{14}$C acid and 5-phenyl-5-oxopentanoic-x-$^{14}$C acid obtained above was dissolved in 20 ml. of 95%

ethanol. To this solution was added 4.8 g. (0.058 mole) of sodium acetate and 20 ml. of water; the solution was heated to the boiling point. Semicarbazide hydrochloride (3.2 g., 0.029 mole) was added and dissolved. As the solution cooled to room temperature, fine white needles were formed. A 49% (1.732 g.) yield of 5-phenyl-5-oxopentanoic-x-$^{14}$C acid semicarbazone, m.p. 211-214° (d.) (lit. (107) m.p. 212-213°) was obtained by collecting the needles (washing first with 50-50 ethanol-water and then with water) and recrystallizing them once from ethanol-water (50-50).

The mother liquor from the semicarbazone formation was acidified with 6 N sulfuric acid, steam distilled to remove much of the acetic acid, and continuously extracted with ether. To the crude acid obtained from the ether extract were added 0.8 g., (0.0075 mole) of sodium carbonate, 3 g. (0.0190 mole) of finely-powdered potassium permanganate, and 35 ml. of water. The solution was heated at the reflux temperature of the mixture for 4.0 hr. in a 100-ml., round-bottomed flask fitted with a reflux condenser. The products were cooled, acidified with 6 N sulfuric acid, and heated for 1.0 more hr. Enough sodium bisulfite was then added to remove excess manganese dioxide. Benzoic acid crystallized as the solution was cooled and was collected by continuous extraction with ether. A single recrystallization of the acid obtained from the ether extract gave 0.292 g. (17%) of benzoic-α-$^{14}$C acid, m.p. 122.2-122.8° (lit. (108) m.p. 122.4°).

Fractions 3-6 and 9 (Table III) were combined for oxidation. These fractions contained a total of 0.28 g. (0.00194 mole) of 1-phenylcyclopentene-x-$^{14}$C. The oxidation was carried out using 3.00 g. (0.0190 mole) of potassium permanganate and 100 ml. of pH 7 phosphate buffer solution (prepared as above). Following procedures similar to those described above, 0.152 g. (31%) 5-phenyl-5-oxopentanoic-x-$^{14}$C acid semicarbazone, m.p. 212-214° (d.) (lit. (107) m.p. 212-213°) was isolated. The other degradation products were not isolated.

5-Phenylpentanoic-x-$^{14}$C acid was prepared from 5-phenyl-5-oxopentanoic-x-$^{14}$C acid semicarbazone by the Wolff-Kishner reduction. 5-Phenyl-5-oxopentanoic-x-$^{14}$C acid semicarbazone (1.143 g., 0.00459 mole), potassium hydroxide pellets which had been finely pulverized prior to use, and 25 ml. of diethylene glycol were placed in a 50-ml., round-bottomed flask fitted with a solvent-stripping reflux condenser and a magnetic stirring bar. The temperature of the bath was raised to 220° over a fifteen minute period, and maintained there for 2.5 hr. The products were poured into 75 ml. of water and acidified with 6 N sulfuric acid. Crude 5-phenylpentanoic-x-$^{14}$C acid (0.673 g., 82%) m.p. 55-59°, was obtained. Recrystallization of this material twice from pentane (Norite) and twice from water-ethanol (60-40) afforded 0.557 g. (69%) of small white plates, m.p. 61.0-61.4° (lit. (109) m.p. 61°).

Schmidt Degradation of 5-Phenylpentanoic Acid. A reaction train was assembled similar to that described by Roberts et al. (1b),

consisting of a barium hydroxide (saturated solution, about 0.3 M) wash bottle, a soda-lime trap, reaction flask, empty wash bottle, wash bottle with 5% potassium permanganate in 6 N sulfuric acid, two wash bottles containing barium hydroxide (saturated solution), and a soda-lime trap. The reaction flask was a 100-ml., three-necked, round-bottomed flask fitted with a pressure-equalizing dropping funnel and magnetic stirring bar. The train was flushed with nitrogen for 2 hr. prior to filling the barium carbonate collection bottles with saturated barium hydroxide solution. In the reaction flask were placed 0.500 g. (0.00280 mole) of 5-phenylpentanoic-x-$^{14}$C acid, 1.8 ml. (3.3 g., 0.034 mole) of concentrated sulfuric acid, and 30 ml. of reagent chloroform. Freshly prepared 1.23 M hydrazoic acid (93) (2.7 ml., 0.0033 mole) and 10 ml. of reagent chloroform were placed in the pressure-equalizing dropping funnel. The reaction flask was placed in an oil-bath thermostated at 45°, and the system was flushed with nitrogen for 0.5 hr. No barium carbonate collected; therefore, the hydrazoic acid was slowly added to the 5-phenylpentanoic-x-$^{14}$C acid over a 45 min. period. The heating was continued for 2.0 hr.

The wash bottle containing the barium carbonate was isolated from the rest of the train by pinchcocks, taken out of the train, and transferred to a dry box filled with carbon dioxide-free nitrogen. The barium carbonate (0.469 g., 85%) was collected by suction filtration, washed with filtered carbon dioxide-free, distilled water, washed with filtered reagent acetone, and dried at 25° and 0.1 mm.

The chloroform of the reaction mixture was removed under reduced pressure and the reaction products were made strongly basic with 40% sodium hydroxide. Benzoyl chloride (1.0 ml.) was added, and the resulting white precipitate was filtered. A single recrystallization from ethanol yielded 0.0652 g. (9%) of the benzamide of 4-phenyl-1-aminobutane-x-$^{14}$C, m.p. 83.0-83.7° (lit. (115) m.p. 83.5°).

Schmidt Degradation of Succinic-x-$^{14}$C Acid. Succinic-x-$^{14}$C acid (0.1002 g.), m.p. 186.0-186.8° was added to 0.2397 g. of succinic acid, m.p. 186.4-187.2°. The mixture was dissolved in a minimum amount of hot, filtered acetone; the acetone was removed under reduced pressure. Diluted succinic-x-$^{14}$C acid was obtained, m.p. 186.0-187.0° (lit. (106) m.p. 184.5-185.0°).

In an apparatus identical to that described above for the degradation of 5-phenylpentanoic-x-$^{14}$C were placed 0.175 g. (0.00148 mole) of the diluted succinic-x-$^{14}$C acid, 1.8 ml. (3.3 g., 0.034 mole) of concentrated sulfuric acid, and 30 ml. of reagent chloroform. Furthermore, 2.0 ml. (0.0034 mole) of 1.7 M hydrazoic acid and 10 ml. of reagent chloroform were placed in the pressure-equalizing dropping funnel. Following closely the procedure outlined for the degradation of 5-phenylpentanoic-x-$^{14}$C acid, the hydrazoic acid was added to the succinic-x-$^{14}$C acid over a 1.25 hr. period; heating was continued for 3.0 hr. Barium carbonate (0.210 g., 72%) was collected.

1,2-Diaminoethane-x-$^{14}$C was isolated as the dibenzamide, 0.0635 g. (16%), m.p. 250.8-251.1° (lit. (116) m.p. 249°).

Oxidation of 5-phenyl-5-oxopentanoic-x-$^{14}$C acid semicarbazone, obtained from the oxidation of 1-phenylcyclopentene-x-$^{14}$C, to benzoic-α-$^{14}$C acid was accomplished using alkaline potassium permanganate. 5-Phenyl-5-oxopentanoic-x-$^{14}$C acid semicarbazone (0.500 g., 0.00200 mole), 0.8 g. (0.0075 mole) of sodium carbonate, 4.0 g. (0.025 mole) of finely-powdered potassium permanganate, and 500 ml. of water were placed in a 100-ml., round-bottomed flask fitted with a reflux condenser. The solution was heated at the reflux temperature of the mixture for 4.0 hr., cooled, acidified with 6 N sulfuric acid, and refluxed for 1.0 hr. Enough sodium bisulfite was added to remove excess manganese dioxide. Benzoic acid was isolated by continuous extraction of the colorless reaction mixture with ether. Recrystallization from water of the crude acid obtained from the ether extract afforded 0.192 g. (79%) of benzoic-α-$^{14}$C acid, m.p. 122.0-122.7° (lit. (108) m.p. 122.4°).

Degradation of 1-Chlorocyclopentene-1-$^{14}$C. A. Hydrolysis. About 25 ml. of 75% (vol.) sulfuric acid and 2.969 g. (0.0290 mole) of diluted 1-chlorocyclopentene-1-$^{14}$C (1.548 g. of 1-chlorocyclopentene-1-$^{14}$C diluted to 2.969 g. with 1-chlorocyclopentene) were placed in a 100-ml., round-bottomed flask fitted with a magnetic stirring bar. The mixture was stirred for 1.25 hr. at room temperature. Initially there were two phases; the second disappeared after about 45 min. The reaction mixture was neutralized by adding 40% sodium hydroxide dropwise. The neutral solution was continuously extracted with ether, and the ether extract was dried successively over anhydrous sodium

sulfate and Drierite. Most of the ether was removed through Heli-Pak Column C. The cyclopentanone was flash-distilled under vacuum (5 mm.) to a Dry-Ice trap. The yield of crude cyclopentanone was 1.82 g. (75%).

B. 1-Phenylcyclopentene-1-$^{14}$C from Cyclopentanone-1-$^{14}$C. In a 200-ml., three-necked, round-bottomed flask fitted with a pressure-equalizing dropping funnel, magnetic stirring bar, and dry-nitrogen inlet was placed 72 ml. (0.058 mole) of 0.81 M phenyllithium solution (38) in ether. To this solution 1.82 g. (0.0216 mole) of cyclopentanone-1-$^{14}$C was added dropwise. The reaction mixture was cooled with an ice bath. After the addition was completed, the reaction products were poured into water and neutralized with 3 N sulfuric acid. The ether layer was separated, washed once with water, and dried over anhydrous sodium sulfate. The ether was distilled through Heli-Pak Column C, and 25 ml. of 90% formic acid was added to the residue. The formic acid solution was stirred for 2.0 hr. and poured into 100 ml. of water. 1-Phenylcyclopentene-1-$^{14}$C, which appeared as a second phase during the dehydration, was separated with the aid of pentane; the aqueous layer was extracted twice with pentane. The combined pentane extracts were washed three times with water, and dried over anhydrous calcium chloride. The pentane was removed through Heli-Pak Column C, leaving 2.98 g. (96%) of 1-phenylcyclopentene-1-$^{14}$C.

C. Oxidation of 1-Phenylcyclopentene-1-$^{14}$C to 5-Phenyl-5-oxopentanoic-5-$^{14}$C Acid Semicarbazone. The method was as described for the oxidation of 1-phenylcyclopentene-x-$^{14}$C. 1-Phenylcyclopentene

(2.98 g., 0.0207 mole) and 50 ml. of spectrograde isooctane were added to a pre-equilibrated (30°) solution of potassium permanganate (13.2 g., 0.0835 mole) dissolved in 300 ml. of pH 7 phosphate buffer solution (prepared from 105 ml. of 0.128 M carbonate-free sodium hydroxide solution and 6.80 g. potassium dihydrogen phosphate diluted to 200 ml.). 5-Phenyl-5-oxopentanoic-5-$^{14}$C acid semicarbazone (2.33 g., 45%), m.p. 213-215° (d.) (lit. (107) m.p. 212-213°), was obtained. Since the cyclopentanone-1-$^{14}$C and 1-phenylcyclopentene-1-$^{14}$C were not carefully purified, it is more correct to base the yield of semicarbazone on 1-chlorocyclopentene-1-$^{14}$C. Accordingly, the overall yield was 32%.

D. Oxidation of 5-Phenyl-5-oxopentanoic-5-$^{14}$C Acid to Benzoic-α-$^{14}$C Acid. The method was as employed for the oxidation of 5-phenyl-5-oxopentanoic-x-$^{14}$C acid. 5-Phenyl-5-oxopentanoic-5-$^{14}$C acid (1.000 g., 0.00401 mole), sodium carbonate (1.6 g., 0.015 mole), potassium permanganate (8.0 g., 0.05 mole), and 100 ml. of water afforded 0.406 g. (83%) of benzoic-α-$^{14}$C acid, m.p. 122.2-122.8° (lit. (108) m.p. 122.4°).

Dimethyl 2,5-dibromoadipate was synthesized following the procedure of Buchman (45). In a 5-ℓ., three-necked, round-bottomed flask fitted with a mechanical stirrer, pressure-equalizing dropping funnel, and reflux condenser was placed 730 g. (5.00 moles) of adipic acid. A total of 1200 g. (10.1 mole) of thionyl chloride was added to the adipic acid at 2-hr. intervals; the reaction was conducted at 70°. Heating was continued for 2.0 hr. after the addition of the thionyl chloride. Bromine

(1630 g., 10.2 moles) was added dropwise over a 10-hr. period, and the temperature was raised to 100° for 11 hr. The crude acid halide was poured with stirring into 1.0 ℓ. of reagent methanol which was cooled in an ice bath. Solid dimethyl ester (920 g.), presumably dimethyl meso-2,5-dibromoadipate (45), crystallized from the cooled methanol solution; a portion of the solid dimethyl ester which was recrystallized from methanol melted 73.1-73.8° (lit. (45) 73.5-74.0°).

The methanol was removed from the mother liquor by distillation through a 30 cm. (16 mm. i.d.) Vigreux column. Additional dimethyl 2,5-dibromoadipate (450 g.) was obtained, b.p. 170° (2 mm.), lit. (45) b.p. ca. 163° (3 mm.). A total of 1370 g. (82%) of dimethyl 2,5-dibromoadipate was collected.

Diesters of 1-cyano-1,2-cyclobutanedicarboxylate were prepared in best yield using a modified procedure of the Fuson ring-closure (45, 46). Table IV summarizes the yields obtained using the Fuson method and the modified method.

In a typical run of the modified procedure 752 g. (2.09-2.26 moles) of a mixture (unknown composition) of the diethyl and dimethyl 2,5-dibromoadipates (117) and 400 ml. of methanol was placed in a 2-ℓ., two-necked, round-bottomed flask fitted with a mechanical stirrer and reflux condenser. The reaction was stirred at the reflux temperature for 55 hr. The condenser was removed and replaced with a distillation head. After distillation of the methanol from the reaction mixture, the

Table IV

Preparation of the Diesters of 1-Cyano-1, 2-cyclobutanedicarboxylate

| Trial | Method[c] | Reactants(s), moles | Yield, % |
|---|---|---|---|
| 1 | F | 2.11[a] | 56 |
| 2 | F | 1.38-1.50[b] | 73-76 |
| 3 | F | 1.89-2.05[b] | 56-59 |
| 4 | M | 2.09-2.26[b] | 81-86 |
| 5 | M | 1.49-1.62[b] | 79-83 |

[a]Reactant was dimethyl 2, 5-dibromoadipate. [b]Reactants were a mixture of diethyl and dimethyl 2, 5-dibromoadipates. [c]Method F is that of Fuson (46). Method M is the modified procedure described above.

organic products were taken up in methylene chloride. The contents of the reaction flask were washed onto a sintered-glass Buchner funnel and thoroughly washed with methylene chloride. The methylene chloride solution was washed several times with water, filtered to remove some fluffy, black solid, dried over anhydrous calcium chloride, and distilled through a 25-cm. (12 mm. i.d.) column of 10-mm. glass helices. A mixture of diethyl and dimethyl 1-cyano-1, 2-cyclobutanedicarboxylates (388 g., 81-86%), b.p. mainly 125-145° (2 mm.), lit. (45) b.p. ca. 128° (3 mm., dimethyl ester) was obtained.

Cis-1, 2-cyclobutanedicarboxylic acid was synthesized following the method of Buchman (45); a summary of 1, 2-cyclobutanedicarboxylic

acid syntheses is presented in Table V. A typical synthesis of cis-1,2-cyclobutanedicarboxylic acid is described here.

In a 2-ℓ. round-bottomed flask fitted with a reflux condenser were placed 198.6 g. (0.88-0.99 mole) of a mixture of diethyl and dimethyl 1-cyano-1,2-cyclobutanedicarboxylates and 500 ml. of 6 N hydrochloric acid. The resulting solution was refluxed 36 hr. The hydrolysis products were taken to dryness by heating the hydrolysate on a steam bath for 5.0 hr. The organic reaction products were taken up in acetone; the acetone was distilled and the residual crude acid was heated at 170-180° (30 mm.) for 3 hr. to decarboxylate any remaining 1,1,2-cyclobutanetricarboxylic acid.

1,2-Cyclobutanedicarboxylic acid was purified by forming cis-1,2-cyclobutanedicarboxylic acid anhydride. The crude 1,2-cyclobutanedicarboxylic acid was heated with 450 g. of acetyl chloride at the reflux temperature of the solution for 3 hr. The unreacted acetyl chloride was removed by distillation, and the mixture was heated at 150-160° (30 mm.) for 2 hr. From the black, viscous material remaining, 37.3 g. of cis-1,2-cyclobutanedicarboxylic acid anhydride, b.p. 142-145° (9 mm.) was obtained. Recrystallization of the anhydride from benzene-hexane gave 34.4 g. (28-31%) of white plates, m.p. 75.9-76.8° (lit. (45) m.p. 76.5-77.0°).

About 25 ml. of water and 34.4 g. (0.252 mole) of cis-1,2-cyclobutanedicarboxylic acid anhydride were heated on a steam bath.

Table V

1,2-Cyclobutanedicarboxylic Acid Preparations

| Trial | Method[a] | Reactant(s), mole(s) | Yield, % |
|---|---|---|---|
| 1 | A | 0.88-0.99[b] | 28-31[d] |
| 2 | A | 3.99-4.55[b] | 37-42[d] |
| 3 | B | 0.0407[c] | 100[e] |
| 4 | B | 2.98[c] | 98.5[e] |

[a]Method A is the procedure of Buchman (45). Method B is the procedure for the preparation of a mixture of cis- and trans-1,2-cyclobutanedicarboxylic acids described below. [b]Reactants were a mixture of diethyl and dimethyl 1-cyano-1,2-cyclobutanedicarboxylates. [c]Reactant was dimethyl 1-cyano-1,2-cyclobutanedicarboxylate. [d]Yield based on cis-1,2-cyclobutanedicarboxylic acid anhydride. [e]Yield based on a mixture of cis- and trans-1,2-cyclobutanedicarboxylic acids.

Upon cooling a white solid formed. The solid was dried and recrystallized from benzene-dioxane, yielding 29.8 g. (80%) of cis-1,2-cyclobutanedicarboxylic acid (white prisms), m.p. 139.4-140.0° (lit. (45) m.p. 139.5-140.0°).

Cis- and Trans-cyclobutanedicarboxylic Acids. Carbon dioxide was evolved in the hydrolysis of the mixture of diethyl and dimethyl esters of 1-cyano-1,2-cyclobutanedicarboxylates. To determine the extent of decarboxylation in the hydrolysis step, 8.03 g. (0.0407 mole) of dimethyl 1-cyano-1,2-cyclobutanedicarboxylate was hydrolyzed affording 8.45 g. (105%) of barium carbonate and 5.88 g. (100%) of

1,2-cyclobutanedicarboxylic acid (101% purity by titration). Since a mixture of cis- and trans-1,2-dicarboxylic acids was suitable for subsequent synthetic steps, the following hydrolysis procedure was adopted.

In a 3-ℓ. round-bottomed flask fitted with a reflux condenser were placed 588.5 g. (2.98 moles) of dimethyl 1-cyano-1,2-cyclobutanedicarboxylate and 1500 ml. of 6 N hydrochloric acid. As the reactants were heated, the solid diester went into solution; the reaction was maintained at the boiling point of the solution for 50 hr. The acid obtained by hydrolysis was continuously extracted with ether, yielding 421.9 g. (98.5%) of 1.2-cyclobutanedicarboxylic acid (100.3% purity by titration) as slightly discolored white crystals, m.p. 68-97° (lit. (45) cis-1,2-cyclobutanedicarboxylic acid, m.p. 139.5-140.0°; trans-1,2-cyclobutanedicarboxylic acid, m.p. 130.5-131.0°).

Disilver 1,2-cyclobutanedicarboxylate was prepared in nearly quantitative yields. A typical preparation follows. 1,2-Cyclobutanedicarboxylic acid (400.0 g., 2.78 moles, recrystallized once from benzene, m.p. 92-120°) was neutralized with 548 ml. (5.56 moles) of 10.16 N carbonate-free sodium hydroxide. While the solution was still warm, it and 944 g. (5.56 moles) of silver nitrate, which had been dissolved in a minimum amount of water, were added simultaneously to a large beaker fitted with a mechanical stirrer. The white salt obtained was collected by filtration, washed thoroughly with carbon dioxide-free distilled water, and dried in a vacuum dessicator. Final drying was accomplished in a 2-ℓ., round-bottomed flask which was covered with

a black cloth and maintained at 75° and 1 mm. The disilver 1,2-cyclobutanedicarboxylate (944 g., 100%) was analyzed by ignition (118) (99.3% purity) and stored at 75° and 1 mm.

Trans-1,2-dibromocyclobutane was synthesized following the general method of Conly (129), who showed that trans-1,2-dibromocyclobutane (no cis-isomer) was formed from the Hunsdiecker reaction in comparable yields from both cis- and trans-1,2-cyclobutanedicarboxylic acids. It was thus not surprising that mixtures of cis- and trans-diacids gave similar yields. The results of a number of trans-1,2-dibromocyclobutane preparations are summarized in Table VI; a procedure is described that gave reproducible 21-25% yields.

A 3-ℓ., three-necked, round-bottomed flask was fitted with a powder-dropping funnel, mechanical stirrer with a glass paddle, and an adapter which was connected to a reflux condenser and a 250-ml., pressure-equalizing dropping funnel. The reflux condenser led to a Dry-Ice trap and then to an apparatus to measure carbon-dioxide evolution by water displacement. All of the apparatus was thoroughly dried in an oven at 110°. A quantity of disilver 1,2-cyclobutanedicarboxylate (196.2 g., 0.548 mole) was divided into two equal portions and placed in two powder-dropping funnels. To the pressure-equalizing dropping funnel was added 194 g. (1.16 moles) of freshly-opened reagent bromine; about 500 ml. of reagent carbon tetrachloride (dried over phosphorous pentoxide and distilled, $n_D^{25}$ 1.4573) was added to

Table VI

Trans-1,2-Dibromocyclobutane Preparations

| Trial | Disilver salt, mole | Carbon dioxide liberated, % | Silver bromide recovered, % | Analyzed yield v-p-c, % |
|---|---|---|---|---|
| 1 | 0.0125[a] | -- | 94 | 26 |
| 2 | 0.200[a] | -- | 99 | 28 |
| 3 | 0.284[a,c] | -- | 87 | -- |
| 4 | 0.208[a,d] | -- | 99 | 25 |
| 5 | 0.618[a,d] | -- | 99 | 2.8 |
| 6 | 0.286[b] | 58 | 99.5 | 21[f] |
| 7 | 0.448[b] | 65 | 99 | 21[f] |
| 8 | 0.548[b] | 65 | 98 | 25 |
| 9 | 0.609[b] | 71 | 99.4[e] | 23.6[g] |
| 10 | 0.443[b] | 73 | 99.4[e] | 23.6[g] |
| 11 | 0.400[b] | 70 | 99 | 23.6[g] |

[a]Disilver salt of cis-1,2-cyclobutane dicarboxylic acid. [b]Mixture of disilver cis- and trans-1,2-cyclobutanedicarboxylates. [c]The acid used in trial 3 was obtained from mother liquors of recrystallization. [d]All of the silver salt was added as quickly as possible; the reaction was subsequently heated at the reflux temperature of carbon tetrachloride. [e]Trials 9 and 10 were run consecutively in the same reaction vessel. [f]The reaction products of trials 6 and 7 were combined for distillation. [g]The reaction products of trials 9, 10, and 11 were combined for distillation.

the reaction flask. The carbon tetrachloride was brought to its boiling point, and bromine was added. Disilver 1,2-cyclobutanedicarboxylate was added in small portions; as carbon-dioxide evolution slowed down, more silver salt was added. The bromine was added so that it was always in moderate excess. All of the reactants were added and the reaction was heated until carbon-dioxide evolution ceased. About 65% (corr.) of the theoretical yield of carbon dioxide was collected. The reaction mixture was filtered and the silver bromide precipitate was extracted with carbon tetrachloride in a Sohxlet extractor. Silver bromide (202 g., 98%) was recovered in high yield. The combined carbon tetrachloride solutions were extracted several times with 40% sodium hydroxide solution and water. The solvent was removed through Heli-Pak Column C. Reduced pressure distillation of the products gave 48.0 g. (41%) of crude trans-1,2-dibromocyclobutane (25% yield, v-p-c analyzed, Perkin-Elmer Column A, 170°), b.p. 70-78° (20 mm.) $n^{25}_D$ 1.5360 (lit. (129) b.p. 72-74° (20 mm.), $n^{25}_D$ 1.5352).

The distilled trans-1,2-dibromocyclobutane (132.3 g.) from a number of trials was combined and carefully fractionated through Heli-Pak Column C. The distillation is recorded in Table VII. Fractions 4 and 5 were trans-1,2-dibromocyclobutane of 100% and 97% purity, respectively, as indicated by v-p-c analysis (Perkin-Elmer Column A, 155°).

Table VII

Distillation of Trans-1,2-Dibromocyclobutane

| Fraction | Wt., g. | B.p. | Press., mm. | Bath, temp. | Reflux ratio | $n_D^{25}$ |
|---|---|---|---|---|---|---|
| 1 | 0.65 | 67 | 19 | 78 | 30:1 | 1.5630 |
| 2 | 1.54 | 67 | 19 | 79 | 30:1 | 1.5402 |
| 3 | 10.90 | 71 | 19 | 81 | 30:1 | 1.5369 |
| 4 | 58.2 | 71 | 19 | 81 | 10:1 | 1.5366 |
| 5 | 19.04 | 73 | 18 | 88 | 30:1 | 1.5370 |
| 6 | 22.16 | 79 | 18 | 104 | 30:1 | 1.5464 |
| 7 | 5.44 | 85 | 18 | 114 | 50:1 | 1.5487 |
| 8 | 1.67 | 87 | 18 | 118 | 50:1 | 1.5481 |
| 9 | 6.04 | (residue) | | | | |

The Stability of Trans-1,2-Dibromocyclobutane Under the Hunsdiecker Reaction Conditions. Trans-1,2-dibromocyclobutane (225.9 mg., 0.00105 mole), silver bromide (287.2 mg., 0.00154 mole), bromine (0.30 g., 0.0019 mole), and carbon tetrachloride (5 ml.) were placed in a 50-ml., round-bottomed flask fitted with a reflux condenser. The mixture was heated at the reflux temperature of the solution for 2.0 hr. and 45 min. Trans-1,2-dibromocyclobutane (186.8 mg., 83%) was recovered using the normal Hunsdiecker isolation procedure; the dihalide was homogeneous to v-p-c (Perkin-Elmer Column A, 175°) and was identical in infrared spectrum to the starting material.

Preparation of 1-Bromocyclobutene by the Method of Willstätter. (14). A 25-ml. Erlenmeyer was connected by a short piece of glass

tubing to a flask immersed in a Dry-Ice-acetone slurry; the second flask was in turn connected to a Dry-Ice trap. Finely ground potassium hydroxide (1.73 g., 0.0308 mole) and 0.629 g. (0.00293 mole) of trans-1,2-dibromocyclobutane were blended into a smooth paste in the Erlenmeyer flask, and the flask was lowered into an oil bath maintained at 115°. The reaction was heated at this temperature for 40 min., and any product remaining in the flask or connecting tube was forced over to the collection flask with a gentle flame. The flask containing the reaction products was warmed to room temperature. No gases, condensible at Dry-Ice temperatures, were collected in the second trap. 1-Bromocyclobutene, 0.102 g. (26%) $n_D^{25}$ 1.5035, was obtained. The infrared spectrum of this material revealed that a contaminant was present which absorbed strongly at 1792 $cm.^{-1}$.

The inorganic reaction residue was transferred quantitatively to a 250-ml. volumetric flask, and the bromide ion liberated during the reaction was determined following the Volhard procedure (110). A quantity (141%) in excess of the theoretical amount (based on 1-bromocyclobutene as the sole product) was observed.

1-Bromocyclobutene was prepared in best yield and in high purity using sodium methoxide in diethylene glycol as the dehydrohalogenating reagent. The results of a number of preparations of 1-bromocyclobutene by this method are summarized in Table VIII.

In a 50-ml., round-bottomed flask fitted with a reflux condenser and magnetic stirring bar were placed 13.00 g. (0.0608 mole) of

Table VIII

1-Bromocyclobutene Preparations

| Trial | Dibromide,[a] mole | Base,[b] mole | Reflux time, hr. | Recv'd dibromide, % | Yield, % | Liberated halide,[c] % |
|---|---|---|---|---|---|---|
| 1 | 0.0796 | 0.11 | 5 | 3 | 46 | --- |
| 2 | 0.0876 | 0.132 | 5.5 | 10 | 54 | 114 |
| 3 | 0.140 | 0.420 | 10 | 11 | 56 | 109 |
| 4 | 0.0608 | 0.0912 | 12 | 10 | 48 | 107 |

[a] Trans-1,2-dibromocyclobutane. [b] Sodium methoxide in diethylene glycol. [c] Assuming one mole of bromide is liberated in the reaction.

trans-1,2-dibromocyclobutane, 5.12 g. (0.0912 mole based on a neutralization equivalent of 56.2 g./equiv. wt.) of sodium methoxide, and 25 ml. of diethylene glycol. The reactants were stirred at 115-125° for 12 hr. The reaction products were poured into water, and the resulting mixture was extracted with pentane. The pentane solution was washed six times with water and dried twice over 1-2 g. portions of anhydrous calcium chloride. Most of the pentene was removed using Heli-Pak Column C, while final distillation was carried out through semimicro Column F. 1-Bromocyclobutene (3.61 g., 48%, 98% purity), b.p. 92-95% (745 mm.) (lit. (28) 175° (760 mm., calc.)), was obtained in high purity (v-p-c analysis, Perkin-Elmer Column A, 100°, 175°). The aqueous portion of the reaction products contained 107% of the theoretical bromide ion (Volhard procedure (110)). The 1-bromocyclobutene

redistilled through micro Column G, b.p. 89.5-90.0° (745 mm.), was homogeneous to v-p-c (Perkin-Elmer Column A, 93°), gave a positive test with 1% aqueous potassium permanganate, and gave a negative test with 2% alcoholic silver nitrate solution. The infrared spectrum possessed absorption bands at 1580 $cm.^{-1}$ and 850 $cm.^{-1}$ reasonably associated with a tri-substituted double bond in a four-membered ring (95). The n-m-r spectrum (60 Mc., benzene external standard) showed three distinct absorption signals, vinyl-hydrogen (3.26 p.p.m.) and methylene hydrogens (6.50 p.p.m. and 6.80 p.p.m.). The three signal areas were in ratio of 1:2:2, respectively.

Anal. Calcd. for $C_4H_5Br$: C, 36.12; H, 3.80; Br, 60.09. Found: C, 35.87; H, 3.76; Br, 60.24.

1-Phenylcyclobutanol. In a 200-ml., three-necked, round-bottomed flask fitted with a magnetic stirring bar and pressure-equalizing dropping funnel were placed 22 ml. (0.0286 mole) of 1.30 M phenyllithium (38) solution and 25 ml. of anhydrous ether. Cyclobutanone (1.00 g., 0.0143 mole) in 25 ml. of ether was added dropwise with cooling by an ice bath. The reaction products were poured into water; the ether layer was separated, washed with water, and dried over anhydrous sodium sulfate. Ether and benzene were removed under reduced pressure with a rotary evaporator. The residual material was recrystallized twice from pentane affording 1.88 g. (89%) of 1-phenylcyclobutanol, m.p. 41.2-41.6° (lit. (111) m.p. 38.0-39.0°).

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.01; H, 8.23.

1-Phenylcyclobutene was synthesized by the action of potassium diethylene glycolate on 1-phenylcyclobutyl bromide. Employment of this dehydrohalogenating reagent enabled 1-phenylcyclobutene to be cleanly and easily separated from solvolysis reaction products.

In a 50-ml., round-bottomed flask fitted with a magnetic stirrer were placed 1.50 g. (0.0101 mole) of 1-phenylcyclobutanol and 10 ml. (0.089 mole) of 48% aqueous hydrobromic acid. The mixture was stirred 2.0 hr. at room temperature (24-25°). Methylene chloride and water were added; the methylene chloride phase was separated and dried over anhydrous calcium chloride. The methylene chloride was removed through semimicro Column F.

Potassium diethylene glycolate was prepared by adding (under dry nitrogen) 4.0 g. (0.10 mole) of potassium cut into small pieces to 50 ml. of reagent diethylene glycol. This basic solution was heated to 85° and added to the crude 1-phenylcyclobutyl bromide; the solution was stirred at 85° for 15 min. and poured into water. The reaction products were taken up in pentane; the pentane solution washed several times with water and dried over anhydrous calcium chloride. The dried pentane solution was chromatographed on a column (13 mm. i.d.) of alumina (75 g.), using pentane as an eluent (300 ml.). The pentane was removed through Heli-Pak Column C, and the residue was transferred to a 5-ml., round-bottomed flask and was distilled using Huisgen micro Column E. 1-Phenylcyclobutene (0.525 g., 40%), b.p. 64-68°, $n_D^{25}$ 1.5690 was obtained which was homogeneous to v-p-c (Perkin-Elmer Column C, 165°).

Anal. Calcd. for $C_{10}H_{10}$: C, 92.26; H, 7.74. Found: C, 92.10; H, 7.85.

The ultraviolet spectrum of 1-phenylcyclobutene in cyclohexane had $\lambda_{\text{shoulder}}$ 267 mμ, $\lambda_{\text{max}}$ 257 mμ ($\epsilon$13,100), $\lambda_{\text{shoulder}}$ 250 mμ, $\lambda_{\text{max}}$ 220 mμ ($\epsilon$10,500), $\lambda_{\text{max}}$ 213 mμ ($\epsilon$13,600). The n-m-r spectrum (60 Mc., external standard) was consistent with 1-phenylcyclobutene; it possessed four distinct signal absorptions whose areas were quite compatible with a 5:1:2:2 ratio. The following proton-signal assignments were made: phenyl hydrogen, 2.82 p.p.m.; vinyl hydrogen, triplet (J~1 c.p.s.), 3.91 p.p.m.; methylene hydrogens, 7.43 c.p.s. and 7.70 c.p.s. Infrared absorption bands were present at 1597 $cm.^{-1}$, 1576 $cm.^{-1}$ (conj.), 1492 $cm.^{-1}$, and 1451 $cm.^{-1}$ and are characteristic of a conjugated phenyl group. A weak absorption at 1616 $cm.^{-1}$ was assigned to the phenyl-conjugated, cyclobutene double bond. Conjugated double bonds usually come at 1625 $cm.^{-1}$ and are of enhanced intensity (95). Strong absorption at 1692 $cm.^{-1}$ appears quite anomalous, for it does not arise as an obvious combination and is not a first overtone.

A sample of 1-phenylcyclobutene (0.169 g., 0.00130 mole), b.p. 83-90° (10 mm.), $n_D^{25}$ 1.5712, 10 mg. of 10% palladium on charcoal, and 3 ml. of absolute ethanol were placed in a 50-ml., round-bottomed flask fitted with a magnetic stirring bar. The 1-phenylcyclobutene was hydrogenated. The hydrogenation product was poured into water and taken up in pentane. The pentane solution was washed six times with water and dried over anhydrous calcium chloride. Distillation was

accomplished through micro Column G. 1-Phenylcyclobutane, 0.136 g. (79%), was obtained which was identical in infrared spectrum to an authentic sample.

The Reaction of 1-Bromocyclobutene with Phenyllithium at 135°. In an oven-dried, 500-ml., stainless-steel bomb were placed 17.73 g. (0.133 mole) of 1-bromocyclobutene and 375 ml. (0.405 mole) of 1.08 N phenyllithium solution (38). The bomb was sealed, heated in an oil bath at 135 ± 5° for 2.25 hr., and cooled successively in water, ice water, and Dry Ice-acetone slurry. The top of the bomb was removed, and the bomb immediately fitted with a one-hole rubber stopper which was connected to two Dry-Ice traps and a water-displacement, gas-measuring device placed in series. The steel bomb warmed to room temperature (5.5 hr.); 5-10 ml. of colorless liquid collected in the first trap. This liquid boiled above room temperature and was shown to be ether (v-p-c, Perkin-Elmer Column A, 25°). About 1300 ml. (corr., S.T.P.) of gas was collected. The gas was forced by nitrogen through two wash bottles in series; the first contained 0.4 M ammoniacal silver nitrate solution, and the second contained 10% bromine in carbon tetrachloride. No precipitate was formed in the silver nitrate wash bottle. The carbon tetrachloride solution from the second wash bottle was washed successively with 20% sodium hydroxide solution and water and dried over anhydrous calcium chloride. Analysis of the resulting solution by v-p-c (Perkin-Elmer Column A, 175°, 125°) revealed a peak with a retention time identical to that of ethylene dibromide; no trans-1,2-dibromocyclobutane was present. The carbon tetrachloride was removed

through Heli-Pak Column C leaving ethylene dibromide (9.21 g., 0.049 mole) which was identical in infrared spectrum to an authentic sample. The quantity of ethylene based on the gas collected was 0.058 mole.

The reaction products were removed from the bomb by washing with water and ether. The ether layer was generated and dried twice over anhydrous calcium chloride. Heli-Pak Column A was used to remove the ether (500 ml., reflux ratio 8:1). Final distillation was accomplished through semimicro Column F (Table IX).

Table IX

Distillation

| Fraction | Wt., g. | B.p. | Press., mm. | Pot temp. |
|---|---|---|---|---|
| 1 | --- | 78 | 745 | 85-130 |
| 2 | 0.42 | 73 | 87 | 30-117 |
| 3 | 1.67 | 73-75 | 87 | 117-144 |
| 4 | 0.60 | 75-78 | 87 | 145-175 |
| 5 | 0.94 | 97 | 10 | 175 |
| 6 | 9.45 | (residue) | | |

A small peak with a retention time less than that of ether was observed by v-p-c analysis of the ether that was removed from the reaction mixture. Addition of bromine to the ether solution formed a compound with a v-p-c retention time identical to that of trans-1,2-dibromocyclobutane. Bromine was added to 50 ml. of the ether solution. Having washed the ether solution with dilute sodium hydroxide

and water, it was dried over anhydrous calcium chloride. Distillation of the ether through Column F left 0.20 g. of trans-1,2-dibromocyclobutane which was identified by its infrared spectrum. The total calculated yield of cyclobutene in the ether solution from the distillation was 7.1%.

Fractions 2-5 (Table IX) consisted of benzene, ethylbenzene, and phenylacetylene. The latter two compounds were identified by chromatographing fractions 2-4 on Perkin-Elmer Preparative Column A. Ethylbenzene and phenylacetylene were obtained which were identical in infrared spectra to authentic samples. Quantitative analysis of the distilled fractions by v-p-c (Perkin-Elmer Column A, 130°) showed that 2.00 ± 0.39 g., (15 ± 3)%, of phenylacetylene and 0.82 ± 0.16 g., (1.9 ± 0.4)% (based on phenyllithium), of ethylbenzene were formed.

The distillation residue (9.45 g.) was divided into a pentane-soluble portion (3.64 g.) and a pentane-insoluble portion (5.81 g.). The pentane-soluble fraction was almost wholly biphenyl, contaminated only with small amounts of phenylacetylene and ethylbenzene (infrared; v-p-c, Perkin-Elmer Column C, 175°). The pentane-insoluble fraction was a light-brown amorphous solid which was slightly soluble in ether and very soluble in benzene. The material could not be fractionated on acid-washed chromatographic alumina (pentane). Sodium fusions demonstrated that the pentane-insoluble residue was halogen-free.

Anal. Found: C, 88.30; H, 6.46.

The residue was precipitated from various solvents and examined with a phase microscope; well-defined crystals were not obtained. Precipitation of the residue three times from benzene by adding pentane gave a semi-crystalline, brown solid which softened rather sharply at 180-190° but did not become fluid until 225-230°.

Anal. Found: C, 82.80; H, 5.95.

The infrared spectrum of the recrystallized residue showed absorption bands characteristic of a phenyl group at 1600 $cm.^{-1}$, 1496 $cm.^{-1}$, 1448 $cm.^{-1}$, 756 $cm.^{-1}$, and 700 $cm.^{-1}$ No band was noted at 1580 $cm.^{-1}$ which is definitive for conjugated double bonds. Weak bands were present at 3400 $cm.^{-1}$ and 1700 $cm.^{-1}$ In addition, weak absorptions were noted at 910 $cm.^{-1}$ and 965 $cm.^{-1}$ in the cyclobutane correlation (112) regions. Phenylcyclobutane has absorption bands at 902 $cm.^{-1}$, 916 $cm.^{-1}$, 965 $cm.^{-1}$ Considerable difficulty was encountered in obtaining n-m-r spectra of the residue, for marked signal broadening was observed. The n-m-r spectrum consisted of two broad signal absorptions. The ratio of the areas of these two peaks varied considerably; ratios ranging from 5:4.6 to 5:2.2 were obtained on a number of trials using various solvents and varying concentrations. The sharpest signal (0.300 g./0.75 ml. of carbon tetrachloride, external standard) at 2.7 p.p.m. reasonably represents phenyl hydrogens. The second signal was very broad at $8.3 \pm 1.0$ p.p.m. The region 4.0 - 5.3 p.p.m. showed little or no absorption.

The pentane-insoluble residue was degraded with alkaline

permanganate. In a 50-ml. round-bottomed flask fitted with a reflux condenser and magnetic stirring bar were placed 0.176 g. of residue, 0.1 g. of sodium carbonate, 0.8 g. of potassium permanganate, and 25 ml. of water. The mixture was heated at reflux for 3.5 hr., acidified with 6 N sulfuric acid, and refluxed for 0.5 hr. Excess manganese dioxide was removed by adding sodium bisulfite. The nearly colorless solution was continuously extracted with ether. The ether was removed and the crude acid sublimed affording 32.2 mg. of benzoic acid, m.p. 117-121° (lit. (108) m.p. 122.4°).

Analysis of the aqueous portion of the 1-bromocyclobutene-phenyllithium reaction products revealed that 91.6% of the theoretical quantity of bromide was liberated and a roughly equivalent amount of base was consumed (106%).

The Reaction of 1-Bromocyclobutene and Phenyllithium at 100°. Precisely 15.0 ml. of 0.228 M 1-bromocyclobutene (0.00342 mole) in anhydrous ether and 11.2 ml. of 1.53 M phenyllithium (0.0171 mole, 1.59 M lithium bromide) solution (38) were sealed in an ampule. The ampule was maintained at 100 $\pm$ 0.5° for 145 min. The ampule was cooled, opened, and reaction products were removed by washing with water and ether. The ether phase was separated, washed with water, and dried successively over calcium chloride and Drierite. Most of the ether was removed with semimicro Column F. Final distillation was accomplished with Huisgen micro Column E. Analysis of distilled material (0.52 g., b.p. 50-100°, 10-20 mm.) by v-p-c (Perkin-Elmer

Column A, 167°) showed 0.09 ± 0.04 g., (25 ± 11)%, of phenylacetylene to be present. Ethylbenzene was also present; the phenylacetylene : ethylbenzene ratio was 7.5:1. A number of high-boiling products were noted in chromatographs at high sensitivity, but biphenyl was the only one in significant quantity.

Analysis of the aqueous portion of the reaction mixture revealed that 120% of the theoretical bromide was liberated (Volhard procedure (110)) and 102% base (based on 1-bromocyclobutene) was consumed.

In order to see if phenylacetylene and ethylbenzene were formed by heating phenyllithium solution alone, 25.0 ml. (0.0220 mole) of 0.88 M phenyllithium solution was sealed in an ampule and heated at 100 ± 0.5° for 155 min. The reaction products were examined following the above procedure. A 4% yield of ethylbenzene was formed, but no phenylacetylene was observed. A number of other products were formed in very small yield. Bromide ion (2.3%) was liberated.

The Reaction of 1-Bromocyclobutene and Phenyllithium at 75°.

Following the procedure used at 100°, 0.500 g. (0.00376 mole) of 1-bromocyclobutene and 20.00 ml. (0.0262 mole) of 1.31 M phenyllithium solution (38) were sealed in an ampule and heated at 75 ± 1° for 5.0 hr. Distilled liquid, b.p. 25-80° (34 - 1 mm.), contained 0.104 ± 0.010 g., (27 ± 10)%, phenylacetylene and ethylbenzene in the ratio of 8.0:1, respectively. Biphenyl was the only high-boiling product formed in significant quantity. About 80% of the theoretical halide ion was liberated.

The Reaction of 1-Bromocyclobutene and Phenyllithium at 42°. Following the procedure used at 100°, 0.537 g. (0.00404 mole) of 1-bromocyclobutene and 25.00 ml. (0.0220 mole) of 0.88 M phenyllithium solution were sealed in an ampule and heated at 42 ± 2° for 165 min. The phenylacetylene : ethylbenzene ratio was 11.2:1. Some 1-bromocyclobutene remained unreacted. Biphenyl (0.32 g.) was recovered. Although a number of high-boiling components were formed, none were formed in significant quantity. About 60% of the theoretical amount of bromide ion was liberated.

1-Phenylcyclobutene and Phenyllithium at 53°. 1-Phenylcyclobutene (0.20 g., 0.0015 mole) and 7.2 ml. (0.0045 mole) of 0.626 M phenyllithium solution (38) were sealed in an ampule and heated at 53 ± 1° for 19.0 hr. The contents of the ampule were removed by washing with water and ether. The ether layer was separated, washed with water, and dried over anhydrous calcium chloride. The ether was removed using Huisgen micro Column E, and the residual material was examined by v-p-c (Perkin-Elmer Column A, 166°). A significant amount (50-100% by comparison with the ethylbenzene formed) of the 1-phenylcyclobutene survived the treatment. No phenylacetylene was formed. As a control, 1-bromocyclobutene and phenyllithium were heated at 53 ± 1° for 19.0 hr.; phenylacetylene was formed.

Reaction of Lithium Acetylide, Bromobenzene and Phenyllithium at 75°. The appropriate quantities of lithium acetylide (34), bromobenzene, and phenyllithium (Table X) were sealed in ampules and placed

Table X

Reaction of Lithium Acetylide, Bromobenzene, and Phenyllithium

| Bromobenzene | | Lithium acetylide | | Phenyllithium 0.90 M | | Peak heights of products | | |
|---|---|---|---|---|---|---|---|---|
| g. | mmole. | g. | mmole. | ml. | mmole. | benzene | bromo-benzene | ethyl-benzene |
| 1.0 | 6.37 | 0.40 | 12.5 | 0 | 0 | 0 | 200 | 0 |
| 1.0 | 6.37 | 0.40 | 12.5 | 14.2 | 12.7 | 560 | 85 | 0.5 |
| 1.0 | 6.37 | 0.40 | 12.5 | 21.2 | 19.1 | 1088 | 58 | 0.5 |
| 0.20 | 1.27 | 0.40 | 12.5 | 21.2 | 19.1 | 640 | 6 | 0.5 |
| 0.20 | 1.27 | 0.40 | 12.5 | 35.4 | 31.8 | 1600 | 5 | 1.5 |
| 0 | 0 | 0.40 | 12.5 | 35.4 | 31.8 | 1792 | 1.5 | 2.5 |

in a thermostated oil-bath at 75 $\pm$ 1° for 5.0 hr. The ampules were opened and decomposed with water. The ether layer was separated and made up to 25.0 ml. with additional ether; the solutions were subjected to v-p-c analysis (Perkin-Elmer Column A, 165°). The observed peak heights of benzene, bromobenzene, and ethylbenzene for a 50 microliter sample injection are reported in Table X. No phenylacetylene was observed in any of the trials. Lithium acetylide which was prepared by passing acetylene into a phenyllithium solution was no more effective in attempts to form phenylacetylene from lithium acetylide, bromobenzene, and phenyllithium.

# PART II

## THE COUPLING REACTION OF PHENYLLITHIUM AND CYCLOPROPYL CHLORIDE AND THE ACTION OF STRONG BASES ON 1-BROMOADAMANTANE

# INTRODUCTION

Nucleophilic substitution reactions of cycloalkyl derivatives have been carefully studied in recent years (56). Table XI summarizes the changes in reactivity observed with variation in ring size in typical nucleophilic substitution reactions.

For solvolytic reactions in simple cycloalkyl systems ( R = H ) the order of reactivity is cyclobutyl > cyclopentyl > cyclohexyl >> cyclopropyl; on the other hand, for the solvolyses of 1-methylcycloalkyl chlorides and the action of lithium iodide on cycloalkyl bromides in acetone, the sequence cyclopentyl > cyclohexyl > cyclobutyl >> cyclopropyl holds. These studies amply demonstrate that cyclopropyl halides and sulfonate esters are exceptionally inert toward direct nucleophilic substitution relative to acyclic models, being less reactive by a factor $10^{-4}$ - $10^{-6}$.

Gustavson (57) noted as early as 1891 that cyclopropyl chloride was inert toward hot alcoholic potassium hydroxide and was comparable in reactivity to 1-chloropropene. Roberts and Chambers (58) report that no reaction can be detected between potassium iodide and cyclopropyl bromide at 100° or with cyclopropyl chloride at 200° in acetone. In interpreting the extreme unreactivity of cyclopropyl systems, analogy to vinyl and phenyl systems has been made (58). In this respect both theoretical studies (59) and a host of physical measurements on

Table XI

Relative Reactivities of Cycloalkyl Systems

in Nucleophilic Displacement Reactions

| $(CH_2)_{n-1}CRX$ | R=H, X=OTs | R=H, X=Cl | $R=CH_3$, X=Cl | $R=CH_3$, X=Br | R=H, X=Br |
|---|---|---|---|---|---|
| | $CH_3COOH$ | $50\%C_2H_5OH$ | $50\%C_2H_5OH$ | $50\%C_2H_5OH$ | LiI, Acetone |
| | 60° | 95° | 30° | 130° | 25° |
| n = | (58, 56a) | (58, 56a) | (56d, 62) | (56d) | (90, 58, 56a) |
| $(CH_3)_2CRX$ | 1.00 | 1.00 | 1.00 | 1.00[c] | 1.00 |
| 3 | $2 \times 10^{-5}$ | 0.005 | $2 \times 10^{-6}$ | $1.2 \times 10^{-6}$ | $1 \times 10^{-4}$[b] |
| 4 | 12 | 15 | 0.074 | 0.25 | 0.0075 |
| 5 | 14 | 5.2 | 41[a] | --- | 1.6 |
| 6 | 0.88 | 0.36 | 0.35[a] | --- | 0.010 |

[a]Calculated values utilizing activation parameters (62) and the Grunwald-Winstein equation (89) assuming m = 1.113 (same as for t-butyl chloride in this system (56d, 62)). [b]Estimated upper limit (56a). [c]t-Butyl bromide rate constant at 130° calculated from data of Cox (56d).

cyclopropane and its derivatives (60, 61, 56) reveal that the cyclopropane ring atoms possess greater electronegative character than normal tetrahedral carbon atoms. Brown has rationalized the chemical reactivity of alicyclic systems in terms of the I-strain concept (62).

Slabey (63) observed Wurtz coupling in the reaction of cyclopropyl chloride with lithium in ether. In addition to a 10-12% yield of bicyclopropyl, other products obtained were cyclopropane (42%, 32% obtained prior to decomposition of the reaction mixture), unreacted cyclopropyl chloride (21%), olefins, acetylenes, and tar.

Two general mechanisms have been suggested for the Wurtz reaction (64). In the first mechanism, alkali metal reacts with the alkyl halide to form free radicals, which may couple or disproportionate. The second mechanism visualizes the preliminary formation of an alkylmetallic compound, which subsequently couples with remaining halide. Both homolytic and heterolytic routes have been suggested for the final coupling step (64, 47).

Cyclopropyl radicals have been observed in the vapor-phase chlorination (65) and nitration (66) of cyclopropane, the Kolbe electrolysis of potassium cyclopropanecarboxylate (67), the photolysis of methyl cyclopropyl ketone (68), the thermal decomposition of the peroxide of cyclopropanecarboxylic acid (69), and probably the formation of cyclopropyl bromide via the Hunsdiecker reaction (70). Trotman-Dickenson and Steacie (71) and McNesby and Gordon (72) have conducted quantitative hydrogen-atom abstraction studies with various hydrocarbons

using methyl radicals, and they find that it is nearly as difficult to remove a hydrogen atom from cyclopropane as from benzene. At low temperatures the products derived from cyclopropyl radicals are not generally rearranged (65, 66, 68, 70). It seems reasonable, therefore, that the known chemical nature of the cyclopropyl radical would not prevent its entering into a Wurtz reaction forming bicyclopropyl.

Recently there has been an increasing amount of experimental evidence and discussion which favors the non-radical coupling process as the exclusive mechanism for the Wurtz reaction in solution (47, 64, 73, 74), although radicals may be involved as transient intermediates in the formation of the organometallic intermediate (64, 75). It has been stated (73) that the reactions of organoderivatives of the alkali metals proceed almost exclusively by polar mechanisms in solution. The main exceptions are the redox reactions of organoalkali compounds in the presence of various salts such as cobaltous bromide (73).

If radical coupling processes can be eliminated, the Wurtz coupling observed by Slabey would involve the reaction of cyclopropyllithium with cyclopropyl chloride via a polar course. Owing to the relatively poor nucleophilicity expected of cyclopropyllithium and the inertia of cyclopropyl chloride toward direct nucleophilic substitution processes, it seems unlikely that coupling takes place by an $S_N1$ or $S_N2$ reaction. Of the alternative mechanistic routes of coupling, elimination-addition is particularly reasonable.

Ingold (76) observed in 1921 that 1-bromo-1,2-cyclopropanedicarboxylic acid did not afford silver bromide upon boiling with silver nitrate and nitric acid. He states that unusually high temperatures were required to precipitate silver bromide; on the other hand, boiling with 2 N sodium carbonate solution or concentrated aqueous-methanolic potassium hydroxide solution gave 1-hydroxy-1,2-cyclopropanedicarboxylic acid or a mixture of the hydroxydicarboxylic acid and 1-methoxy-1,2-cyclopropanedicarboxylic acid, respectively. Ingold did not comment on the mechanistic course of the reaction, but it would seem probable that it occurs via the elimination-addition mechanism. Wiberg recently determined that ethyl trans-2-bromocyclopropanecarboxylate is converted exothermically to ethyl trans-2-t-butoxycyclopropanecarboxylate by potassium t-butoxide in t-butyl alcohol by the elimination-addition mechanism (77). Under the reaction conditions potassium t-butoxide does not react with isopropyl bromide; furthermore, the bromo ester failed to react with either sodium iodide in acetone or alcoholic silver nitrate solution.

These reactions amply demonstrate that nucleophilic substitution can occur in cyclopropyl systems by way of elimination-addition. Nevertheless, it is difficult to assess the likelihood of substitution occurring via the elimination-addition mechanism in non-activated cyclopropyl halides. Two rather obvious factors should govern the facility with which an elimination-addition course is followed. First, systems which favor elimination should favor the elimination-addition mechanism. The

effect of the structure of the halide, nature of the base and the solvent, stereochemistry, and temperature are important in this respect and have been discussed at length (78). Relevant data pertaining to elimination reactions in non-activated cyclopropyl halides is very limited and was discussed above under direct nucleophilic substitution. A number of related investigations yield information concerning the difficulty of introducing a double bond into a cyclopropane ring. Cyclopropene has been prepared via the Hofmann elimination, but unusually high temperatures (330-350°) were required (79). Both unfavorable stereochemistry with respect to elimination and internal ring strain in cyclopropene are probable factors contributing to the stability of 1,2-diiodocyclopropane (79b) and the inability of 1,2-dibromocyclopropane to eliminate bromine when treated with zinc (79a). In general, elimination reactions involving non-activated cyclopropyl halides appear energetically quite difficult and probably require forcing elimination conditions.

The second factor in assessing the likelihood of cyclopropyl systems to undergo substitution via the elimination-addition mechanism is the ability of the intermediate cyclopropene to add nucleophilic reagents. It would be expected that cyclopropenes which can undergo Michael-type addition should add nucleophiles readily. The addition of potassium t-butoxide to ethyl cyclopropenecarboxylate testifies to this, but assessing the ease with which a non-activated cyclopropene adds nucleophiles is

a more difficult question. Wiberg (80) obtained only polymer while trying to add potassium t-butoxide to cyclopropene. The conditions under which this reaction was carried out were not stated. It is well known that the addition of most nucleophilic reagents to non-activated carbon-carbon double bonds is very difficult (47); however, the addition of organolithium compounds to unactivated double bonds has been reported. Ziegler and Gellert (49) found that n-butyllithium adds to ethylene at room temperature at 100 to 500 atmospheres, while Bartlett (48) reports that i-propyllithium and t-butyllithium avidly absorb ethylene in ether even at -50°.

Having discussed elimination-addition reactions in cyclopropyl systems in general, it is interesting to note two rather remarkable aspects concerning the reaction of potassium t-butoxide with ethyl trans-2-bromocyclopropanecarboxylate. In view of the difficulty of introducing a double bond into a three-membered ring and the fact that the reaction involves a cis elimination, it is evident that the carbethoxy group enhances the reactivity of this bromide significantly. Such an enhancement is not altogether expected, since there is evidence that this and other activating groups have little influence on the reactivity of cyclopropanes. For example, the acidity of nitrocyclopropane is low (66); sodium amide and sodium triphenylmethide react at the carbonyl group rather than the α-hydrogen in ethyl cyclopropanecarboxylate (81); further, ethylmethylacetonitrile racemizes almost eighty-eight times faster than does 2,2-diphenylcyclopropyl cyanide in sodium methoxide

in methanol (82). Secondly, the final step in the formation of ethyl trans-2-t-butoxycyclopropanecarboxylate, Michael addition to the cyclopropene intermediate, might be expected to be less facile owing to the diminished stabilization offered by the carbethoxy group (i.e., the conjugated cyclopropyl carbanion is of higher energy owing to I-strain). This effect may be more than compensated for by the relief of internal strain, and the addition step could be highly exothermic. If such were the case, it would provide a very reasonable interpretation of the overall energetics of the substitution reaction.

When organolithium compounds are employed as nucleophilic reagents, halogen-metal interconversion may afford a low-energy path to coupling. Interconversion would be expected to be quite important when cyclopropyl bromides and iodides are employed (38). Walborsky and Impastato (83) have recently obtained interconversion with a cyclopropyl bromide and butyllithium. Other factors influencing halogen-metal interconversion have been discussed elsewhere (38, 37). Accordingly, if halogen-metal interconversion can occur with facility and if the products couple readily, then interconversion could provide a low-energy path to coupling products.

Coupling by way of the elimination-addition mechanism may provide a practical route for nucleophilic substitution in non-activated cyclopropyl halides. To explore this possibility, the reaction of cyclopropyl chloride with phenyllithium has been studied.

Substitution reactions at the bridgeheads of polycarbocyclic systems have been reviewed (84) recently and will not be discussed in detail here. Some essential points will be noted, however. Since bimolecular nucleophilic displacements occur with Walden inversion, they have not been observed at bridgeheads (84a, 85). In $S_N1$ reactions (solvolyses) bridgehead halides react only with great difficulty. The inertia of these systems has been attributed to the instability of the tetrahedral carbonium ion, which has been estimated to be 22-24 kcal./mole greater than the planar carbonium ion (85, 86). In most polycarbocyclic compounds the bridgehead carbon atom is held rigidly in a tetrahedral position. The carbonium ions derived from such rigidly held centers thus possess great instability. As the bridgehead becomes more flexible, however, increased solvolytic activity is observed (84). 1-Bromoadamantane, for example, gives an immediate precipitate with alcoholic silver nitrate and differs in rate from t-butyl bromide by only a factor of three thousand (87), which is quite remarkable for a bridgehead halide. Steric inhibition of solvation of the incipient carbonium ion may also be important (85, 86).

Homolytic and electrophilic reactions proceed with greater ease at bridgeheads than do carbonium ion reactions (74). Thus free-radical and electrophilic substitution reactions are relatively favored. The significance of this has been discussed (74).

Considerable interest attends the possibility of obtaining substitution products via the elimination-addition mechanism with bridgehead

halides. Such a mechanism requires the introduction of a double bond at a bridgehead, which formally violates Bredt's Rule. The application and extension of Bredt's Rule to transient reaction intermediates has been discussed (88). Viewing the remarkable solvolytic reactivity of 1-bromoadamantane, it appeared that its large, flexible frame might also be capable of forming a double bond to the bridgehead. Attempts were made, therefore, to effect substitution of this bromide under vigorous elimination conditions.

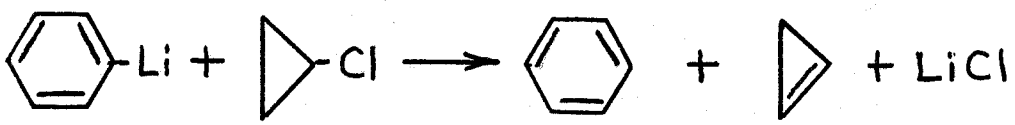
## RESULTS AND DISCUSSION

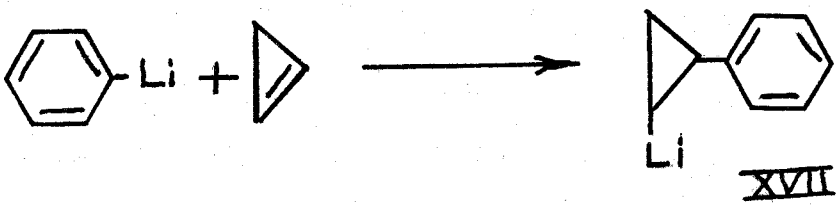
Cyclopropyl chloride was prepared in 47% yield by the photochlorination of cyclopropane. A 5.5% yield of 1, 1-dichlorocyclopropane was obtained as a by-product.

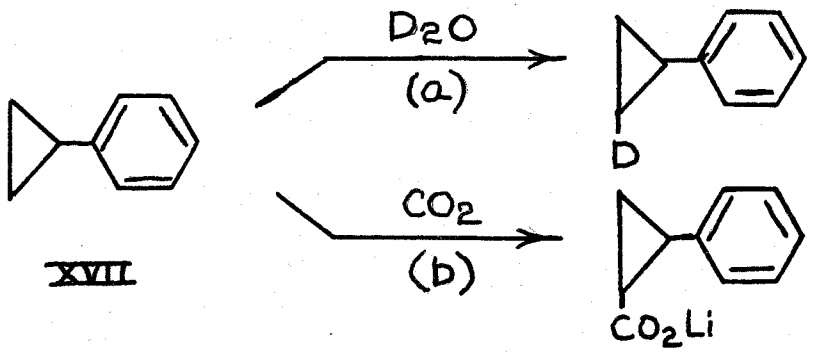
Phenyllithium and cyclopropyl chloride were heated under reflux in ether for 35 hr. and afforded a (10 ± 2)% yield of phenylcyclopropane. A similar reaction was conducted in the presence of piperidine to see if an increased yield of coupled product could be obtained. Piperidine is known to produce a dramatic increase in the yield of coupled product in substitution reactions which follow the elimination-addition mechanism (21, 34). A (15 ± 2)% yield of phenylcyclopropane was found. The observed increase in coupled product is not nearly as large as that observed for chlorobenzene (21, 34). Additional studies would be necessary to determine the magnitude of the catalytic effect or whether an effect even exists.

Having established that coupling can occur between an organolithium compound and a cyclopropyl halide, an attempt was made to demonstrate that the observed substitution reaction between cyclopropyl chloride and phenyllithium occurred via the elimination-addition mechanism. Assuming that the reaction proceeds by elimination-addition [27, 28], one-half of the reaction products were decomposed with deuterium oxide [29a] and one-half with a carbon-dioxide slurry in ether

[29b]. It was hoped that the 2-phenylcyclopropyllithium (XVII) resulting from the addition step [28] could be detected in this manner. Phenylcyclopropane was obtained in 5.0% yield from the portion decomposed with deuterium oxide. It did not differ significantly in infrared spectrum from an authentic sample of phenylcyclopropane. A quantity of benzoic acid accounting for 19.2% of the original phenyllithium was the sole acidic product of the carbonation reaction.

[27] 


[28] 


[29] 

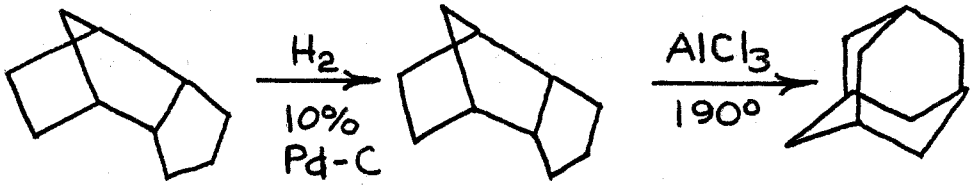

The low yield of benzoic acid seems explicable only by assuming that a corresponding amount of phenyllithium was present at the end of

the reaction, since the carbonation of phenyllithium is known to proceed in high yield (47). In addition to reacting with cyclopropyl chloride, phenyllithium could conceivably be used up by ether cleavage and by reaction with moisture or oxygen which leaked into the system. Since the reaction was conducted under dry nitrogen, loss of a large portion of phenyllithium by reaction with external water and oxygen is not very probable, but it cannot be rigorously ruled out. More likely the observed low yield of benzoic acid resulted from reaction of phenyllithium with the solvent (47). If, in fact, the loss of phenyllithium was predominantly by this course, even greater loss of the 2-phenylcyclopropyllithium would be expected. Such a conclusion follows from the fact that the carbon-hydrogen bonds of a cyclopropane ring are intermediate in bonding character between the carbon-hydrogen bonds of saturated and olefinic carbon; additionally, it is well known that organolithium compounds derived from saturated hydrocarbons react much faster with ether than does phenyllithium (47). Cleavage of ether by cyclopropyllithium has been observed (63).

The possibility of extensive ether cleavage by the 2-phenylcyclopropyllithium prevents a unique interpretation of this experiment. It would be advisable in subsequent work to use a hydrocarbon solvent in place of ether in order to prevent reaction of the organolithium compounds with the solvent. However, phenyllithium cannot be used in a hydrocarbon solvent; an alkyllithium compound would have to be used in its place.

In summary, it has been established that coupling does occur between phenyllithium and cyclopropyl chloride. Although an attempt to establish elimination-addition as the coupling mechanism was unsuccessful, information was obtained which may prove valuable in designing future experiments.

Adamantane (XX) was synthesized by the remarkable rearrangement reported by Schleyer (120) [30]. Hydrogenation of dicyclopentadiene

[30] 

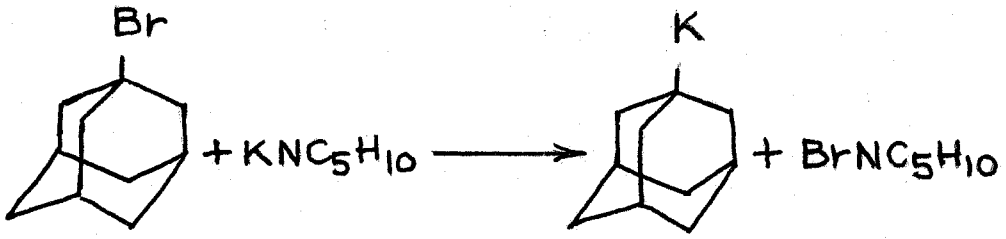

XVIII XIX XX

(XVIII) afforded excellent yields of endo-trimethylenenorbornane (XIX). Adamantane was prepared in 20.4% yield by vigorously boiling the latter compound in the presence of 10% of its weight of anhydrous aluminum chloride for 18 hr. A 55% yield of 1-bromoadamantane was obtained by the bromination of adamantane.

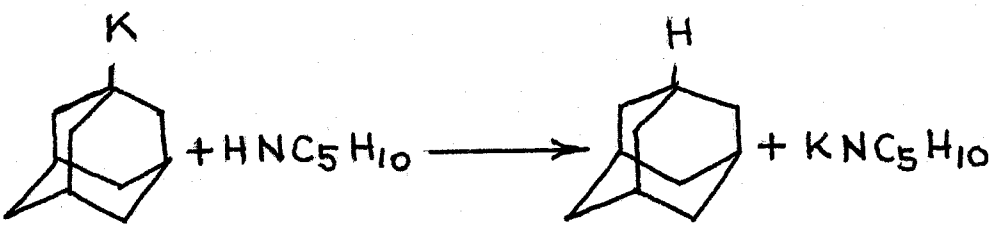
1-Bromoadamantane was stirred for 3 hr. with four times its molar equivalence of potassium amide in liquid ammonia. About 81% of the 1-bromoadamantane was recovered unchanged. No evidence was obtained to suggest that the bromide had reacted to any significant extent.

These results indicate that more vigorous conditions are necessary to obtain reaction. Bunnett (121) reports that sodium piperidide in refluxing piperidine is an exceptionally potent reagent for affecting aromatic nucleophilic substitution. The action of potassium piperidide in refluxing piperidine on 1-bromoadamantane was investigated. The sole product of the reaction was an 89% yield of adamantane. Reduction of halides by this reagent is not without precedent (121, 122). Reduction probably occurs via halogen-metal interconversion [31a] followed by reduction of the bridgehead compound by the solvent [31b]. Halogen-metal inverconversion at a bridgehead carbon atom has been observed (123).

[31a]




[31b]



## EXPERIMENTAL(91)

Cyclopropyl Chloride. An assembly similar to that described by Roberts and Mazur (124) for the vapor-phase chlorinating of cyclobutane was used for the chlorination of cyclopropane. A total of 222.0 g. (5.28 moles) of cyclopropane was chlorinated in five separate trials.

In a typical experiment about 40 g. of Matheson cyclopropane was condensed in a 100-ml. flask cooled to Dry-Ice temperature. The reaction chamber was illuminated with an ultraviolet lamp (Keese Engineering Company) and the chlorine flow was maintained at 0.16 g./min. as measured by a Matheson Universal Flowmeter, Model No. 102. The chlorination was allowed to proceed until the boiling point of the hydrocarbon-chloride mixture approached room temperature. About 8 hr. were required to complete the run.

The combined chlorination products were distilled through spinning-band Column B (Teflon band, 1800 r.p.m.). The yield of cyclopropyl chloride was 148.5 g. (36.7%), b.p. 42.5-43° (745 mm.), $n^{25}D$ 1.4088 (lit. (65) b.p. 43°, $n^{20}D$ 1.4101). 1,1-Dichlorocyclopropane, 32.4 g. (5.5%), b.p. 74-75° (745 mm.), $n^{20}D$ 1.4400 (lit. (65) b.p. 74-75°, $n^{20}D$ 1.4400) was obtained as a by-product.

The Coupling Reaction of Phenyllithium and Cyclopropyl Chloride. In a 500-ml., three-necked, round-bottomed flask fitted with a reflux condenser, pressure-equalizing dropping funnel, and a nitrogen inlet

was placed 165 ml. (0.225 mole) of 1.37 M phenyllithium (38) in anhydrous ether. A positive dry-nitrogen atmosphere was maintained within the flask during the reaction using a mercury pressure valve (125).

Cyclopropyl chloride, 7.65 g. (0.100 mole), in 50 ml. of anhydrous ether was added slowly. Immediate reaction was not observed, and the remaining chloride was added. The reaction was refluxed for 35 hr., and the products of the reaction were poured onto 100 g. of ice. The ether layer was separated and dried over anhydrous sodium sulfate.

The ether was removed utilizing Column C. The remaining 40 ml. of solution was fractionally distilled through the spinning-band Column H (1200 r.p.m.). Fractions containing more than a single component were analyzed using vapor-phase chromatography (Perkin-Elmer Column A). Phenylcyclopropane, 1.21 g. (12%), was obtained. The main fraction b.p. 55-60° (9 mm.), $\underline{n}^{25}_{D}$ 1.5328 (lit. (126) b.p. 60-63° (11 mm.), $\underline{n}^{25}_{D}$ 1.5320) was contaminated with a small amount of bromobenzene. Phenylcyclopropane was identified by comparison of its infrared spectrum with that of an authentic sample prepared by the method of Simmons and Smith (127). Cyclopropyl chloride (2.3 g., 0.030 mole, 30%), benzene (20.9 g., 0.26 mole), bromobenzene (0.75 g., 0.005 mole), and biphenyl (4.8 g., 0.031 mole) were also obtained.

The Coupling Reaction of Phenyllithium and Cyclopropyl Chloride in the Presence of Piperidine. A mixture of 385 ml. (0.500 mole) of 1.30 M phenyllithium solution (38), 13.8 g. (0.180 mole) of cyclopropyl

chloride, 6.8 g. (0.080 mole) of redistilled piperidine and 100 ml. of anhydrous ether were placed in a 1-ℓ., three-necked, round-bottomed flask fitted with a reflux condenser and dry-nitrogen inlet. This solution was refluxed for 12 hr. More piperidine, 3.4 g. (0.040 mole), was added and the solution was heated for another 12 hr. The reaction mixture was poured into 200 ml. of water, and the ether layer was separated. The basic components of the reaction mixture were removed by extraction with 6 N hydrochloric acid, and the ether solution was dried over anhydrous calcium chloride.

The reaction mixture was fractionally distilled and analyzed as described previously, and 3.22 ± 0.36 g., (15 ± 2)%, of phenylcyclopropane was obtained. The main fraction had a boiling point 58-66° (10 mm.), $n^{25}_D$ 1.5298 (lit. (126) b.p. 60-63° (11 mm.), $n^{25}_D$ 1.5320; $n^{25}_D$ 1.5309 (127), and was at least 95% pure as estimated by v-p-c.

Phenylcyclopropane Formation. Attempted Detection of 2-Phenylcyclopropyllithium. A solution of 333 ml. (0.399 mole) of 1.20 M phenyllithium solution (38) and 13.8 g. (0.18 mole) of cyclopropyl chloride were placed in a 1-ℓ., three-necked, round-bottomed flask fitted with a reflux condenser and a dry-nitrogen inlet. The solution was maintained at reflux for 19 hr.

One-half of the reaction mixture was decomposed by the slow addition of 4.96 g. (0.275 mole) of deuterium oxide (99.8% deuterium) with stirring. Additional common water was then added. The ether layer was separated, dried over anhydrous calcium chloride, and distilled

using spinning-band Column B (Teflon band, 1800 r.p.m.). Phenylcyclopropane, 0.53 g. (5.0%), b.p. 40-60° (5-12 mm.), $n^{25}D$ 1.5295-1.5296 (lit. (126) b.p. 60-63° (11 mm.), $n^{25}D$ 1.5320; $n^{25}D$ 1.5309 (127)), was obtained. The infrared spectrum and n-m-r spectrum (40 Mc.) of this material did not differ significantly from the appropriate spectra of non-deuterated phenylcyclopropane.

The second half of the reaction mixture was added with stirring to a slurry of powdered Dry-Ice and ether. Water was then added and the ether layer separated. The aqueous layer was acidified and continuously extracted with ether. Evaporation of the ether extract afforded 4.68 g. (19.2% based on phenyllithium) of a tan solid, m.p. 101-117°, that possessed an infrared spectrum nearly identical to that of benzoic acid.

Endo-Trimethylenenorbornane was prepared by the catalytic hydrogenation of dicyclopentadiene (128). Ten percent palladium on charcoal (129) was used as the catalyst and absolute ethanol as the solvent. A total of 278.5 g. (2.10 mole) of dicyclopentadiene was hydrogenated affording 235.2 g. (84%) of endo-trimethylenenorbornane, m.p. 76.5-77° (lit. (128) m.p. 77°).

Adamantane was prepared by the general procedure reported by Schleyer (120). One hundred grams (0.735 mole) of endo-trimethylenenorbornane and 10 g. of reagent anhydrous aluminum chloride were refluxed (about 190-200°) for 18 hr. in a 300-ml., three-necked, round-bottomed flask fitted with a reflux condenser and mechanical stirrer.

Two layers formed as the reaction vessel was cooled to room temperature. The upper, clear layer was poured off. The black, viscous, lower layer was placed in a Soxhlet extractor and extracted for about 12 hr. with ligroin, b.p. 60-70°. The ligroin was removed using Column C, and the residue was combined with the upper layer of the reaction mixture.

The combined reaction products were cooled to Dry-Ice temperature. A solid crystallized, and 17.2 g. of a tan solid was obtained by filtering. An additional 6.4 g. of crude material was obtained by distilling the mother liquor from the cooling step, collecting the fraction boiling 185-200°, and repeating the cooling procedure with this distilled fraction. Fractional sublimation (70°, 745 mm.) followed by recrystallization of the crude adamantane from methanol gave 20.4 g. (20.4%) of adamantane, m.p. 269.2-270.2° (sealed ampule), (lit. (120) m.p. 269.6-270.8°).

1-Bromoadamantane was prepared by the method of Landa (130). Adamantane, 1.50 g. (0.0110 mole), and 3.6 ml. (11.2 g., 0.070 mole) of bromine were heated in a sealed tube at 100° for 2 hr. The reaction mixture was dissolved in 30 ml. of carbon tetrachloride, washed successively with water and sodium sulfite solution, and dried over anhydrous calcium chloride. The carbon tetrachloride was removed using Column D. Sublimation of the residue (1.62 g.) gave 1.30 g. (55%) of 1-bromoadamantane, m.p. 118.6-119.4° (lit. (130) m.p. 119.5-120.0°).

Treatment of 1-Bromoadamantane with Potassium Amide. Anhydrous liquid ammonia (350 ml.) was poured into a 500-ml., three-necked, round-bottomed flask fitted with a Dry-Ice condenser and mechanical stirrer. About 10 mg. of anhydrous ferric chloride was added. Potassium, 0.70 g. (0.0179 mole), was cut into small pieces and added to the liquid ammonia. To the resulting potassium amide solution was added 0.809 g. (0.00376 mole) of 1-bromoadamantane, and the solution was stirred for 3 hr. Ammonium chloride, 12.0 g. (0.0225 mole), was added to decompose unreacted potassium amide, and the ammonia was allowed to evaporate.

The reaction flask was washed with carbon tetrachloride and dilute base. The organic layer was separated, dried over anhydrous sodium sulfate, and the carbon tetrachloride was removed using Column D; 0.65 g. of solid remained. Sublimation of this material afforded 0.59 g. of white solid, m.p. 110.0-116.6°. Analysis of this material by v-p-c (Perkin-Elmer Column C) showed that it was identical to the starting material. Additionally, the infrared spectrum of the recovered 1-bromoadamantane was identical to that of the starting material.

Reaction of 1-Bromoadamantane with Potassium Piperidide. Fifty milliliters of anhydrous liquid ammonia was poured into a 100-ml., three-necked, round-bottomed flask fitted with a glass mechanical stirrer and Dry-Ice condenser. A few mg. of anhydrous ferric chloride and 2.00 g. (0.051 mole) of potassium (cut into small pieces) was added to the liquid ammonia.

Piperidine (20 g.) was added and the liquid ammonia evaporated under a stream of dry nitrogen. The Dry-Ice condenser was replaced with a reflux condenser. 1-Bromoadamantane, 1.000 g. (0.004165 mole), was added and the solution refluxed for 13 hr. under nitrogen. Unreacted potassium piperidide was decomposed by adding 5.4 g. (0.10 mole) of anhydrous ammonium chloride.

The reaction mixture was taken up in benzene and water. The organic phase was separated, washed with dilute acid, and dried over anhydrous calcium chloride. The acid extract was combined with the original aqueous layer.

Analysis of the benzene solution revealed, in addition to the solvent, a single compound with a retention time identical to that of adamantane. Most of the benzene was removed using Column C. The remaining solvent was taken off in a sublimation apparatus under reduced pressure (25°, 20 mm.).

A white solid, 0.505 g., m.p. 155-165°, was obtained by sublimation (70°, 745 mm.). This material possessed an infrared spectrum identical with that of adamantane (130). Recrystallization from pentane-ethanol gave white crystals, m.p. 269.8-270.2° (lit. (120) m.p. 269.6-270.8°). The yield of adamantane based on sublimed material was 89%.

The aqueous portion containing the basic component(s) of the reaction mixture was made strongly alkaline and continuously extracted with ether. The ether extract was subjected to analysis by vapor-phase chromatography, but only piperidine and ether could be detected.

# APPENDIX

## SPECIAL EQUIPMENT AND SERVICES

A. Analyses were performed by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, California.

B. Infrared absorption spectra were determined using a Perkin-Elmer double-beam infrared spectrometer, Model 21.

C. Ultraviolet absorption spectra were obtained using a Cary recording spectrophotometer, Model 11 M.

D. Nuclear magnetic resonance (n-m-r) spectra were taken at 60 Mc. on a Varian Model V4300D spectrometer equipped with Super Stabilizer, constant-temperature magnet cooling, and field homogeneity control coils. Chemical shifts were measured by means of a Hewlett-Packard Model 200 AB audio-oscillator and Model 521 C frequency counter. Chemical shifts are quoted as tau-values in parts per million (p.p.m.) relative to tetramethylsilane as an internal standard, unless otherwise stated.

E. Vapor-phase chromatographs were obtained with either a Perkin-Elmer Vapor Fractometer, Model 154-B, or an F & M Model 202A Gas Chromatograph. The columns for the Perkin-Elmer Vapor Fractometer were made of stainless steel and were 2.0 m. in length (6.3 mm. o.d.). The solid phase was unspecified. Column A had diisodecyl phthalate as the liquid phase, and Column C had DC-200 silicone oil (dimethyl siloxane polymer) as the liquid phase. The F & M Chromatograph column was made of stainless steel and was 1.3 m. in length (4.8 mm. i.d.). The packing was silicone rubber.

F. Distillation Columns.

Column A was an 80 cm. (13 mm. i.d.) column fitted with a magnetic-take off distillation head and a heating jacket. The column was packed with 1.3 x 2.5 x 2.3 mm. Heli-Pak packing.

Column B was a 61 cm. Precision Distillation Company (Santa Monica, California) spinning-band column (10 mm. i.d.).

Column C was a 20 cm. (13 mm. i.d.) column fitted with a variable-reflux distillation head and a heating jacket. The column was packed with 1.3 x 2.5 x 2.3 mm. Heli-Pak packing.

Column D was a modified Claisen head with a 10 mm., heated Vigreux column.

Column E was a Huisgen micro molecular distillation apparatus. It consisted of two S-shaped, standard-taper sections which were connected in series to a 5-ml., round-bottomed flask.

Column F was a semimicro column similar to that of C. W. Gould, Jr., G. Holzman and C. Niemann, Anal. Chem., 20, 361-363 (1948).

Column G was a 0.2-ml. micro-distillation column similar to that of L. C. Craig, Ind. Eng. Chem., Anal. Ed., 8, 219-220 (1936).

Column H was a 25 cm. (6 mm. i.d.) spinning-band column with a stainless-steel gauze band.

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# PROPOSITIONS

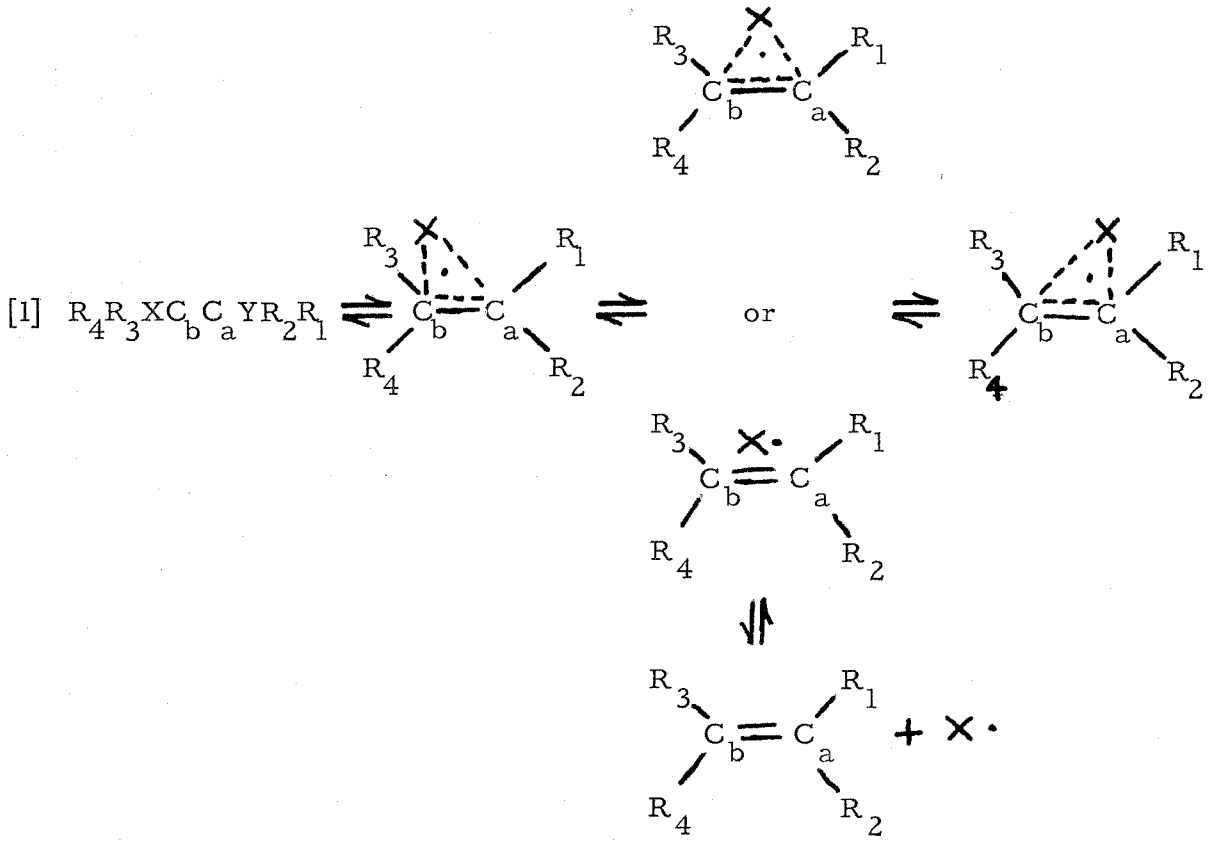
1. Phenylacetylene and cyclobutene are included in the products of the reaction of 1-bromocyclobutene and phenyllithium (1). The mechanism of this unusual phenylacetylene-forming reaction has been investigated briefly, and a few possible mechanistic routes have been eliminated (1). A series of experiments, based on the probable ways that 1-bromocyclobutene and phenyllithium might react, is proposed to study this reaction further.

2. Huisgen (2) has suggested that the selectivity of various arynes in competing for phenyllithium and lithium piperidide is a measure of their "hotness." The selectivity of cyclohexyne and cyclopentyne toward these nucleophiles should be determined. In addition to indicating the stability of cyclohexyne and cyclopentyne relative to benzyne, the selectivities could be valuable in assessing the likelihood of substitution occurring via the elimination-addition mechanism in cyclobutenyl halides.

3. There is an appreciable energy barrier to inversion in aziridines and cyclopropyl "carbanions" (3). A similar barrier to inversion has been predicted for the cyclopropyl radical (3c). Theoretical studies have concluded that the methyl radical should be pyramidal, at least in the ground state (4). Electron paramagnetic resonance (EPR) experiments found the methyl radical to be planar (5). The cyclopropyl radical should be examined by EPR to see if a pyramidal structure is the more stable form.

4. Optically active 2-octyllithium with retained configuration has been prepared at -70° by halogen-metal interconversion (6). It is significant that interconversion occurs at low temperatures. A possible, but not unique, explanation of the facility with which interconversion is undergone is that bond-making and bond-breaking processes closely follow one another. A bimolecular $S_Ei$ mechanism seems a very reasonable mechanistic course for halogen-metal interconversion at saturated carbon. Two approaches would be helpful in elucidating the mechanism of interconversion. First, a kinetic study of the reaction of 2-bromooctane and s-butyllithium is proposed. Secondly, the stereochemical course of both carbon centers undergoing interconversion should be determined.

5. A few cases are known where either an intramolecular rearrangement or a loss of neighboring halogen occurs in a free radical reaction (7). A number of stereospecific radical additions of hydrogen bromide and thiols have been reported (7). The possibility should be explored that these three reactions are related in mechanism and that they may involve common or similar bridged radical intermediates [1]. It would be valuable in this respect to generate radicals at the $C_a$ carbon atom of an appropriately substituted series of compounds, $R_3R_4XC_bC_aYR_1R_2$ [1], and examine the reaction products. It would be of particular interest to study the stereochemical course of a non-rearranging substitution reaction at $C_a$.

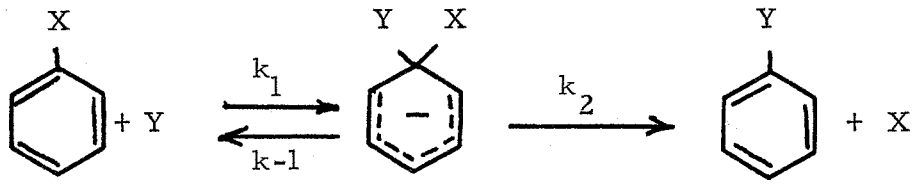



6. Although considerable evidence has accumulated that suggests that the acid hydrolysis [2] of the octahedral complexes of cobalt (III) follow an $S_N1$ mechanism (8), it has not been possible to detect an in-

[2] $$CoA_5X^n + H_2O \longrightarrow CoA_5H_2O^{n+1} + X^-$$

termediate of reduced coordination number in these reactions. The kinetics of hydrolysis should be studied in competition with anion substitution in aqueous-methanol solutions. Similar studies provided strong evidence for the intervention of carbonium ion intermediates in the solvolysis of alkyl halides (9).

7. The order of halogen mobility in direct nucleophilic aromatic substitution of nitroaryl halides is usually $F > Cl \gtrsim Br \gtrsim I$ (10). The reactions of 1-halo-2,4-dinitro benzenes with iodide ion (11) and N-methylaniline (12), however, follow the order $Br > Cl > F$. The observed reactivities have been explained in terms of a two-step mechanism [3],

[3] 


in which the halogen mobility is controlled by the relative magnitudes of $k_{-1}$ and $k_2$. Tronov and Kruger observed the order of reactivity $I > Br > Cl > F$ for the substitution reactions of phenyl halides with piperidine and sodium methoxide (13). Bottini and Roberts found the sequence $I > Br > Cl$ for the direct displacement reactions of halotoluenes with hydroxides (14). The order of halogen mobility in these reactions is not reasonably correlated by the two-step mechanism. It should be established whether or not the reaction of piperidine with phenyl halides is a direct and not a rearranging substitution reaction. In the event that direct substitution occurs, it would be valuable to know if the rate of substitution is subject to base catalysis.

8. A semiquantitative correlation of the relative reactivities of ten mixed haloforms toward hydrolysis in aqueous solution is proposed. A good quantitative correlation using six parameters has been reported (15). The relative reactivities, nevertheless, may be correlated in terms of the dihalomethylene reaction mechanism [4] using only the substituent constants $\sigma_I$ (16) and $\sigma_R^+$ (16). The rates of hydrolysis have a range of five powers of ten; the average deviation of the rate

[4] $$HCX_1X_2X_3 + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} {}^-CH_1X_2X_3 + H_2O$$

$$^-CX_1X_2X_3 \xrightarrow{k_2} CX_2X_3 + X_1^-$$

constants from the correlation is $\pm$ 20%.

9. Wittig has trapped benzyne with cyclic 1,3-dienes to form Diels-Alder adducts (17). The reactions of trans-1,4-disubstituted-1,3-butadienes and benzyne generated from o-diazonium benzoate should be studied to obtain chemical information relating to the electronic structure of benzyne.

10. A mechanism is proposed for the reaction of phosphorous pentachloride with ketones [5,6,7,8]. A similar mechanism has been suggested recently (18). A kinetic study of 7-norbornene with phosphorous pentachloride would be helpful in elucidating the mechanism of

[5] $2\ PCl_5 \rightleftharpoons PCl_4^+,\ PCl_6^-$

[6] $R_1COR_2 + PCl_4^+,\ PCl_6^- \rightleftharpoons R_1\text{-}\overset{+}{C}(OPCl_4)\text{-}R_2,\ PCl_6^-$

[7] $R_1\text{-}\overset{+}{C}(OPCl_4)\text{-}R_2,\ PCl_6^- \longrightarrow R_1\text{-}C(Cl)(OPCl_4)\text{-}R_2 + PCl_5$

[8] $R\text{-}C(Cl)(OPCl_4)\text{-}R_2 \longrightarrow$ products

this reaction. An attempt should be made to isolate the phosphate ester intermediate.

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